# PMDA update on GMP
# &
# QRM related to recall

**The 2nd Indonesia-Japan Symposium**

**21 May 2014**
**Novotel Jakarta Mangga Dua Square**


## Ichiro TSUNOI
**Office of GMP/QMS Inspection**

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# Agenda

- *Regulatory system of Japan*
- *GMP inspection authorities of Japan*
- *PMDA, Office of GMP/QMS Inspection*
- *QRM*
- *QRM: PMDA's GMP inspection*
- *QRM: Recall*
- *International cooperation of GMP inspection authorities of Japan*
- *Recent topics*

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# Regulatory system of Japan

# 薬事法(*"yakujihou"*)

Pharmaceutical Affairs Law (1960 Law No. 145)

Hereinafter referring to it as "J-PAL"

Note: The law revising J-PAL was passed by the National Diet on 20 November 2013. The law will be enacted until November 2014 and thus J-PAL changes its name.

# Basic framework of J-PAL quality perspectives

**MAH (sponsor) (market release)**

**License【GQP】 J-PAL § 12**

**Marketing Authorisation【GMP】 J-PAL § 14**

manage

**GMP**

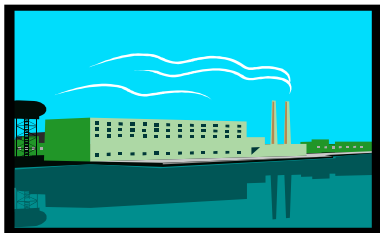
**Manufacturer A (API)**

**License【BFR】 J-PAL § 13**

**GMP**

**Manufacturer B (bulk)**

**License【BFR】 J-PAL § 13**



**GMP**

**Manufacturer C (pack/label)**

**License【BFR】 J-PAL § 13**

**Market release**

Legend:

【】= Prerequisite for license/authorisation and subject to inspections based upon MAH/manufacturer's application (NDA, revision or 5yr)

# Basic framework of J-PAL quality perspectives

Only 4 steps to be aware of the framework.

# J-PAL quality perspectives (1)
# License (*"kyoka"* or *"nintei"*)

Japanese definition: license (*"kyoka" or "nintei"*) is given to companies or persons according to each of their premises.

**Marketing license** – a requirement for marketing any drugs in Japan. Thus, all the marketing authorisation holders (MAHs) (i.e. sponsors) shall have this license.

**Mfg license (*"kyoka"*)**

– a requirement for conducting critical mfg process, e.g. API production, aseptic preparation, packaging & labelling and testing for drugs marketed in Japan.

***"Nintei"*** is required for overseas manufacturers for doing so.

# J-PAL quality perspectives (2)
# Authorisation

Japanese definition: authorisation *("shounin")* is given on a product-to-product basis.

**Marketing authorisation** – a requirement for any drugs marketed in Japan.

When applying for marketing authorisation of a new drug or major changes (i.e.supplements) thereto, GMP inspection (i.e. PAI) application is also required.

GMP inspection (i.e. PoAI) application is required every 5 years to maintain existing marketing authorisation.

# J-PAL quality perspectives (3)
# GxP

**GQP (Good Quality Practice)** – consisting requirements on how to manage manufacturers through contract, surveillance, reporting, etc. – as a prerequisite for the marketing license.

**GMP** as a prerequisite for the marketing authorisation of drugs and authorisation of major changes (i.e. supplements) thereto **as well as** a requirement (not a prerequisite) for the mfg license.

# J-PAL quality perspectives (4)
# BFR

**BFR (Buildings and Facilities Regulation)** as a prerequisite for the mfg license (*"kyoka"* or *"nintei"*).

BFR stipulates general & non product-specific requirements for buildings and facilities according to classification of mfg license – e.g. biologics process, aseptic/terminal sterilization mfg process, other production process… whereas GMP Ordinance stipulates product-specific requirements.

# Now you are well aware of… the basic framework of J-PAL quality perspectives.

**MAH (sponsors) (market release)**

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**Marketing Authorisation【GMP】 J-PAL § 14**

manage

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**Manufacturer A (API)**

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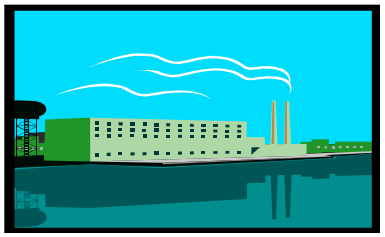

**GMP**

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**Market release**

Legend:

【】= Prerequisite for license/authorisation and subject to inspections based upon MAH/manufacturer's application (NDA, revision or 5yr)

Cabinet Ordinances, Ministerial Ordinances, Notifications…
only in Japanese?

**PMDA website in English**

http://www.pmda.go.jp/english/index.html

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# GMP inspection authorities of Japan

- **MHLW**

ひと、くらし、みらいのために
厚生労働省
Ministry of Health , Labour and Welfare

management and policy development function. In general, only inspection that MHLW conducts with its 8 regional branches is a for-cause inspection.

- **PMDA**

Pharmaceuticals and Medical Devices Agency

- **47 Prefectural govs**

Hokkaido, Aomori, Akita, Yamagata, Iwate, Miyagi, Fukushima, Tochigi, Gunma, Ibaraki, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Nagano, Yamanashi, Shizuoka, Aichi, Gifu, Toyama, Ishikawa, Mie, Fukui, Shiga, Nara, Wakayama, Kyoto, Osaka, Hyogo, Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Kochi, Ehime, Fukuoka, Oita, Miyazaki, Saga, Nagasaki, Kumamoto, Kagoshima and Okinawa.

# GMP inspection authorities:
## PMDA and prefectural governments

| | Domestic mfg sites | Overseas mfg sites |
|---|---|---|
| **New drugs, Biologics*, Radio pharmaceuticals** | **PMDA**** | **PMDA** |
| **Other drugs** | **Prefectural governments** | **PMDA** |

＊ “Biologics”:

1. The Biological Products （e.g. vaccines, antitoxins, toxoids, blood preparations, plasma fraction preparations etc.）
2. The Drugs subject to the National Certification （the drugs designated by the Minister of Health, Labour and Welfare in accordance with PAL Article 43, Paragraph 1. They are de-facto included in the “Biological Products” (1.).）
3. Cell-culture technology applied drugs （e.g. interferon preparations etc.）
4. GM technology applied drugs （e.g. EPO preparations, G-CSF preparations, MAB preparations etc.）
5. Cell/tissue-based drugs （regulated as “regenerative medicines etc. products” after amendment of PAL in 2013.）
6. Specific biological derived products （e.g. human placenta extract preparations etc.）

＊＊ Domestic mfg sites for new drugs or biologics are inspected by the prefectural government if:

1. They manufacture new drugs that are still under the re-examination due to supplement of new indications but one or more re-examination results have been already notified.
2. They manufacture biologics but carry out only the processes after purification of cell-culture and/or GM technology applied drugs.
3. They manufacture export-only non-biologics drugs that are de-facto identical to new drugs in the domestic market.

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# PMDA's philosophy

We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.

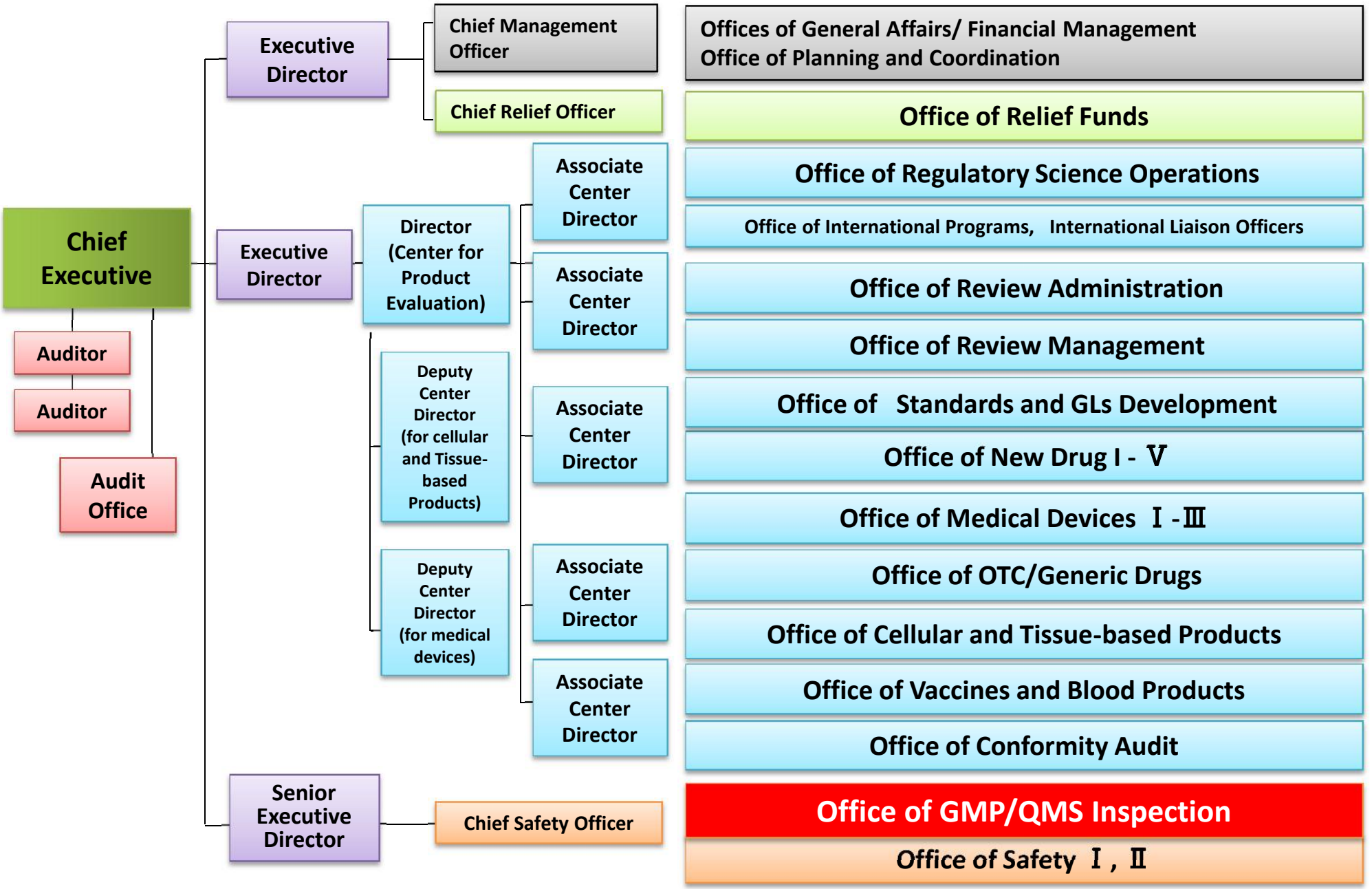
We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.

We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.

We play an active role within the international community by promoting international harmonization.

We conduct services in a way that is trusted by the public based on our experiences from the past.

# Organization Chart of PMDA



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# ICH Q9 EWG members

**H. Gregg Claycamp (Rapporteur)**
Director Scientific Support Staff
A. D'Sa
Compliance Officer, CDER
Diana Kolaitis
District field inspector

Georgia Keresty
Centocor, Inc.,GlobalBiologicsSupply
Vice President, Worldwide Quality
Tobias Massa
Bristol-Myers Squibb
Vice president Global Regulatory Sciences-CMC

Ministry of Health, Labour and Welfare

Yukio Hiyama
Chief, Third Section: Division of Drugs
Ichiro Tsunoi
Assistant Director, Office of Compliance, Pharm.& Food Safety Bureau, MHLW
Tamiji Nakanishi
Reviewer, Office of New Drugs I,PMDA
Mayumi Shikano
Review Director,Office of Biologics,PMDA
Yoshihiro Matsuda
Reviewer, Office of New Drug I,PMDA
Yukio Saito
GMP Inspector, PMDA
Takashi Nagashima
GMP Expert, PMDA

EWG

(as of Step 4)

Emer Cooke
Head of sector Inspections EMEA
Jacques Morenas
Inspection and Companies Directorate
AFSSAPS, FEMEA, PIC/S

Diana Dowthwaite
Compliance and Enforcement Coordination division, Health prod. & Food Branch Inspectorate Health CDN
Christine Mundkur
International Generic Pharmaceutical Alliance
Frederick Razzaghi
Consumer Health Product Association
Sabine Kopp
QA & Safety Medicines, WHO
Markus-Peter Müller
Head of QM-Inspectorate, Swissmedic

Malcolm Holmes
GSK, UK, Global Quality Assurance, Director
Stephan Rönninger
F.Hoffmann-La Roche, CH, Global Quality Manager

Takayoshi Matsumura
Eisai, Assistant Manager, Corporate QA Department
Tetsuhito Takarada
Mochida Pharm.Deputy Director, Quality Control
Hideo Sasaki
Nippon Shinyaku Co Ltd, Manager Anal.Chem.Sect.

Ref. ICH Q9 EWG members: Briefing pack. July 2006

# QRM definitions (Q9)

**Quality**

**Degree to which a set of inherent properties of a product, system or process fulfills requirements**

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**Risk**

**combination of the probability of occurrence of harm and the severity of that harm**

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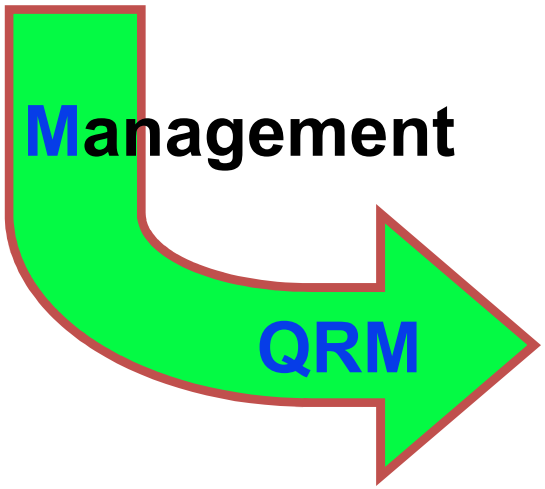
**Management**




**Systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle**

Ref. ICH Q9 EWG members: Briefing pack. July 2006

# QRM principles (Q9)

**The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.**

**The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.**

Ref. ICH Q9 EWG members: Briefing pack. July 2006

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# QRM as a tool for inspections (Q9)

- To define the *frequency and scope* of audits
- Taking into account factors such as:
  - Existing legal requirements
  - Overall compliance status and history of the *company*
  - Robustness of a company's *quality risk management* activities
  - *Complexity* of the site, manufacturing process, product and its therapeutic significance
  - *Compliance status* and history
  - Results of *previous audits/inspections*
  - Number and significance of *quality defects* (e.g, recall)
  - Results of previous audits/inspections
  - Major changes of building, equipment, processes, key personnel
  - *Experience* with manufacturing of a product (e.g. frequency, volume, number of batches)
  - *Test results* of official control laboratories

Ref. ICH Q9 EWG members: Briefing pack. July 2006

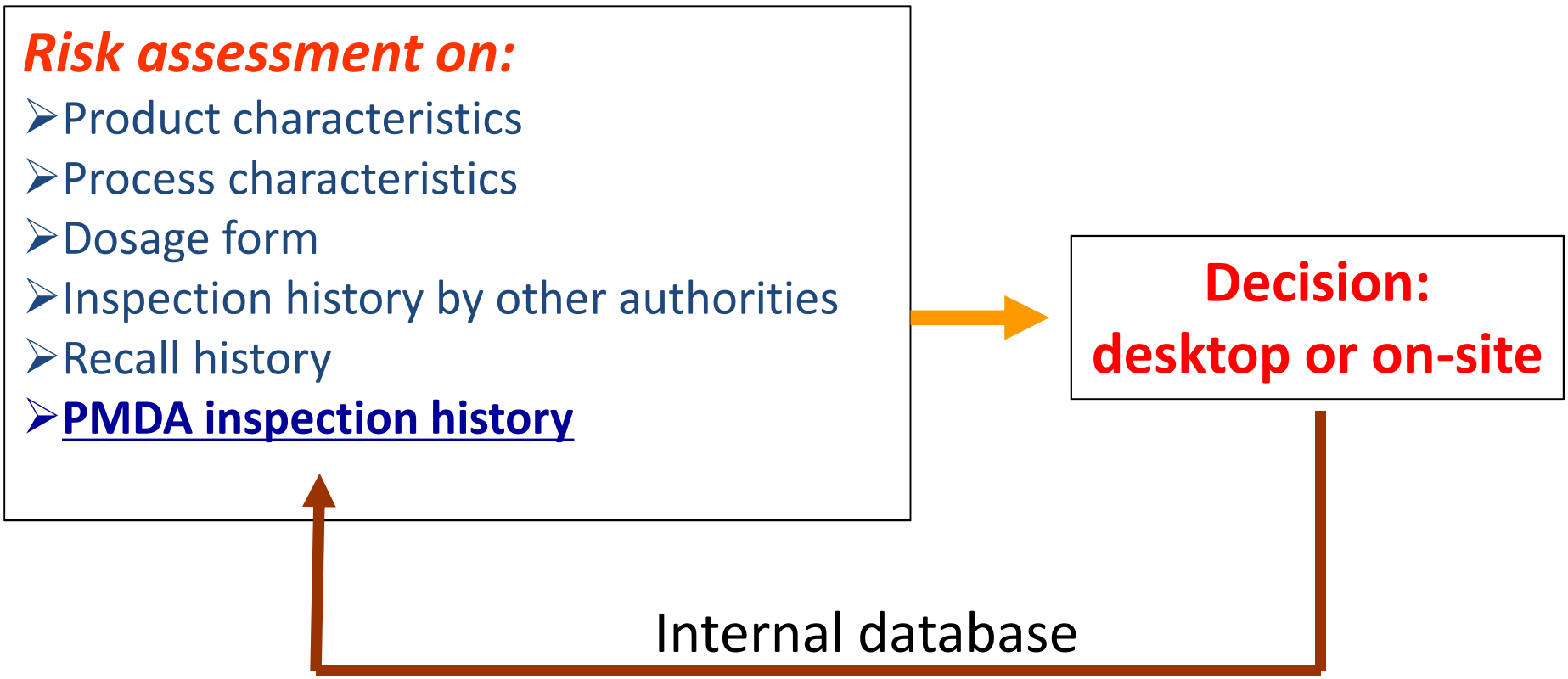
# PMDA's GMP inspection: consideration for risks

- To make efforts to share views on where and how much risks exist at the mfg site between the manufacturer.
- To make efforts to explain background of the observations carefully.
- To make efforts to build capacity of collecting relevant information on the risks and making sound judgment.
- To make efforts to evaluate the extent of product quality to be achieved by the mfg site's actions.
- To make efforts, when any deficiency is identified, to scientifically appraise its impact on the patients and/or public health.

# PMDA's on-site inspections

- In general, 2 inspectors for 3-4 days per each on-site inspection are allocated.
- Notice may be given 3-6 weeks before on-site inspection.
- Submission of site information may be requested prior to on-site inspection.
- May be focused on key points raised by inspectors during inspection planning and, for PAI inspections, by reviewers.

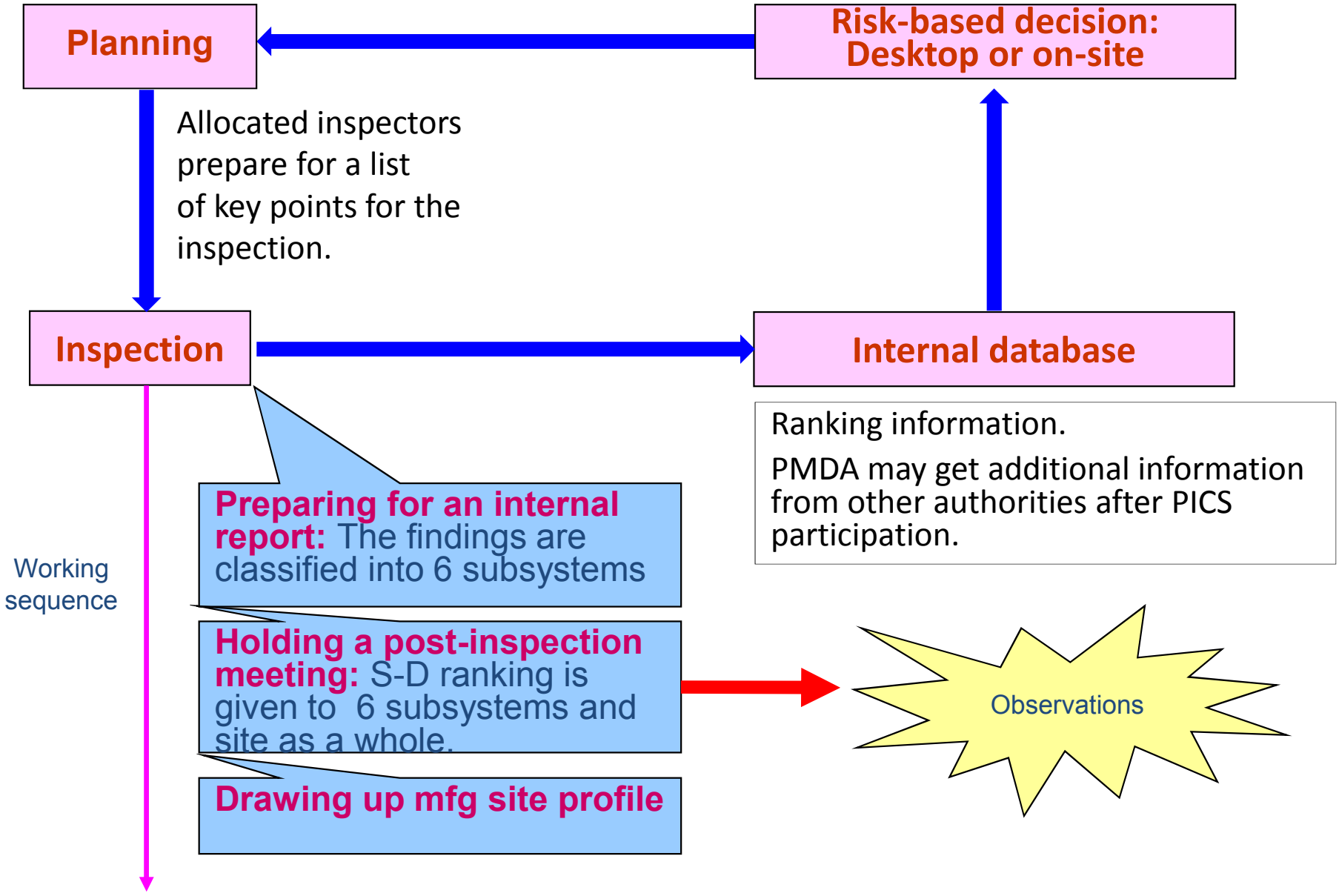
# Risk-based decision making on GMP inspection resource allocation: desktop or on-site




S, A, B, C or D ranking based upon assessment of 6 subsystems:

1) Quality systems; 2) facilities & equipment;
3) materials control; 4) production control, 5) packaging & labelling; and
6) quality control.

# PMDA's on-site GMP inspection cycle



## MHLW's policy : The GMP inspectorates should enforce the GMP regulations on a risk basis in principle.

- GMP requirements stipulated in the legislations should be enforced according to the risk.

- Manufacturers are allowed to apply any manufacturing practices that are not explicitly stipulated in the legislations, however, scientifically sound to achieve equivalent or better quality and/or risk management than the methods defined in the legislations.

Ref. CND, MHLW: [Viewpoints on application of PIC/S GMP Guide] (in Japanese). Administrative Note, 1 Feb. 2012.

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# Guiding principles for drug recall in Japan（1）

The concept on making decisions on necessity of recall.

（1） Efficacy and safety: When the drug is of any concern about safety, shows insufficient efficacy, or is unjustifiable on safety, the drug should be recalled.

（2） Compliance: When the drug is non-compliance with the approval conditions or other legislation requirements, the drug should be recalled.

（3） Foreign substances (according to its type and dosage form of the drug): The type of foreign substances: i.e. intrinsic substances(e.g. glass fibers); extrinsic substances (e.g. wood chips); or biological substances (e.g. hair, worm etc.) should be considered.

When any aseptic drug is contaminated with extrinsic or biological foreign substances, the drug should be recalled.

In case any non-aseptic drug is contaminated with biological foreign substances, the drug should be recalled.

Ref. PFSB-DG, MHLW: [Recall of drugs, medical devices etc.] (in Japanese). *Iyakuhatsu* No.237, 8 Mar. 2000, amended by *Yakushokuhatsu* No.0730008 in 2003, No.0528004 in 2004, No.0331021 in 2005 and No.0322-3 in 2011.

# Guiding principles for drug recall in Japan（2）

The concept on making decisions on scope of the quality defects.

（1） Unless all the following conditions are met, the quality defects should be be regarded as affecting all lots.

① The cause of the quality defects and relevant processes are identified.

② Appropriate actions have been taken to prevent recurrence of the quality defects and no problem is detected on the GMP.

③ There are no abnormalities in quality of the retention samples.

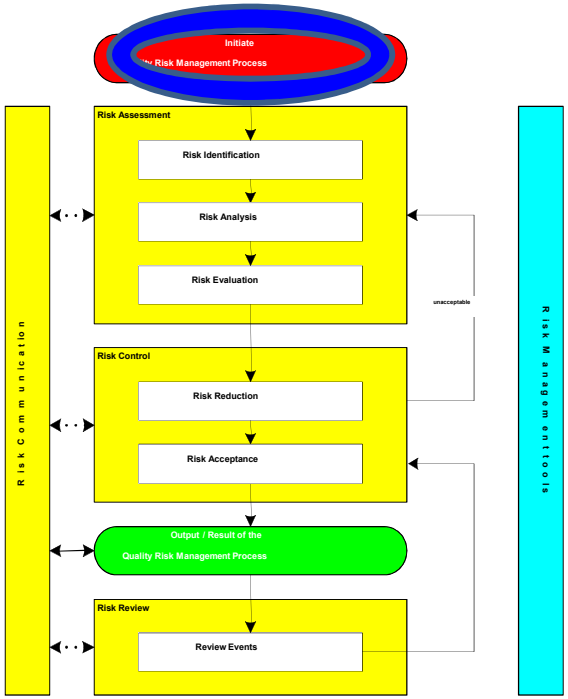
④ No problem is detected on the GQP that affects product quality.

（2）Even though it has been once determined the quality defects do not affect all lots, however, the defects have been indeed detected in two or more settings, the drug should be recalled in light of incidence of the defects.

Ref. PFSB-DG, MHLW: [Recall of drugs, medical devices etc.] (in Japanese). *Iyakuhatsu* No.237, 8 Mar. 2000, amended by *Yakushokuhatsu* No.0730008 in 2003, No.0528004 in 2004, No.0331021 in 2005 and No.0322-3 in 2011.

# QRM: possible scenario to recall

# 1. An event happened…initiation of QRM process



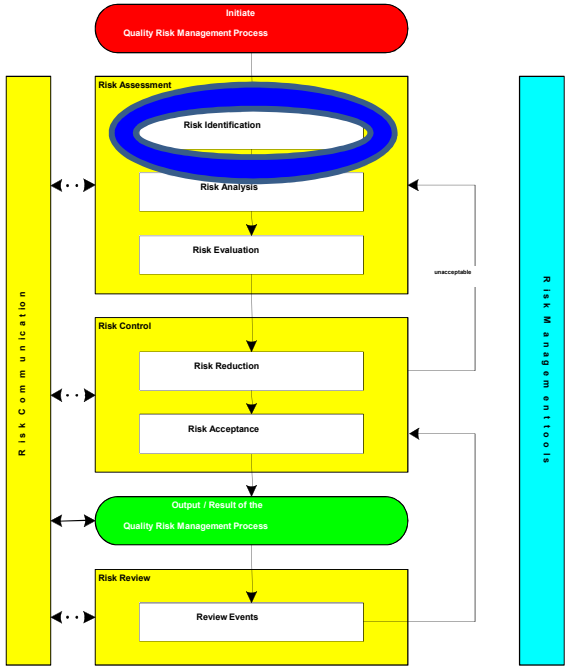

Event = deviation, complaint…

The event triggers a review of the existing QRM decisions whether they are still valid based on the triggers.

Initiation of QRM process

Ref. ICH Q9 EWG members: Briefing pack. July 2006(modified)

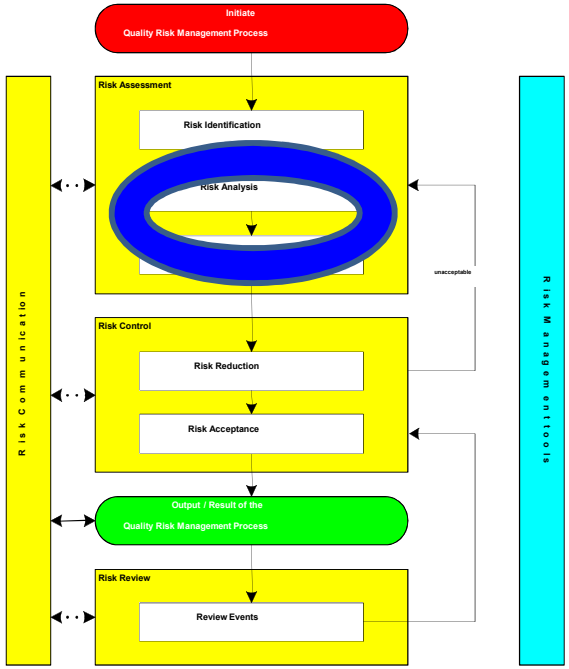
# QRM: possible scenario to recall
# 2. Risk assessment: risk identification




- Define the problem IMPORTANT
  - Horizontal impact（any influence to other lots, other products, other mfg sites, other countries etc. ?）
  - Dosage form（sterile or non-sterile?）
  - Type of the foreign substances（intrinsic, extrinsic or biological?）
  - Impact on the safety and efficacy
  - Compliance?
  - Is recall needed? Class?
  - Others
- Identification of the root cause. IMPORTANT

Ref. ICH Q9 EWG members: Briefing pack. July 2006 (modified)

# QRM: possible scenario to recall
# 3. Risk assessment: risk analysis & risk evaluation




- Assessment of impact of the event on:

-Patient/the public health（including whether it achieves the desired effect and potency）directly

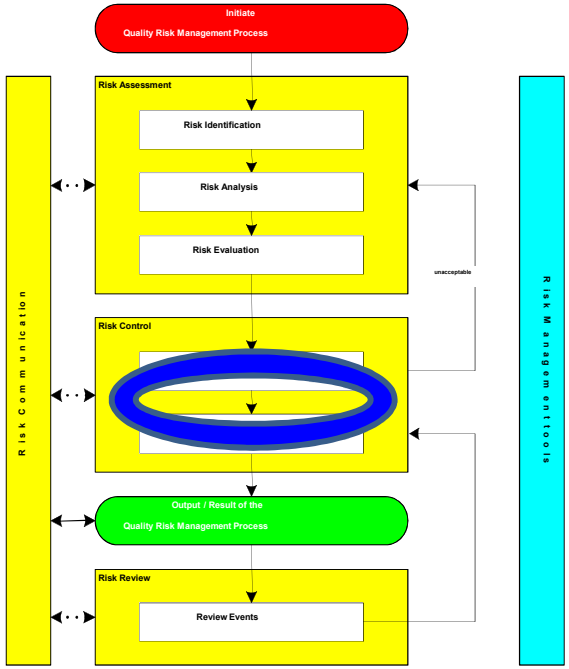
-Quality of the product and, if any, other products

-Availability of the product: potentially insufficient stock levels

-Others

Ref. ICH Q9 EWG members: Briefing pack. July 2006 (modified)

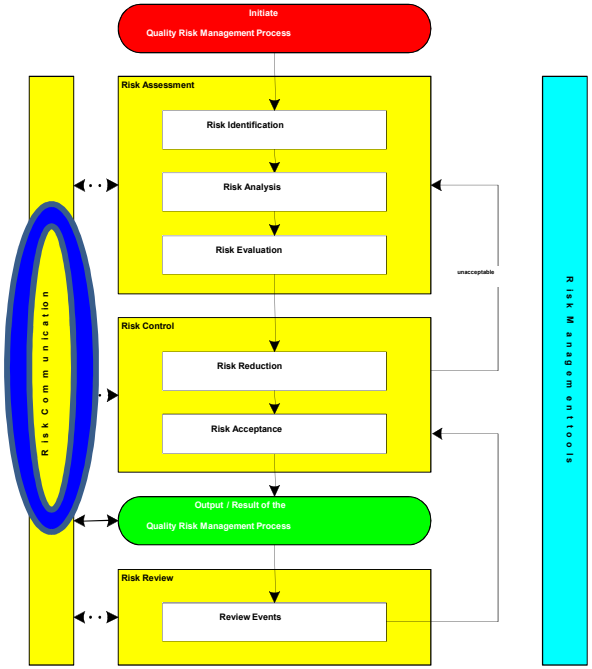
# QRM: possible scenario to recall
# 4. Risk control: risk reduction & mitigation




- Risk reduction
  - Corrective actions
  - Preventive actions
- Risk acceptance IMPORTANT
  - Decisions on disposition of the product
  - Decisions on completion of the CAPA including recall
  - Others

Ref. ICH Q9 EWG members: Briefing pack. July 2006 (modified)

# QRM: possible scenario to recall
# 5. Risk communication

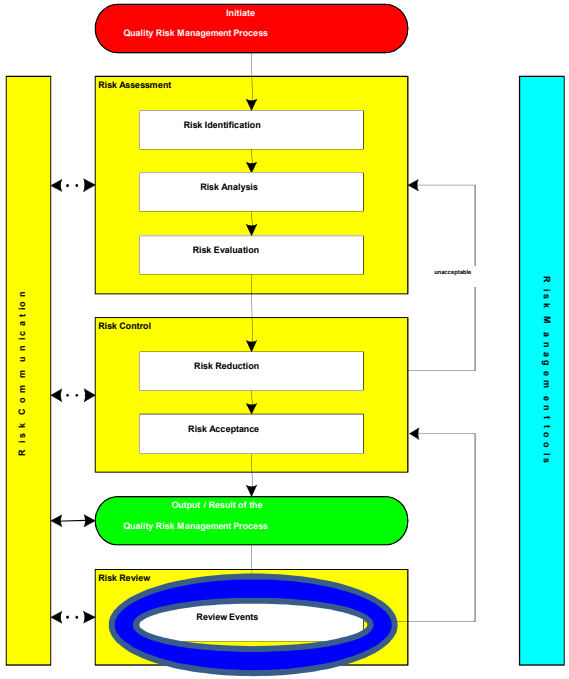



- Internally…
- Frequent interactions (e.g. short daily meetings).
- Training sessions

- Externally…
- Communicate with the competent authority >>> Rapid alert to MRA partners etc.
- Press release
- Letters to medical facilities, pharmacies…

Ref. ICH Q9 EWG members: Briefing pack. July 2006 (modified)

# QRM: possible scenario to recall
# 6. Risk review: review events




- Follow up of the actions.
- Full readiness in case of detection of non-recalled products
- Systematic evaluation (e.g. Product Quality Reviews) and if necessary, further actions.

IMPORTANT

- Others

Ref. ICH Q9 EWG members: Briefing pack. July 2006 (modified)

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# History of international cooperation of GMP authorities of Japan

September 1986 MOUs between MHW and Western German authority on GMP certificates and mutual recognition of QC data.

July 1987 MOUs between MHW and Swedish authority on GMP certificates and mutual recognition of QC data.

June 1988 MOUs between MHW and Swiss authority on GMP certificates and mutual recognition of QC data.

April 1993 EOLs between MHW and Australian authority (TGA) on cooperation for exchanging GMP inspection reports.

December 2000 EOLs between MHW and U.S. authority (FDA) on cooperation for exchanging GMP inspection reports.

November 2001 MHLW notified ICH Q7 implementation.

May 2004 Japan-EC (EU) MRA, GMP Sectoral Annex was enacted after both parties confirmed equivalence of their GMP implementation.

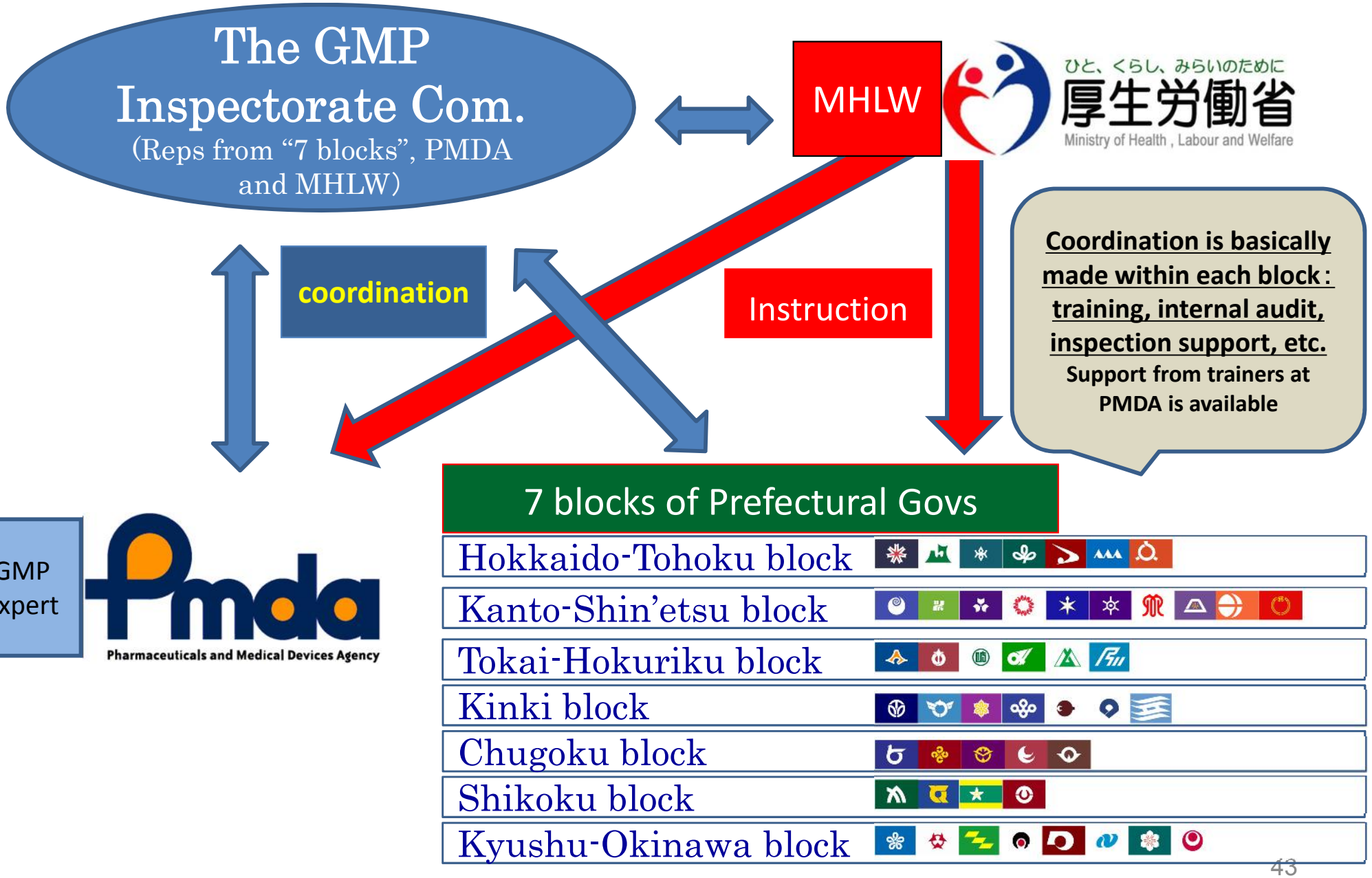
April 2005 New GMP Ordinance was enacted reflected 2002 major J-PAL revisions.

March 2012 GMP authorities of Japan, i.e. MHLW, PMDA and 47 prefectural governments applied for participation in PICS.

# PICS assessment

- 9 Mar. 2012: Submission of application
- 7-8 May 2012: PIC/S Committee meeting in Geneva. Rapporteurs nominated: Sweden, Ireland, Spain, Austria, Australia, Singapore and Switzerland inspectors.
- 15-22 Apr. 2013: On-site inspection I (only on APIs) jointly done by PIC/S rapporteurs and EU Commission.
- 9-13 Sep. 2013: On-site inspection II
- 7-8 Oct. 2013: PIC/S Committee meeting in Ottawa.
- 15-16 May 2014: PIC/S Committee meeting in Rome.

# The GMP Inspectorate Committee



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# New legislation and J-PAL revisions

The National Diet (Parliament) passed the new law on regenerative medicinal products and the law revising J-PAL on 20 November 2013.

J-PAL changes its name:
“The law on ensuring quality, efficacy and safety of drugs, medical devices, etc.”.
”Quality” is clearly shown in the title.

The new legislation and J-PAL revisions will be enacted within 1yr.

# New legislation and J-PAL revisions on Regenerative Medicinal Products

Revisions relevant to regenerative medicinal products – reflecting expectations for innovative medicines (e.g. iPS technology (reprogramming) applied medicines) and focusing features of the products (e.g. non-homogeneity) .


**2012 Nobel prize winner Prof. YAMANAKA & PMDA Chief Executive Dr. KONDO**

# New legislation and J-PAL revisions on Regenerative Medicinal Products

Now, MHLW is preparing for Cabinet Ordinances, Ministerial Ordinances and Notifications.

Such Ministerial Ordinances will include:
・Those applied to such products' mfg sites (e.g. CPCs) including revised BFR; and
・Those applied to mfg control and quality control/assurance in such mfg sites…GMP-alike? QMS-alike??...tbd.

PMDA, Office of GMP/QMS Inspection will be in charge of conducting inspections of the CPCs.

# “PMDA-WEST”
# Kansai Branch of PMDA

- Established in Osaka on 1 October 2013
- In charge of a part of PMDA function:
  1) “Consultation on R&D Strategy” – mainly for universities, research institutes and venture companies possessing promising “seed-stage” research/technologies; and
  2) **GMP inspections (started from 1 April 2014)**.


Osaka

“Kansai” region

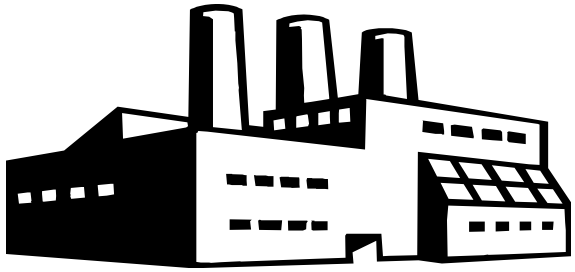
Venue: “Grand Front Osaka” Tower C

# Exemption of the EU's regulatory control on APIs

EU's new regulation（Revised 2001/83/EC：on and after 2 July 2013）

Countries NOT listed on the exemption list

**EU**



Export API

**A written GMP confirmation** of the authority is **required**.

Japan is listed on the exemption list.

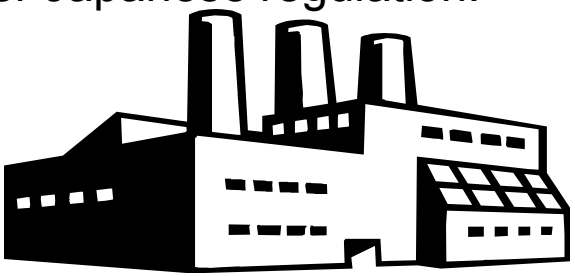
Switzerland, Australia and US are also listed.

**Japan**

**EU**

**The EU confirmed the Japanese system and included the list.**

APIs manufactured in Japan under Japanese regulation.



Export API

**A written GMP confirmation** of the authority is **NOT** required.

# Link with EudraGMP

Since 1 Oct. 2013, MHLW and PMDA have started entering GMP-compliance information on JPN manufacturers, upon their requests, in EMA's "EudraGMDP" DB.

According to EMA's website, this is **the first time** that information from non-EEA regulatory authorities is added to the DB.



# Thank you
# for your kind attention.

http://www.pmda.go.jp/