

Quality Regulation under Revised Pharmaceutical Affair Law

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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)

One set of regulations

- Currently: No inspections at foreign GMP sites/Under GMPI **Foreign inspections by PMDA**
- Currently: Approvals given to API and Product. No legal specs are set for API of imported products **Approvals only to products including API specs**
- Currently: Manufacture contracts NOT allowed for domestic industry **Contracts allowed**

Revision of the Quality Regulation

1. MAH's * responsibility for the quality management

* Marketing Approval Holder

2. Approval Matters Requirements Change

3. Drug Master File system to support CTD based application (eff. July 2003)

4. Consolidation of the Legal Positioning of GMP

5. Revision and Consolidation of GMP standards

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

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

2. Approval Matters Requirement Changes

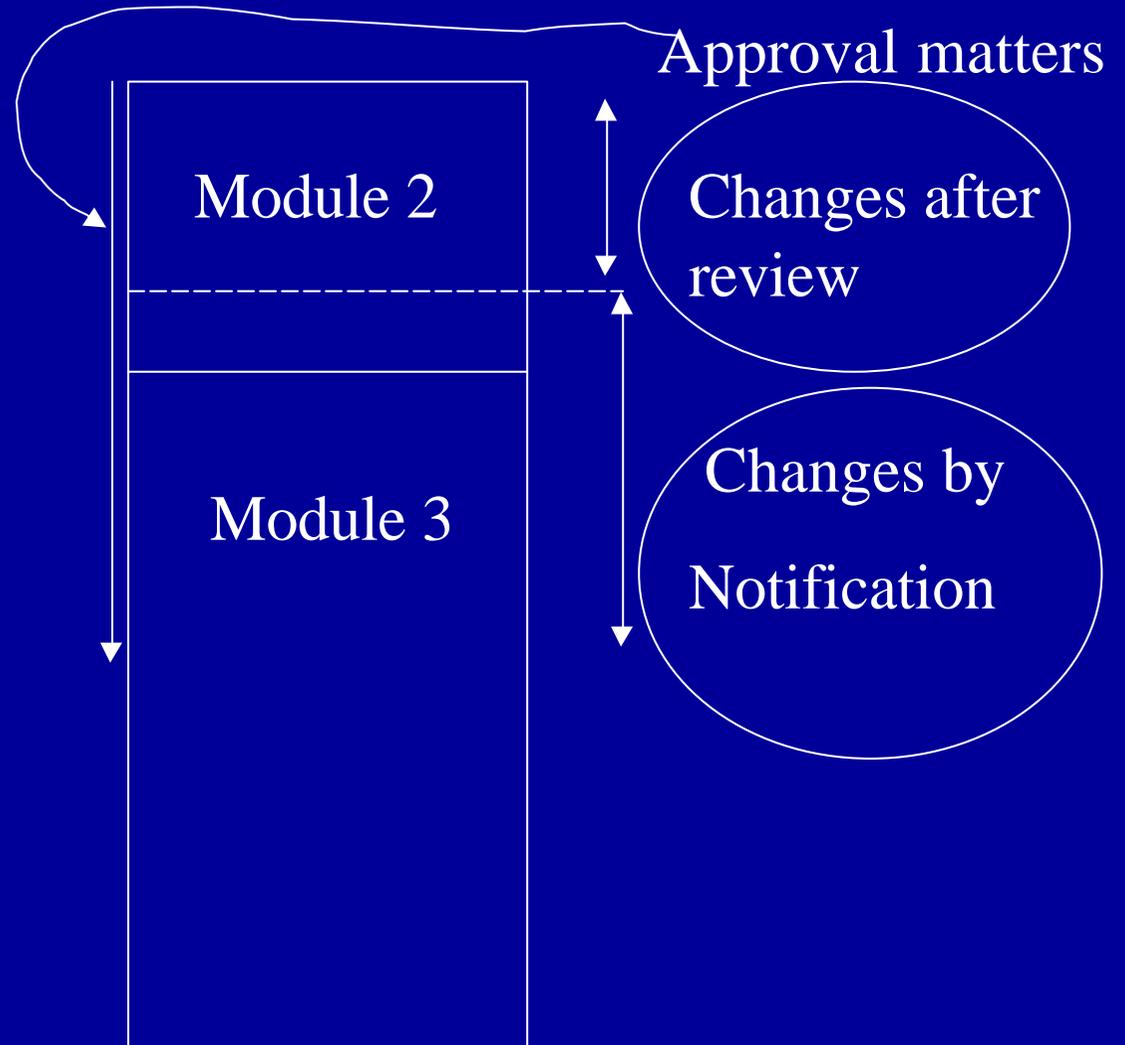
- Old system: Components, Specifications and Test Methods. No manufacturing processes nor raw/packaging materials identified.
- New law: Components, Specifications/Test Methods, Manufacturing Processes (including API on JP), Raw/Packaging Materials

OLD
Application



Little Description
on Formulation
Manufacturing

New Approval Matters for all products



Problems with the OLD application system

- Limited Scope of the approval matters
Contained only spec lists with test methods

Manufacturing process design and controls
had been excluded (and ignored?)

Poor Manufacturing Change Control or Poor Design?

- *Problems revealed from the Re-Evaluation project of generic drugs*
 - **The original protocol was to match dissolution profiles of the innovator's. Inconsistencies of dissolution profiles found in many innovator's products.**
 - **The root cause of the above problem not known (Poor product design or Poor change control or both?), because dissolution data and/or IVIV data Not available in older products**
 - **Product Design and Change Control**

Problems in Regulation and in Industry Practices

- Manufacturing process WAS NOT approval matter but under GMP
- No dissolution specifications for older products (1986(JP11) , 1991(JP12))



No BE requirement
by process change



Dissolution was not
controlled under
GMP

3 Drug Master File system to support CTD based application and the new set of Approval Matters

- Common Technical Document based application for new drugs became mandatory in July 2003
- Detailed Description on Formulation/Process Design And Manufacturing Process Controls
- Expand the scope of approval matters **with rules for minor changes**
- Master Files for API, (key intermediates, products, packaging materials)

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 of the approval matters
- GMP inspection at foreign sites

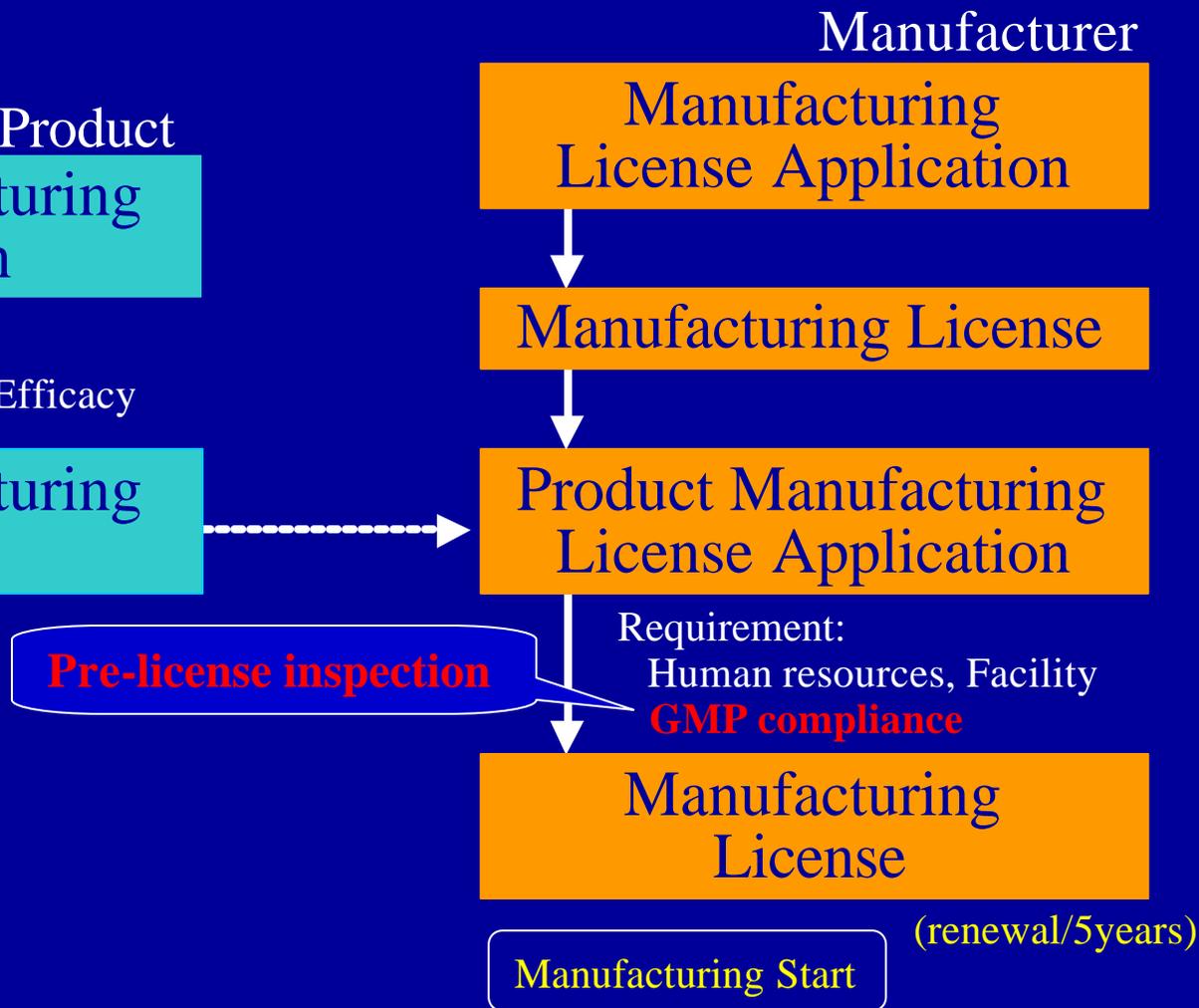
Flowchart of Approval and License

(current system /will become old system)

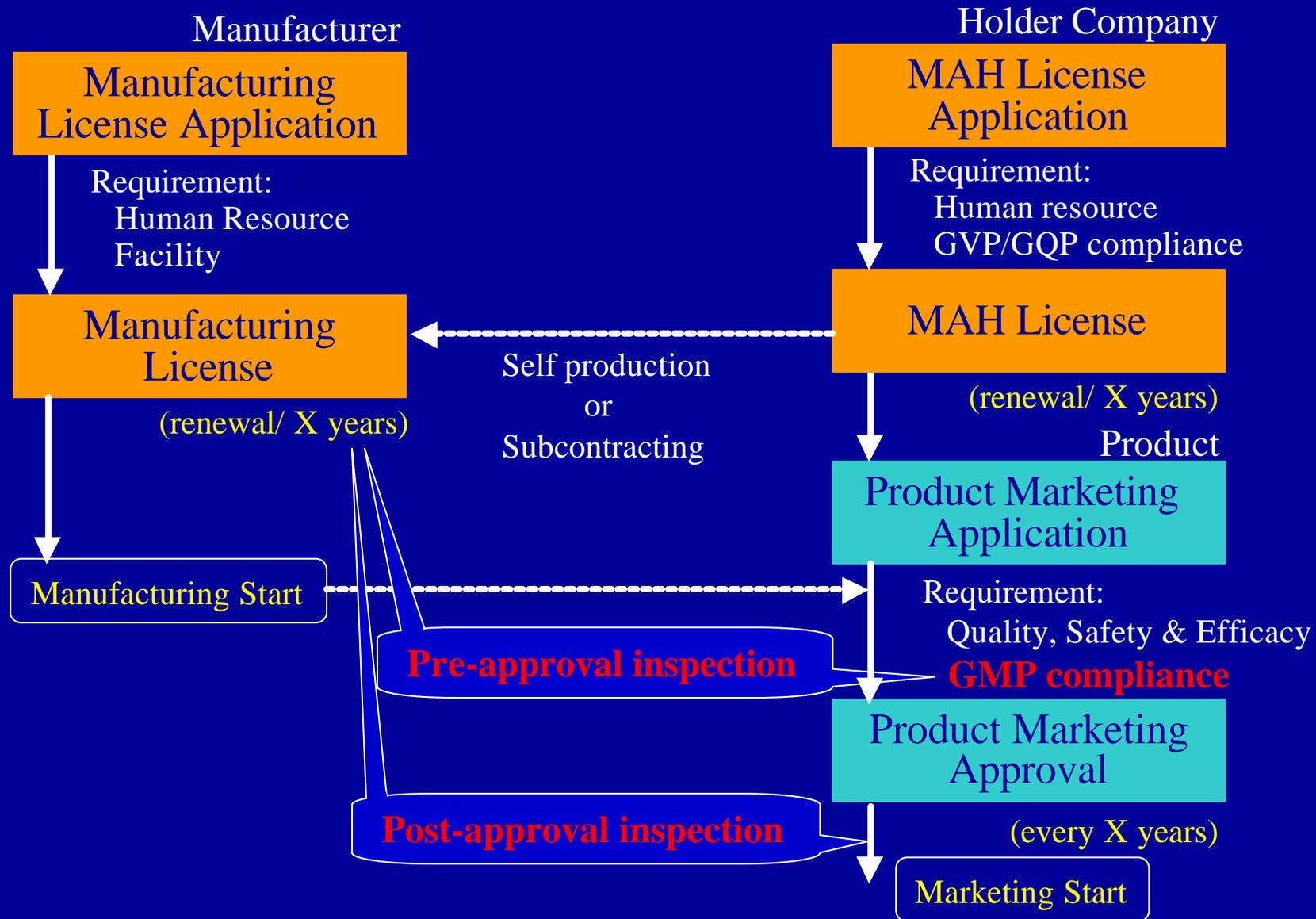
< Approval scheme >



< License scheme >



Flowchart of Approval and License (revised system)



5. Revision/Consolidation of GMP Standards

- Pharmaceutical Affair Law Changes
- Global Environment
- Perceived Problems

Perceived Problems

- **Superficial approaches to GMP** -non validated procedures, little connection with QC results, procedures override science
- **Regulations** encourage good practices?
- **Poor communication between R&D and Manufacturing Plant**
- **Poor development and or change control of manufacturing**
- **Detail GMP related guidance and inspection manuals are NOT readily available in Japan**

System Development Activities by Health Science Studies

*GMP guideline (2002-2005) Y.Hiyama

*Manufacturing Change Control(2001-
2002) Inspection Policy/System(2003-
2006) N.Aoyagi

*Approval Matters and Minor Changes
(2003-2006) H.Okuda

GMP Studies in 2002-2004

- (A) Quality systems and Inspection Policy *T.Nishihata (Santen)*
- (B) GMP regulations and GMP guideline *Y. Koyama (Fujisawa, Eli Lilly)*
- (C) Tech transfer *K.Morikawa (NIHS) , I.Saitoh (Shionogi)*
- (D) Lab control *S. Tadaki (Saitama Pref. Lab)*

*Members:Industry , Government (Prefecture Compliance, Prefecture Lab, NIHS , **not central MHLW**)*

Work Principles: Bring Data/Experience, not just Position/Opinion

GMP guidance studies 2003-2004

- **Product GMP Guideline** (Level is similar to ICH Q7A. With emphasis of Periodical Quality Review Technology Transfer, Process Validation Strategy, Site Qualification of Pharmacopoeia Tests)
- **Technology Transfer Guideline** (emphases on R&D responsibility and on Study Report ICH Q8)
- **Laboratory Control Guideline**

The report including guideline proposals are posted at NIHS web site (and English translation) . Will be finalized this year

2. Approval Matters Requirement Change

System Development Activities by Health Science
Studies 2

GMP guideline (2002-2005)

Inspection Policy/System(2003-2006)

Approval Matters and Minor Changes
(2003-2006)

Approval Matters Policy

- Manufacturing Process : Principles and end points of the critical manufacturing steps with key operational parameters of the commercial scale will become approval matters. **Principle and quality end point for each manufacturing step** will be subject to pre approval review.

Approval Matters Policy-2

- 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

Benefits of this system

- Better process understanding gives (straightforward process control, less variability by process) high quality products
- Good process understanding can identify goal of each manufacturing step
- Once goal is identified, industry can change process without submitting pre-approval application

System Development Activities by Health Science Studies 2

GMP guideline (2002-2005)

Inspection Policy/System(2003-2006)

Regulator :Why inspect, what to inspect, what do we accomplish? Classify, set objectives, inspection procedures New product/Change approvals, Reduce possibility of quality problems in market

System based, Quality (science/risk) management, Technical ability/qualification relative to Application

Approval Matters and Minor Changes
(2003-2006)

Role of Module 2 in Japan

- Module 2 bridges NDA Application Form and Module 3
- Module 2 is one of key review documents
 - Reviewers review Module 2 and then narrow down into Module 3 or 4 or 5 when they need more detailed information.
 - Module 1 and 2 together with review reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

Opportunities by CTD 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---Module 2 is the place!

Challenges

- Training for reviewers and inspectors
process/manufacturing sciences
- Industry side

Reluctant or unable to give a complete story

Regulatory personnel training

Superficial development (meeting specs is all) Are you still doing this?

Establishment of Pharmaceuticals and Medical Devices Agency (PMDA)

- Integration of review division, safety information management division and GMP inspection division
- Strengthening resources for review and inspection
- Established in April 2004



- ✧ Efficient review system
- ✧ More emphasis on pharmaceuticals with high risks