ICH Harmonisation and Japanese Pharmaceutical Regulations

APEC LSIF ICH Quality Guidelines Q8 and Q9
Challenges of Implementations

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Presentation Outline

- Pharmaceutical Affairs Law (PAL) changes, ICH discussion and MHLW studies
- Quality Regulations under the Revised Pharmaceutical Affairs Law
- Commitment of Manufacturing Process as Approval Matters and Role of ICH Q8, Q9 and Q10

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.)

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

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;

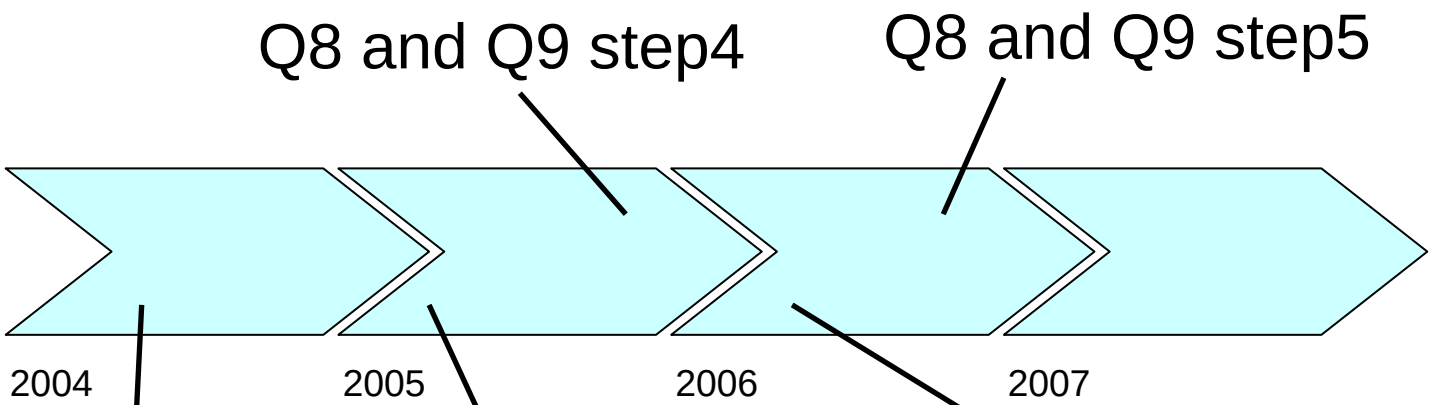
  - Risk management

  - Technology transfer

  - Change control, etc.

ICH and Quality regulation in Japan

ICH



JAPAN

- PMDA established
- Revised PAL enforced
  Approval matters policy
  Inspection policy
- GMP guidance

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**
2004	GMP workshop in Brussels	CTD mock
PMDA established	Q8 and Q9 started	Approval matters
New GMP standards	**2004**	Inspection Policy
2005	Q8 reached step 2	**2004**
Approval matters policy	**2005**	Approval matters
Revised PAL enforced	Q9 reached step 2	GMP guidelines
Inspection policy published	Q8 and Q9 reached step4	**2005**
2006	Q10 started	Inspection Policy
Product GMP guidance	**2007**	Skip Test guidance
	Q10 reached step 2	Inspection Checklist
		2006-2008
		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)

Revision of the Quality Regulation

1. **MAH's* responsibility for the Quality management**
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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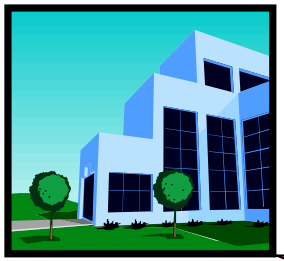
6. Establishment of Pharmaceuticals and Medical Devices Agency (PMDA)

***Marketing Authorization Holder**

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.

Marketing and Manufacturing



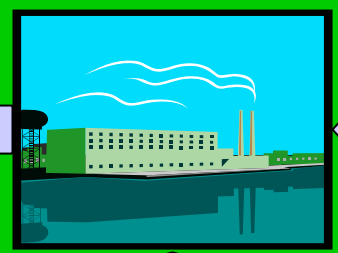
Marketing Approval Holder
in M prefecture

- Supervise and manage the manufacture
- Ensure proper release to market

GQP

Market Release

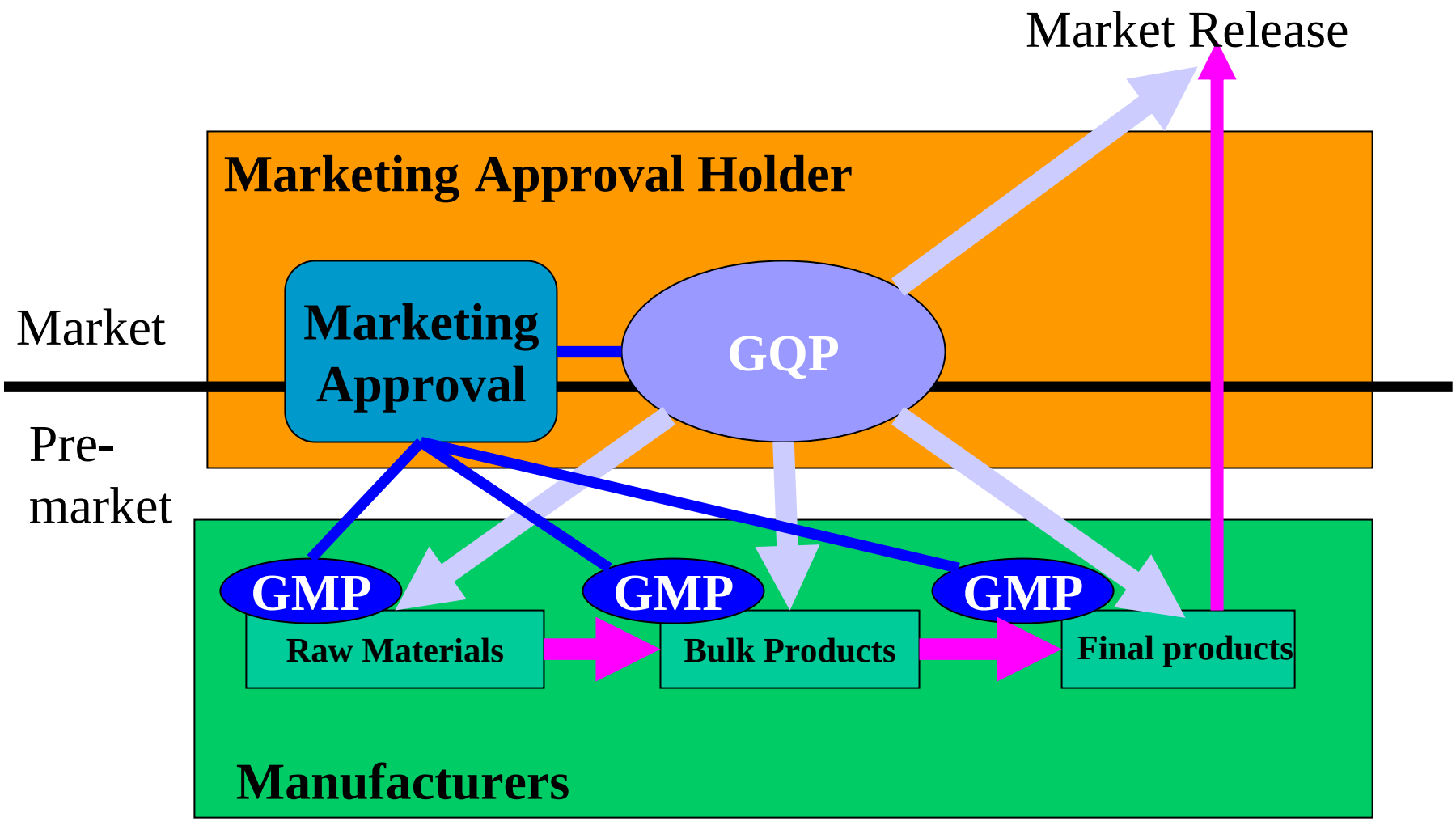
Manufacturer C (packaging, label) In C prefecture	Manufacture B (bulk product) In B prefecture	Manufacturer A (API) In country X



Manufacturers

External
Testing laboratory

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.

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

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.

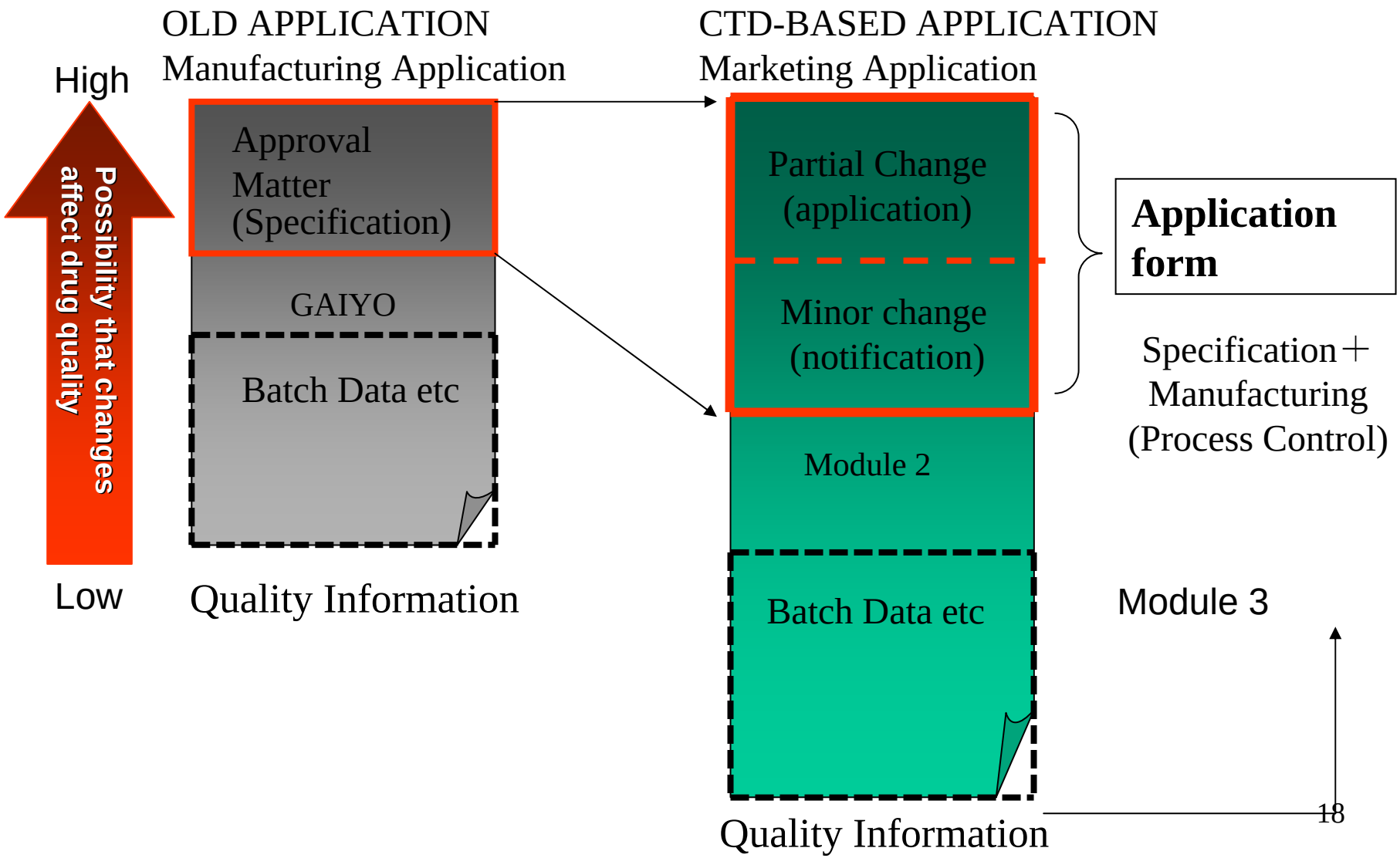
Approval Matters Policy (continued)

- 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

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	

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law

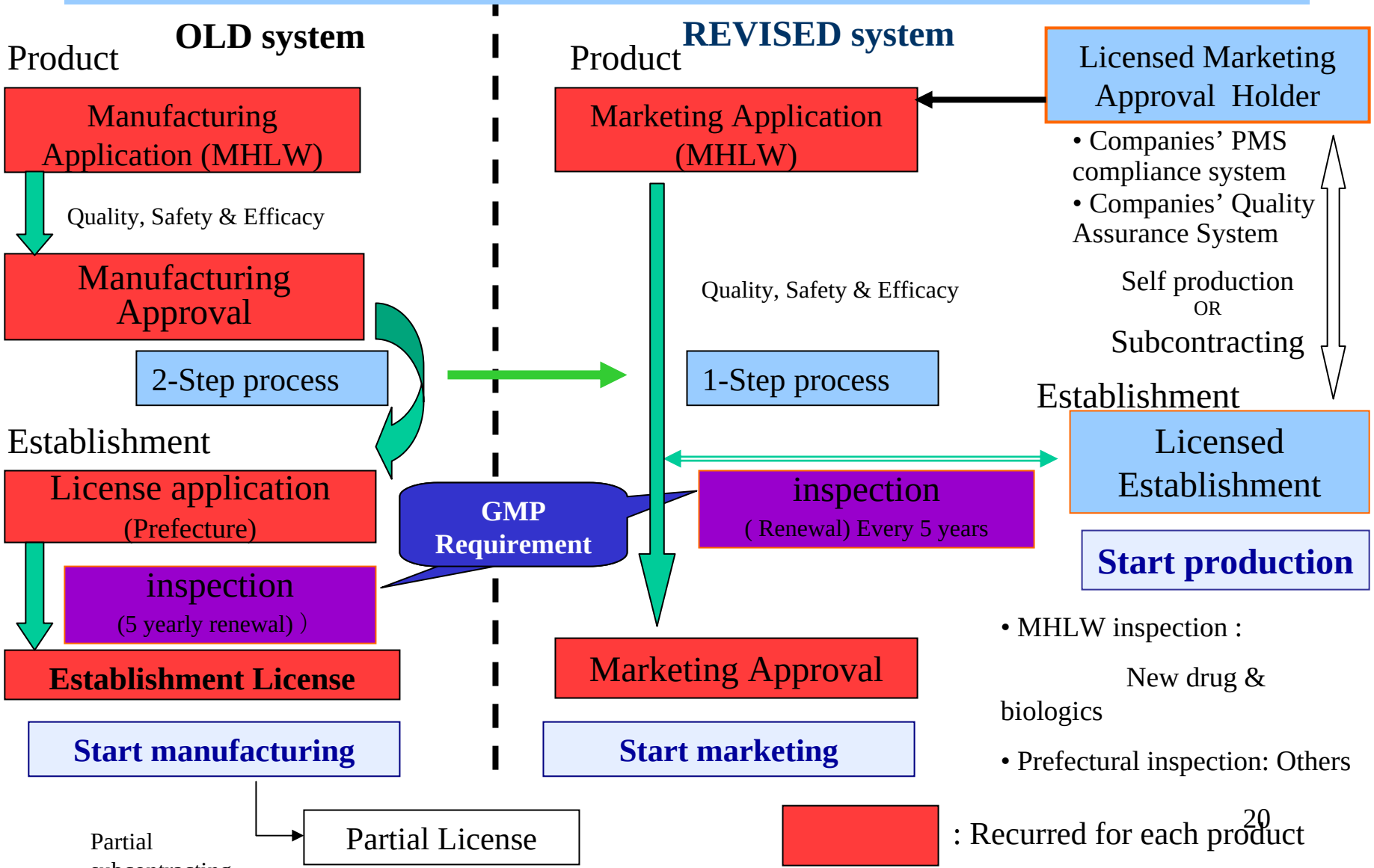


4. Consolidation of the Legal Positioning of GMP

- **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**

Comparison Flowcharts of Approval and License

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



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)

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

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.

Relationship between Application Form and CTD Documents

Application form (in Japanese)

Analytical procedures (JP style) & acceptance criteria

Manufacturing process

Module 2 (QOS) (in Japanese)

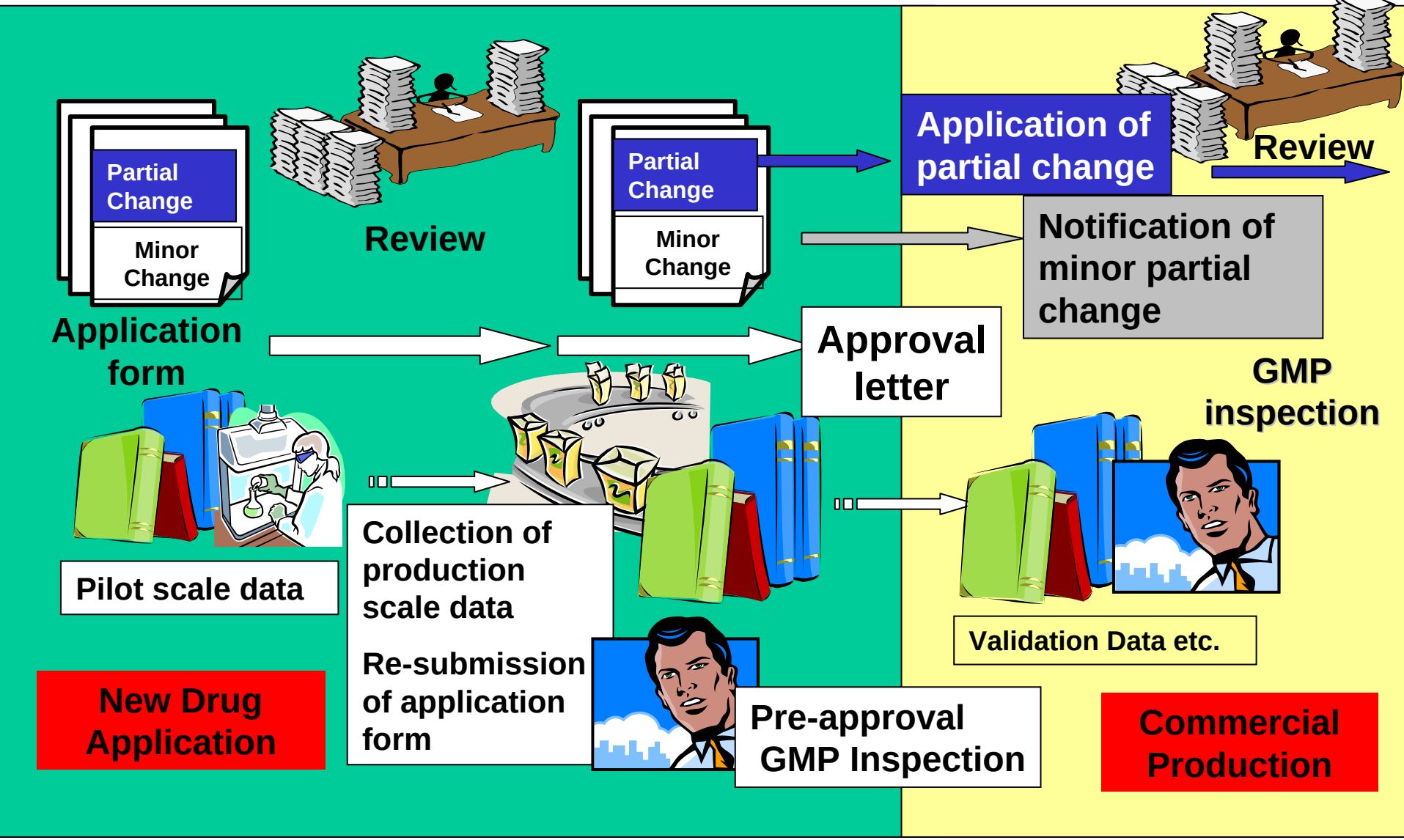
- Specifications
- Analytical procedures
- Pharmaceutical Development
- Manufacturing Process
- batch analyses
- Justification etc.

Module 3 (in Japanese or English)

3.2.S4.1 Specification
3.2.S4.2 Analytical procedures
3.2.S4.3 Validation of analytical procedures
3.2.S4.4 Batch analyses
3.2.S4.5 Justification of specification

Raw data

Framework for Review and Inspection



Challenges when implementing rPAL regulations with ICH Q8

- Baseline expectations need to be clarified

"At minimum(identify risks and risks controlled)" expectations do not seem to be traditionally submitted in Japanese NDA. With "traditionally" submitted contents, it is difficult to sort out pre-approval matters, minor change matters.← expect Q8(R) address this

- Range for excipients as a design space: scientific basis, description in approval letter←under consideration with "approval matters" study group
- Design spaces with interacting multi-variables and with interacting unit operations:description in approval letter←see industry's creativity
- Real time release:process and facility dependence ←Need final scale data to justify. Specification with test method would not go away because of need for later evaluations including generics

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**

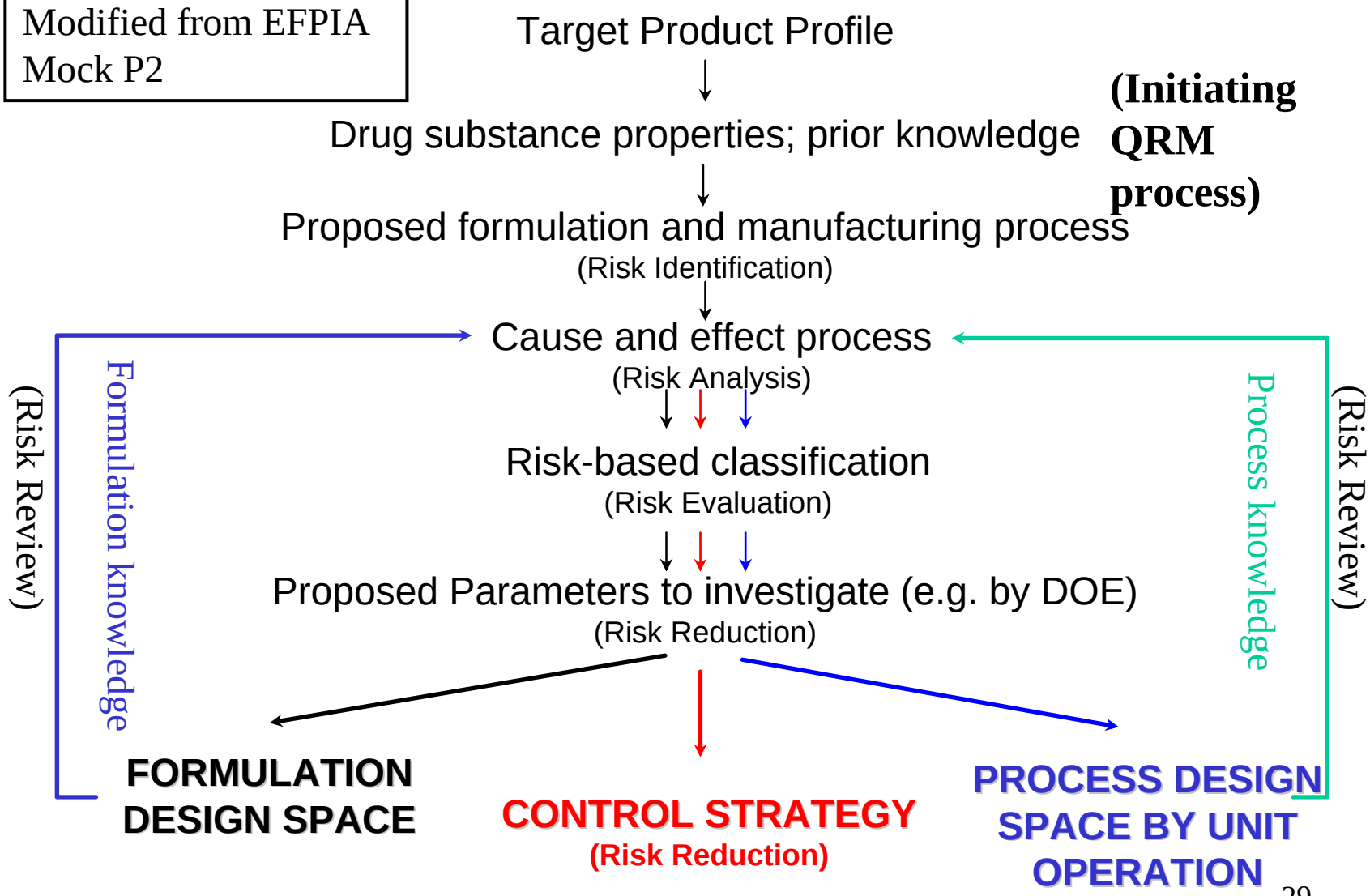
Opportunities by Q9

- Integration to Industry's Pharmaceutical Quality Systems

  (ICH Q10 will address this area)
- Integration to Regulatory Authorities' work process (e.g. QS for GMP inspectrate)
- Integration to Guidance Development and Pharmacopoeia Policy (Government and Industry joint effort)

A QRM process from Development to Manufacturing

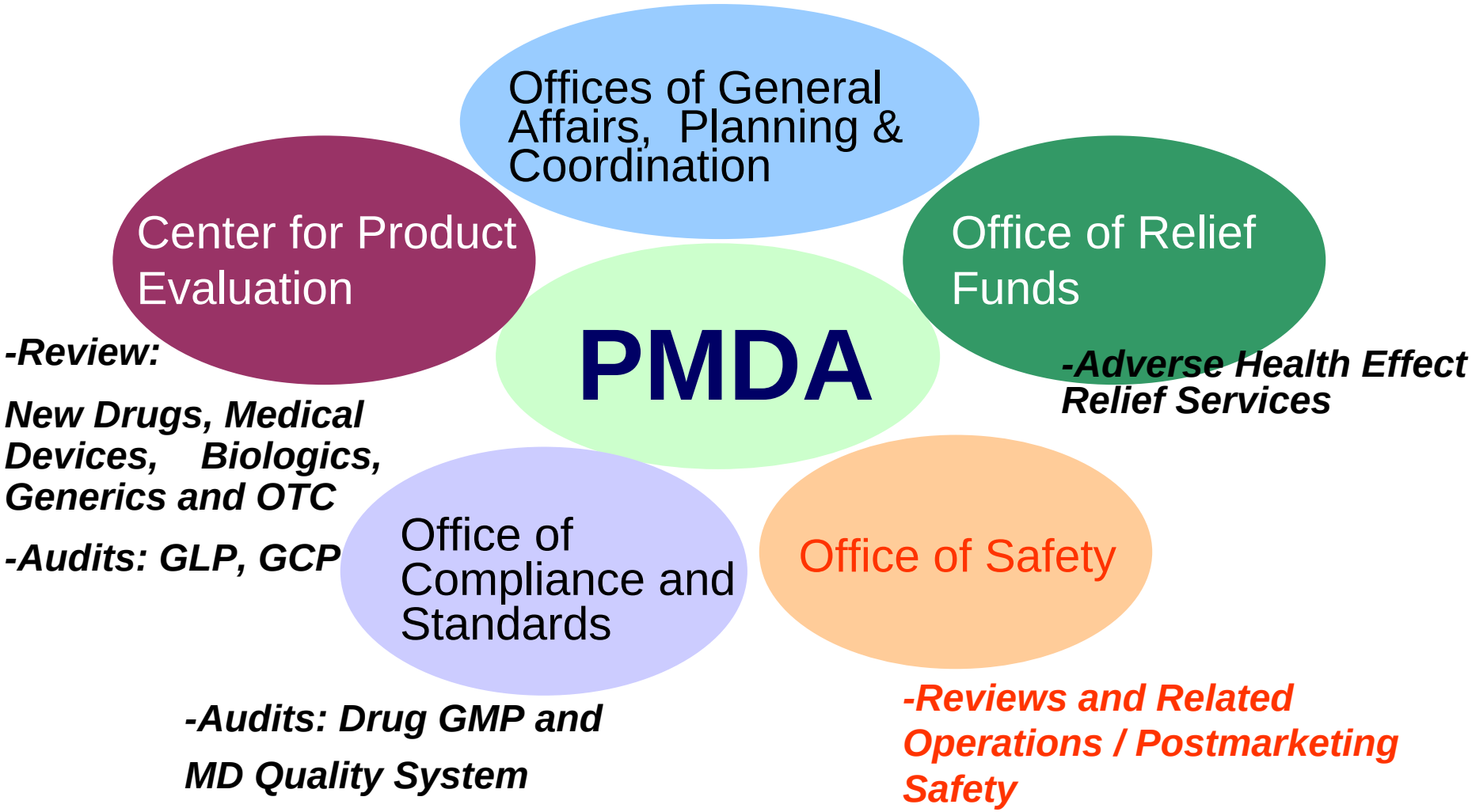
Modified from EFPIA Mock P2



6. Establishment Pharmaceuticals and Medical Devices Agency (PMDA)

- Reviews and Related Operations
  - Approval reviews of pharmaceuticals and medical devices GMP/QMS audits to assess pharmaceutical and medical device facilities, processes, and quality management systems
  - Re-assessment and re-evaluation based on Pharmaceutical Affairs Law etc.
- Post-marketing Safety Operations
- Adverse Health Effect Relief Services

Organization of PMDA

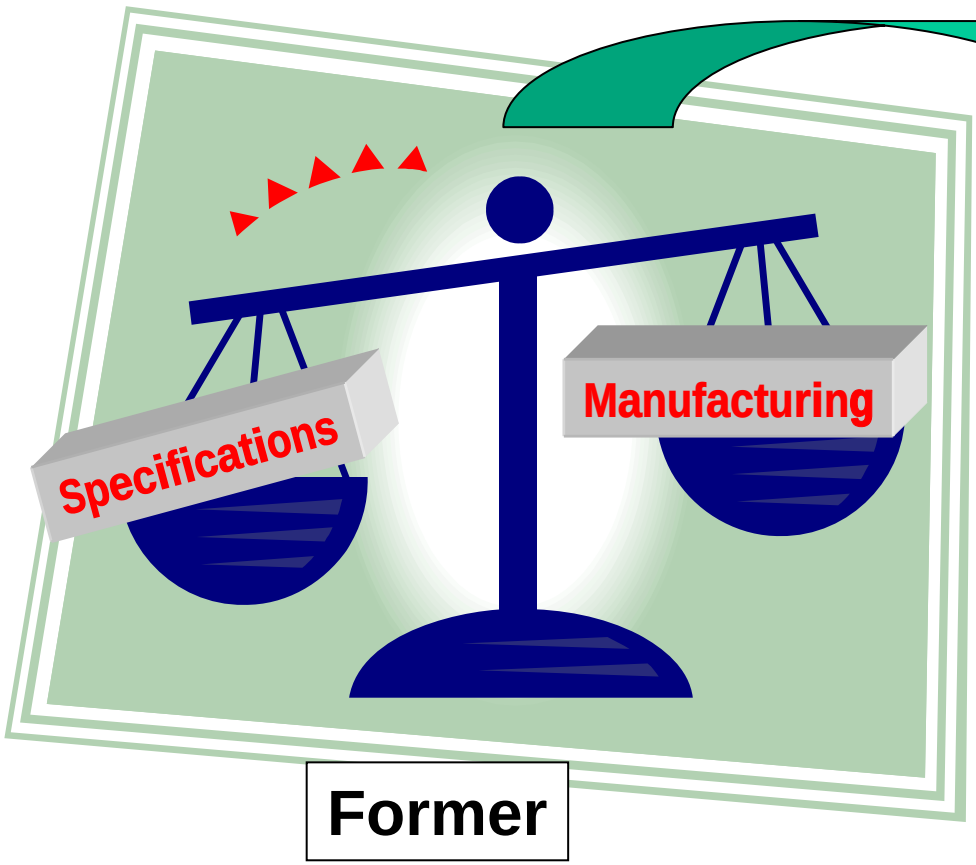


Balance between “Specification” and “Control of Manufacturing”

- Implementation of ICH-CTD (July, 2003)
- Revision of Pharmaceutical Affairs Law (April, 2005)

ICH Q8, Q9&Q10

Help us to implement rPAL



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