- Development of sterilization methods of facilities and validation of sterilization
- Validity of in-process control of sterile operation (culture media filling test, etc.)
- Methods of environmental management and monitoring data (methods of sterilization)
- Control parameters of important processes and process test data
- Data of all batches including those used in non-clinical and clinical studies

6.4.3 Development Report

The development report should contain the following elements.

- Rationale for the selection of dosage forms
- Explanation of formula design
- Change histories of compositions and manufacturing methods
- Consideration of scale-up
- Finally determined manufacturing methods
- Change histories of manufacturing processes
- Quality characteristics of manufactured batches
- Specifications and test methods of final drug products
- Identification of important manufacturing processes and rationale for their control parameters (parameters)
- Control parameters (parameters) in each process and their set values
- References to existing reports and literatures, etc.

6.4.4 Information of Technology Transfer of Drug Products

Cases considered as information of technology transfer are shown as follows.

Information on Manufacturing Methods

- Development report on drug products or those corresponding to the report
- Master batch records of manufacturing (format of manufacturing instructions/records)
- Manufacturing records (batches for establishment of specifications for approval and validation batches, etc.)
- Plan and report of process validations
- Items of in-process control: in-process test (test methods and specifications)
- Investigation report on causes of abnormalities (if occurred)

Information on Test and Packaging

- Test procedures (accuracy of test and limit of defects)
- Container/closure system
- Specifications of primary packaging (moisture proof, light blocking, etc.) and conformity to packaging materials

Information on Cleaning Procedures

- Cleaning instructions
- Plan and report of cleaning validations
- Test methods and specifications
- Validation report on analytical methods used for cleaning validations

Information on Analytical Methods

- Development report on analytical methods or those corresponding to the report
- Test methods and specifications (inactive ingredients, drug substances, final drug products, container/closure system, and packaging materials)
- Validation report on release test methods
- Stability tests (validation report on analytical methods, plan and report of stability tests, packaging conditions, reference standards and relevant reports)
- Investigation report on causes of out-of-specification (OOS) test results (if occurred)

Information on Storage and Transportation Methods

- Specifications of secondary packaging
- Expiry date
- Transportation conditions and tests
- Information on sensitivity to temperature, humidity, and light
- Instructions of temperature monitoring for drug products which need cold storage

Information on Facilities

- Structural materials
- Category and type of main facility

Information on Environmental Management

- Clean area (temperature and humidity, microorganism monitoring, airborne particles, and control of differential pressure)
- Information on safety
  - Safety information of hazardous raw materials, drug substances, and final drug products

Information on Industrial Hygiene/Safety

- Protection for operators
- Protection for products

7. Points of Concern For Preparing Technology Transfer Documentation

For smooth technology transfer, information related to the transfer and necessary items should be appropriately documented and recorded. In this regard, summaries are already described in the above; however, it is recommended to prepare the following documents.

1) Documents to clarify applicable technologies, burden shares, responsibilities, and approval systems, etc. concerning the technology transfer (written agreements, memorandums, etc.)
2) Organizations of technology transfer (at both of transferring and transferred parties)
3) Development report
4) Product specifications
5) Technology transfer plan
6) Technology transfer report

Concerning 1), 3) and 4) which need comments on descriptions, this chapter will show details of items to describe, and points of concern for description.

7.1 Documents To Clarify Applicable Technologies, Burden Shares, Responsibility System, etc. Concerning Technology Transfer

The following chart shows details of items to be described in documents clarifying applicable technologies, burden shares, responsibilities, and approval system, etc. concerning technology transfer, and points of concern for description. Any types and forms of the documents are acceptable if they include the items in the following chart, and no duplications of the items stipulated or described in detail in other technology transfer documents are required.

Items	Details	Remarks
1 Organizations	Organizational framework, organization chart, department (person) in charge, and separation between manufacturing and quality departments	
2 Supervisor	Clarify supervisor of technology transfer	

	(manufacturing supervisor is acceptable) and his/her responsibilities.	
3 Responsibility system	Clarify organization and its responsibilities, document control system, persons in charge of manufacturing department and quality department.	
4 Structure and equipments	Maintenance, inspection and calibration of manufacturing facilities and equipments, antipollution measurements, etc.	
5 Documentation and records	Clarify all technology transfer documentations. Describe control methods of documentation and records, and storage period.	SOP list may substitute the documentation and records, if implemented under the control of GMP; however, "cleaning categories" and "cleaning methods of facilities and equipments" should be described in detail.
6 Manufacturing control	Standard manufacturing procedure, and manufacturing instructions and records Industrial hygiene control methods of buildings and facilities Industrial hygiene control methods of operators Report on manufacturing control and quality control Control methods of raw materials, intermediates, products, etc.	For existing products, existing GMP documents can be used.
7 Quality control	Determination of test results and report methods Control method of reference samples Maintenance and inspection of pilot facilities and equipments Control methods of test results Control methods of reference standards, reagents, and test solutions, etc. Handling of retest	
8 Shipment	Control methods of shipment (procedures and judge)	
9 Validation	Organization for validation Describe communication and confirmation methods, discussion, and approval, etc. concerning validations. Conformation of results of installation qualification	
10 Change control	Specify handling of change controls in advance.	
11 Deviations	Clarify handling of abnormalities, deviations, and out-of-specification (OOS) test results.	
12 Other necessary items		
12.1 Persons in charge	Describe persons in charge at both parties.	
12.2 Periodic report	Describe formats of periodic reports, such as annual report.	
12.3 Changes in technology transfer documentation such as required specifications and product specifications	Describe communication and confirmation methods and necessary formats for changes.	
12.4 Storage of technology transfer documentation such as required specifications	Specify storage period and disposal time.	

and product specifications		
12.5 Revision history	Store revision history.	
12.6 Others	Handling of not specified items	

7.2 Technical information to be Described in the Development Report, Product Specification, etc.

The following chart shows technical information and points of concern to be described in documents such as the development report, product specification, etc. of drug substances.

Items	Details	Remarks
Development report of drug substances		
1 Change history of process design and manufacturing methods during development	• History of manufacturing methods of drug substance used in Phase I, II and III studies, etc., bioequivalence of drug substance quality, and justification for starting materials and manufacturing methods, etc.	
2 Information on final product		
2.1 Product name	• Scheduled brand name in the certificate of approval	• Not necessary, if not yet determined.
2.2 Specifications and test methods	• Describe all of specifications and test methods described in the certificate of approval.	• Describe agreed specifications as well, if any.
2.2.1 Raw materials	• Specifications and test methods of raw materials to be used	• Clarify suppliers. • Test results
2.2.2 Container and closure	• Specifications and test methods of container and closure to be used	• Clarify suppliers. • Test results
2.2.3 Packaging and labeling materials	• Specifications and test methods of packaging and labeling materials to be used	• Clarify suppliers. • Test results
2.2.4 Intermediates	• Sampling procedures, specifications and test methods of intermediates	• For intermediates not to be isolated, description can be omitted, provided that the rationale should be described in the development report. • Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.5 Drug substance	• Sampling procedures, specifications and test methods of drug substance	• Describe added specifications for trading (such as acceptance criteria for product assessment), if any.
2.2.6 Form of test results	• Attach sample form of manufacturer.	
2.3 Manufacturing methods and procedures, etc.	• Describe manufacturing flows, manufacturing procedures, in-process control, and required facility capacity, etc. as detail as possible.	• Describe scientific evidence based data (including stability data to determine unit operating conditions) in the development report. • Confirm important parameters at the time of predictive validation and change validation.
2.4 Packaging methods and procedures, etc.	• Describe packaging methods and procedures.	
2.5 Storage conditions	• Describe storage conditions of raw materials, intermediates, and drug substances.	• Temperature and humidity ranges, light, and container in use • Describe evidence data in the development report.

2.6 Expiry date	• Expiry dates of raw materials, intermediates, and drug substances	• Describe evidence data in the development report. • Describe stability data as much as possible.
2.7 Transportation conditions	• Describe transportation conditions and cautions for transportation of raw materials, intermediates and drug substances.	
2.8 Information on safety	• Describe information on safety of raw materials, intermediates, and drug substances. • Describe information on safety of each unit operation (reaction and post-treatment, etc.).	• Attach MSDS as much as possible. • Attach safety data of processes as much as possible.
3 Stability		
3.1 Raw materials		• Describe physicochemical safety (temperature, humidity, and light). • Describe microbiological safety.
3.2 Intermediates		
3.3 Drug substances		
4 Information for environmental assessment	• Describe influence on environment. • Describe necessary data for assessment.	• Describe waste disposal methods as well.

The following chart shows technical information and points of concern of drug products to be described in documents such as the development report, and product specification, etc.

Items	Details	Remarks
Development report of drug products		
1 Properties of drug substances	• Physicochemical and pharmaceutical properties necessary for drug product design (such as dissolution, particle size, hygroscopicity, incompatibility, absorbability and stability, etc.)	Describe properties concerning formula to be transferred.
2 Change history of formula design and manufacturing methods during development *	• History of formula and manufacturing methods of drug products used for non-clinical and clinical studies, bioequivalence between different drug products, rational for formula of final drug products and the manufacturing methods, etc.	Describe properties concerning formula to be transferred.
3 Information on final drug product		
3.1 Product name	• Scheduled brand name in the certificate of approval	• Not necessary, if not yet determined.
3.2 Indications and dosage and administration	• Indications in the certificate of approval	• Not necessary, if not yet determined.
3.3 Ingredients/contents	• Ingredients/contents in the certificate of approval	• In case of revision of contents, its rationale should be included.
3.4 Specifications and test methods	• Describe all specifications and test methods in the certificate of approval.	• Describe agreed specifications, if any.
3.4.1 Drug substances	• Specifications and test methods of drug substances to be used	• Clarify suppliers. • Master file registration No., if any. • Test report
3.4.2 Inactive ingredients	• Specifications and test methods of inactive ingredients to be used	• Clarify suppliers. • Master file registration No., if any. • Test report
3.4.3 Primary packaging materials	• Specifications and test methods of primary packaging materials	• Clarify suppliers. • Master file registration No., if any. • Test report
3.4.4 Secondary packaging materials	• Specifications and test methods of secondary packaging materials	
3.4.5 Intermediates	• Specifications and test methods of intermediates	
3.4.6 Final products	• Specifications and test methods of final products	• Describe applied specifications for application and/or specifications before shipment, if any.
3.4.7 Forms of test results	• Attach sample form of an manufacturer.	
3.5 Manufacturing methods and manufacturing procedures, etc.	• Describe manufacturing flows, manufacturing procedures, and in-process control as detail as possible.	
3.6 Packaging methods and packaging procedures, etc.	• Describe packaging flows, packaging procedures, and in-process control as detail as possible.	
3.7 Storage conditions	• Storage conditions of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products	• Temperature and humidity ranges, light and container in use

3.8 Expiry and retest dating	• Expiry date of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products	• Describe rationale for expiry and retest dating. • Describe stability data as much as possible.
3.9 Transportation conditions	• Describe transportation conditions of drug substances, inactive ingredients, primary packaging materials, secondary packaging materials, intermediates, and final products, and cautions for their transportation.	
3.10 Information on safety	• Describe information on safety of drug substances, inactive ingredietns, primary packaging materials, secondary packaging materials, intermediates and final products.	• Attach MSDS as much as possible.
4 Stability		
4.1 Drug substance		• Describe physicochemical safety (temperature, humidity, and light). • Describe microbiological safety as well.
4.2 Intermediates		
4.3 Final products		
5 Environmental assessment	• Clarify information necessary for environmental assessment, and if there is no environmental impact, clarify "no environmental impact."	• Describe waste disposal methods as well.

ISPE Prague Conferences

Marriott Hotel • Prague, Czech Republic

19 > 23 September 2005

Preliminary Programme

Early bird deadline: 5 August 2005

19-21 September

Global Regulatory GMP Conference – New Regulatory Initiatives and Achieving International Harmonisation

20-21 September

- Barrier Isolation Technology Forum
- Biopharmaceutical Facilities and Case Studies

22 September

- *GAMP*® Good Practice Guide for Laboratory Systems Validation

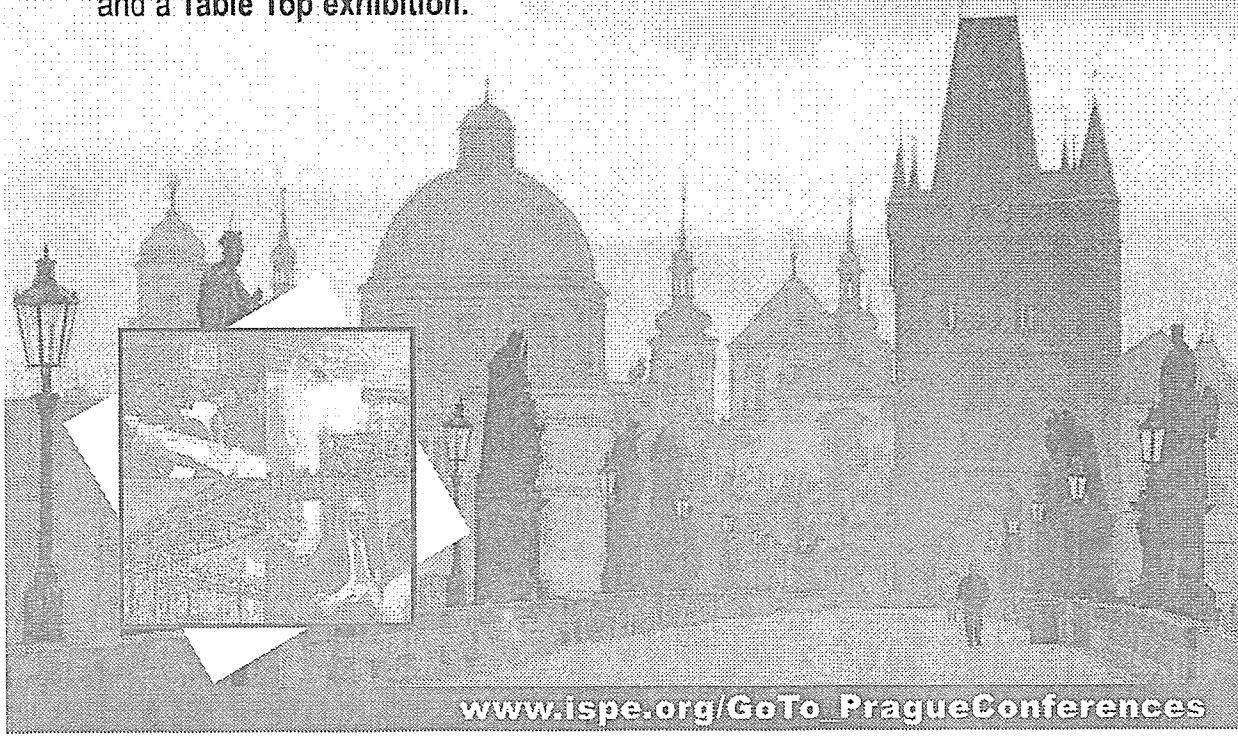
22-23 September

- Planning Strategies for the Effective Management of Global Investigational Medicinal Products (IMP) Supplies in the 21st Century
- The Challenges and Opportunities in Future Science-Based API Manufacture

23 September

- *GAMP 4* -Maintaining the Validated State of Computer Systems

The Conference will also include **networking opportunities, social activities** and a **Table Top exhibition.**



www.ispe.org/GoTo_PragueConferences

Global Regulatory GMP Conference – New Regulatory

19-21 September 2005

Conference Leaders

Charles Hoiberg, Pfizer, USA

Michael Wierer, European Directorate for Quality Medicines Council of Europe

Conference Description

The globalisation of the pharmaceutical industry continues to progress at a rapid pace, adding to the complexity of meeting regulatory requirements and expectations.

This inaugural ISPE Global Regulatory GMP Conference is a key event which will bring together regulators and the pharmaceutical industry from around the world. Leading regulators and senior industry professionals from Europe, USA and Asia will present their insights and address a variety of issues affecting the industry now and in the future.

The Conference will focus on GMPs, manufacturing and inspections, as they pertain to new regulatory initiatives and harmonised international standards. You will have a unique opportunity to gain a competitive edge in your organisation by keeping abreast of the rapidly changing regulatory environment.

On Day Three, delegates will participate in Round Table Discussion Forums on a variety of topics resulting from the previous two days. Here, you will have the opportunity to interact with regulatory and industry speakers and fellow delegates in a relaxed and lively manner, and ask questions which may not have been addressed in the previous two days.

Learning Objectives

At the conclusion of this conference, you will be able to:

- Describe the latest global GMP regulatory initiatives from Europe (EMEA), USA (FDA) and Japan (MHLW)
- Understand the challenges of EU enlargement and new legislation
- Apply the strategies of achieving international harmonisation in a multi-national business
- Appreciate the challenges of global GMP inspections from regulatory and industry perspectives
- Understand the roles and activities of the World Health Organisation (WHO), the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and the International Standards Organisation (ISO) in the global environment
- Discuss the impact on the international arena of emerging pharmaceutical manufacture in Asia
- Update colleagues on the ICH process including Q8, Q9 and Q10
- Apply your insight of European industry experiences of Quality Systems implementation
- Describe the regulatory challenges of supplying Investigational Medicinal Products (IMPs) for global clinical trials
- Discuss and share experiences with fellow regulatory and industry speakers and delegates

Who Should Attend

All personnel in Production, QA, QC, Engineering, Validation, IT, Regulatory Affairs and Compliance in Primary, Secondary and Biopharmaceutical operations will find this conference of importance and value in the much changing global regulatory environment.

Individuals from global regulatory agencies will also benefit from attendance.

Initiatives and Achieving International Harmonisation

Tentative Agenda Topics

- European Regulatory GMP Perspective and Update
- Update on FDA GMP Initiatives
- Global GMP Harmonisation - A Japanese Perspective
- Global Challenges of an Expanded Europe
- WHO Initiatives Toward Globalisation
- PIC/S - A Catalyst for Harmonisation
- ICH Developments - Influence on the Global Environment
- Global Interfaces Between Regulators and Industry
- Challenges of Global GMP Inspections
- Quality Systems in Europe - An Industry Perspective
- Q7A and APIs - A Model for International Harmonisation
- Emerging Pharmaceutical Manufacture in Asia
- Regulatory Challenges of Supplying Investigational Medicinal Products for Global Trials - An Industry Perspective
- ISO/CEN Contamination Control Standards - Update and Relationship with GMPs
- A Regulator's Experiences with Global and MRA Inspections

Round Table Discussion Forums

(Wednesday, 21 September)

The Conference will include several opportunities for delegates to raise questions with the speakers after presentations and in the Panel Discussion sessions, and also to network with industry and regulatory delegates/speakers during the breaks and Networking Reception.

There will be three sessions as follows:

- 09.00 – 10.15
- 11.00 – 12.15
- 13.45 – 15.00

Speakers

Linda Broad, Pfizer, UK
Joseph Famulare, FDA, USA
Gordon Farquharson, Bovis LL Pharma, UK
Lothar Hartmann, Hoffman La Roche, Switerland
Stuart Heir, Novartis, Switzerland
Yukio Hiyama, MHLW, Japan
Sabine Kopp, WHO, Switzerland
Ludevit Martinec, State Institute of Drug Control, Slovakia
Gordon Munro, Watson Pharma, USA
Gopal Nair, Grasp Enterprises, India
Jörg Neuhaus, Germany
Jean Louis Robert, Laboratoire National de Santé, Luxembourg
Kathy Wengel, Johnson and Johnson, Belgium
Representative from the European Medicines Agency (EMEA)
Representative from PIC/S

Regulatory

ISPE Global Regulatory GMP Conference

New Regulatory Initiatives and Achieving International Harmonization
19-21 September 2005 – Prague, Czech Republic

The inaugural ISPE Global Regulatory GMP Conference provided delegates the opportunity to hear presentations and insights from leading regulators and senior industry professionals from Europe, the USA, and Asia. The following articles address a variety of key issues affecting the industry now and in the future.

Full articles are available to ISPE Members only.

Global GMP Harmonization: A Japanese Perspective
Japan instituted sweeping changes to its Pharmaceutical Affairs Law (PAL) to bring it in line with Good Manufacturing Practices, International Conference on Harmonization (ICH), and quality standards in the western world. The changes include revision of its quality regulations, approval matters as they relate to manufacturing, pharmaceutical development, and GMP standards and related guidelines. "The new system is very similar to the Western system," said Yukio Hiyama, Division of Drugs, National Institute of Health Sciences, and Ministry of Health, Labour and Welfare (MHLW).

ISPE Members read the full article...

Harmonizing GMP Requirements – PIC/S Benefits the Global Pharmaceutical Industry
The strengths of the Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S) is its large membership, high criteria for joining, focus on training and the development and revision of GMP guides, according to Robert Tribe, a GMP consultant to regulatory authorities. "And the US Food and Drug Administration (FDA) is expected to apply to join PIC/S," he said.

ISPE Members read the full article...

Globalization and the World Health Organization (WHO)
The World Health Organization's (WHO) strategy over the past decades has been to harmonize pharmaceutical standards to ensure people everywhere have access to the essential medicine they need and that the medicines are safe, effective, and of good quality, said Dr. Sabine Kopp, of WHO's quality assurance and safety team. WHO has 192 Member states and headquarters and WHO's six regional offices work to achieve those goals.

ISPE Members read the full article...

Quality Systems Need to be Integrated – The FDA's Council on Pharmaceutical Quality has a Mission
When the FDA created the Council on Pharmaceutical Quality two years ago, its mission was to help the Agency modernize its regulations governing pharmaceutical manufacturing and product quality. The Council's report, issued in September 2004, is a starting point, not the end of the process and soon the results of the council's expert working groups would be available making it possible for the FDA to carry out the work it wants to do going forward. One goal identified was to develop a plan to rearrange FDA's drug quality program and expand it internationally.

ISPE Members read the full article...

The International Conference on Harmonization (ICH) – Progress Forward
Common standards make it easier to understand the assessment process in the three regions governed by the International Conference on Harmonization, which include Europe, the United States, and Japan. "The outcome of the International Conference on Harmonization is a very positive one and based on discussions from the three regions, industry, and regulatory, we managed to make substantial progress toward

quality of medicinal products," Dr. Jean-Louis Robert, Laboratoire National de Sante', Service du Controle des Medicaments. "Even if at first sight it might look like higher requirements nevertheless they are scientifically sound."

ISPE Members read the full article...

European Regulatory GMP Perspective and Update
In the EU (European Commission and EMEA), there are basically two different procedures to initiate marketing authorizations, including: Mutual Recognition Agreements and centralized procedures. Both systems maintain the same quality, safety, and efficacy standards. "In the last year, one of the challenges of the enlarged EU was how to meet GMP standards throughout the 25 states," explained Dr. Jean-Louis Robert, Laboratoire National de Sante', Service du Controle des Medicaments.

ISPE Members read the full article...

A Regulator's Experience with Global and MRA Inspections
When Good Manufacturing Practices are harmonized flimsy excuses like "it used to be like this" will disappear as a defense when pharmaceutical companies learn that some aspect of their operations fall short. Though it will take "some time" to achieve harmonization of Good Manufacturing Practices (GMP), it is not possible to totally harmonize GMPs in every geographic location because local conditions may demand a modified approach according to Dr. Joerg Neuhaus, Bezirksregierung Koeln, Germany.

ISPE Members read the full article...

Global GMP Harmonisation – A Japanese Perspective

Yukio Hiyama, Ph.D.
Chief, Third Section, Division of Drugs,
National Institute of Health Sciences,
The Ministry of Health Labour and Welfare,
JAPAN

Presentation Key Points

- Changes in Pharmaceutical Affairs Law
- Quality Regulations under the Revised Pharmaceutical Affairs Law
- Commitment of Manufacturing Process as Approval Matters
- Role of ICH Pharmaceutical Development
- Role of the Quality Overall Summary
- GMP Regulations and related Guidelines

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

Revision of approval and license system for pharmaceuticals and medical devices

From Development to Use

Research & Development

MHLW

Evaluation of quality, effect & safety (manufacturing approval for each product)

Prefecture

Manufacturing (manufacturing license)

Sale

Use

Attention to manufacturing — Old system

1. Companies are supposed to have their own manufacturing establishment
2. "Approval" is for "manufacturing", not for "marketing" (**Minister manufacturing approval**)
3. Final manufacturing "license" is issued, based on approval. (Mainly **prefectural manufacturing licensing**)

Attention to whole process (from manufacturing to PMS) — **New System**

1. Introduction of "**Marketing Approval**" for overall evaluating quality, safety & efficacy and manufacturing for marketing
2. Manufacturing establishment license is separated from product authorisation process, which allows companies to subcontract whole manufacturing process
3. Instead, company's ability of pharmacovigilance is subject to review for Marketing Approval Holder (MAH)

Comparison Flowcharts of Approval and License

Points: (1) MAH's requirements for PMS system, (2) Allow complete subcontract manufacturing, (3) Introduce marketing approval system

OLD system

Product

Manufacturing Application (MHLW)

Quality, Safety & Efficacy

Manufacturing Approval

2-Step process

Establishment

License application (Prefecture)

inspection (5 yearly renewal))

Establishment License

Start manufacturing

Partial subcontracting

Partial License

GMP Requirement

REVISED system

Product

Marketing Application (MHLW)

Quality, Safety & Efficacy

1-Step process

inspection (Renewal) Every 5 years

Marketing Approval

Start marketing

Licensed Marketing Approval Holder

• Companies' PMS compliance system
• Companies' Quality Assurance System

Self production OR Subcontracting

Establishment

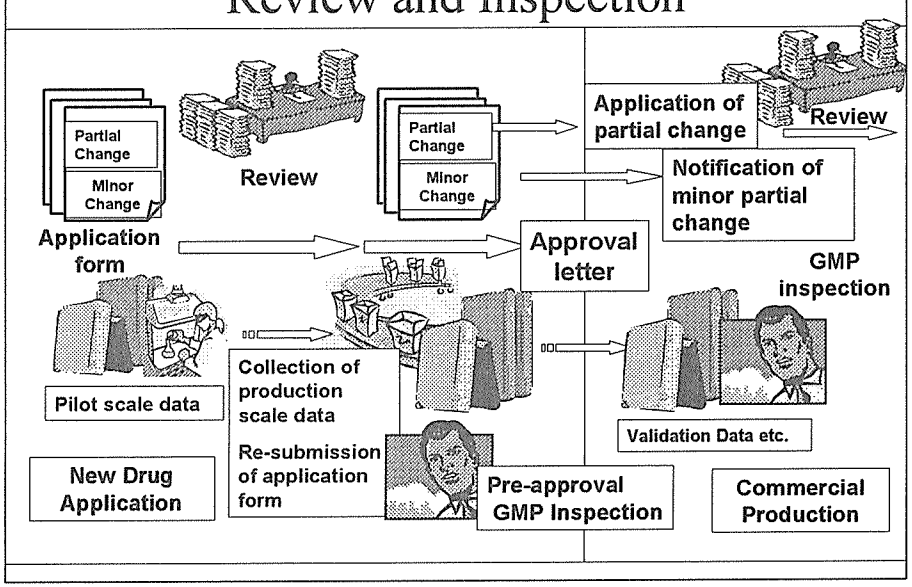
Licensed Establishment

Start production

• MHLW inspection : New drug & biologics
• Prefectural inspection: Others

: Recurred for each product

Framework for Review and Inspection



From Multi sets to One set of regulations

- Previously: No inspections at foreign GMP sites/Under GMPI →Foreign inspections by PMDA
- Previously: Approvals given to API and Product. Only specs are set for API of imported products →Approvals only to products including API specs and manufacturing process
- Previously: Whole Manufacture contracts NOT allowed for domestic industry→ Contracts allowed everyone

Revision of the Quality Regulation

1. **MAH's* responsibility for 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

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.

Revision of the Quality Regulation

1. MAH's* responsibility for 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

2. Application Form and Approval Matters

- 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.

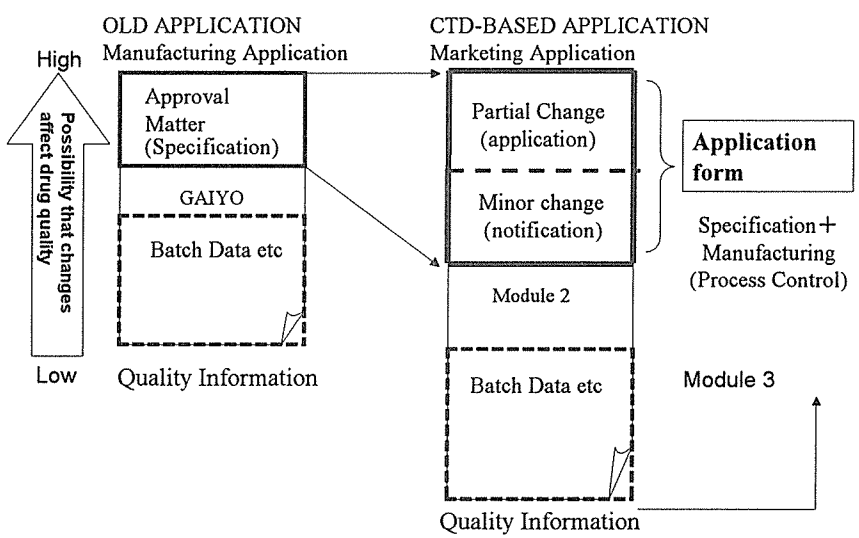
Approval Matters

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

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 assessment and inspection
  - **Introduction of a notification system pertaining to minor change**
    Effective regulatory system

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



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.

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

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

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**

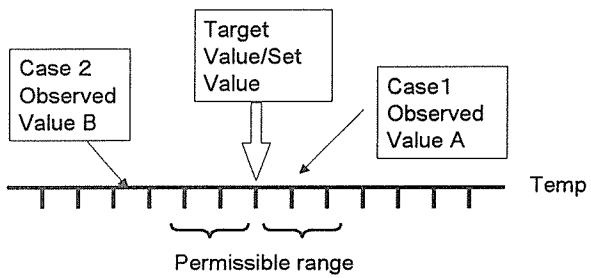
Narrative Description of Manufacturing Process

- **Matters needed for assuring the quality consistency should be selected**

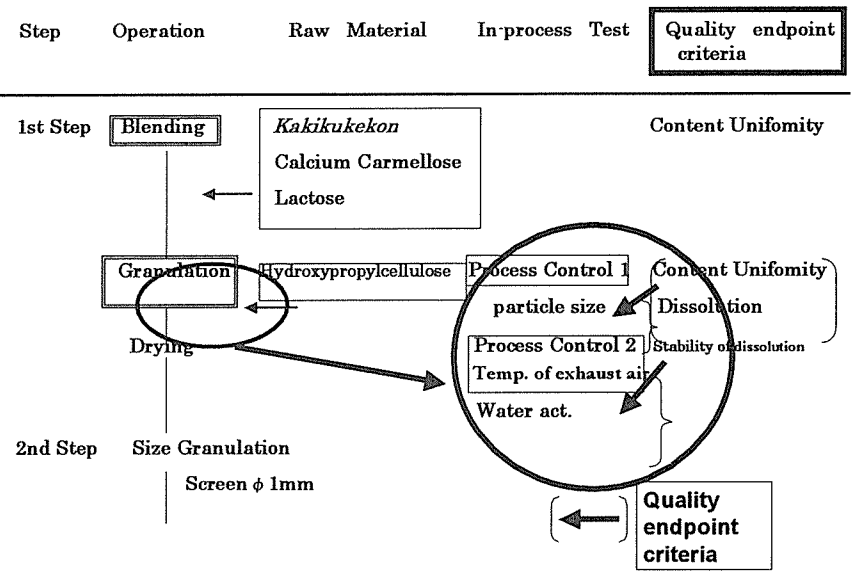
- **Quantities of raw materials, critical processes, process control, equipment, process parameter (speed, time, temp., pressure, pH, etc)**
- **Test and acceptance criteria of critical step and intermediate**
- **Identity and specification of primary packaging material (or manufacturer and type number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

Target Value and Set Value

- In cases where target value/set value are set:
  - Permissible range of target value/set value must be described on the master production documents or SOPs.
- Case 2:
  - The suitability of product should be judged based on GMP.



Flow Diagram of Manufacturing process (Tablet)



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	

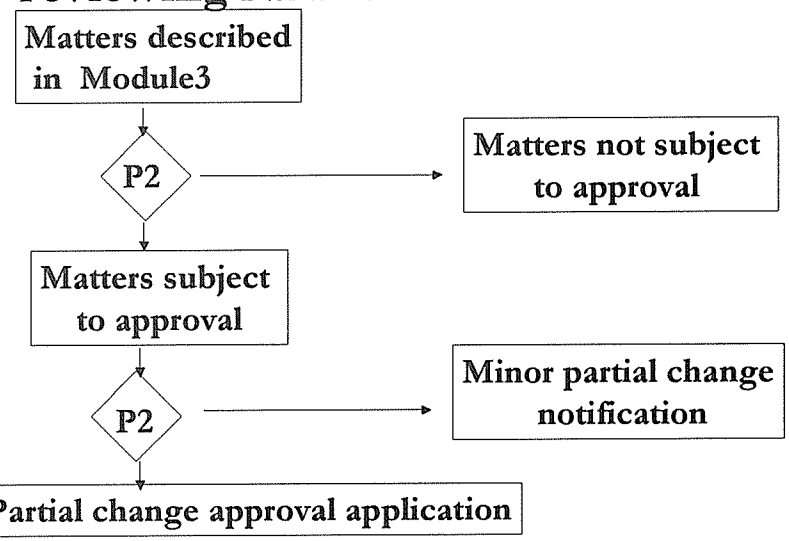
Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - In that case, the evaluation methods which was approved at the time of previous submission might be invalidated.
- 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

The Role of P2 Document in Reviewing New Drug Application (NDA) under Revised Pharmaceutical Affairs Law (PAL)

Some matters are subject to application of partial change, based on the information described in P2.

The Role of P2 document in reviewing NDA under revised PAL



The new requirement regarding the approval letter is applicable to:

1. market applications after April 2005
2. renewals of existing licenses, which may occur by 2010

for case 2, the manufacturing section of approval letter may be rewritten without review/assessment.

For most of those approvals, CTD information was NOT submitted (did not exist).

Opportunities by ICH CTD based application

- Complete description of product specific quality system
- Better knowledge transfer tool within the sponsor organization, between industry and regulator, and within the regulator organizations---QoS:Module 2 plays important roles
- ICH Pharmaceutical Development Q 8 (step 2 in Yokohama)