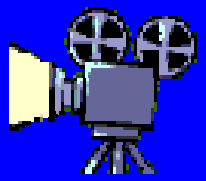
THE 2005 PHARMA, BIOTECH AND DEVICE COLLOQUIUM

THE INTERNATIONAL DRUG SAFETY PARADIGM

June 7, 2005

Shinya Yamauchi
Otsuka Pharmaceutical Co., Ltd.



Outline

- Revision of Japan's Pharmaceutical Affairs Law (JPAL) and the impact of that revision on clinical safety and pharmacovigilance
- Recent revision regarding safety reporting to the PMDA
- Adoption of ICH E2D in Japan
- PV regulations in Selected Asian and Arab countries

April ….

April is the cruellest month, breeding
Lilacs out of the dead land, mixing
Memory and desire, stirring
Dull roots with spring rain.
Winter kept us warm, covering
Earth in forgetful snow, feeding
A little life with dried tubers.

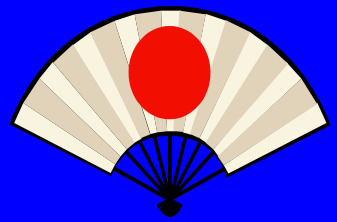
(T. S. Eliot, *The Waste Land*)

FRESHERS

April 1, 2005

- Revision of JPAL
- Revision regarding safety reporting
- Adoption of ICH E2D
- Personal Data Protection Act
- An increase of social insurance contribution …

Revision of JPAL



Effective April 1, 2005

History of Revisions of JPAL

1960 Law established (Old J-PAL)

1979 1st Revision (Re-Examination & Re-Evaluation)

1983 2nd Revision (License for Imported Products)

1993 3rd Revision (Orphan & GMP)

1994 4th Revision (Safety Monitoring System Strengthened)

1996 5th Revision (GCP & GPMSP)

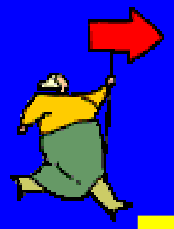
2002 6th Revision (Biggest change, New J-PAL)

2003 1st step Implementation

2004 2nd step Implementation

2005 3rd step Implementation

Types of Licenses and Approvals



Old System	After Revision
Manufacturing Business License	Manufacturing/Marketing Business License
Drug manufacturing Approval	Drug Manufacturing/Marketing Approval
Product Manufacturing License	Manufacturing Business License

Y. Ishii, JPMA (http://www.jpma.or.jp/12english/publications/pub023d_amendment/) (Nov/2004)

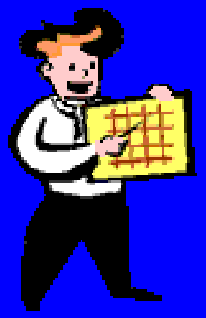
Categories of Licenses

- **Type 1 license for drug marketing business**
  - **Class I** (*Isshu*)

    Prescription Drugs, Specially Controlled Medical Devices
- **Type 2 license for drug marketing business**
  - **Class II** (*Nishu*)

    Non-prescription Drugs (OTC), Controlled Medical Devices
- **Type 3 license for drug marketing business**
  - **Class III** (*Sanshu*)

    Quasi-drugs (*e.g.* insecticide), Cosmetics, General Medical Devices



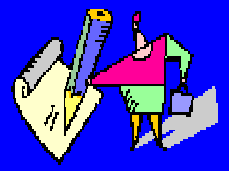
Categories of Medical Devices

"Specially Controlled Medical Device" – Medical devices designated by the Minister (MHLW), after seeking the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), as requiring proper management due to their significant potential risk to human life and health in the event of a malfunction or side effect occurring

"Controlled Medical Device" – Medical devices other than Specially Controlled Devices that are designated by the Minister, after seeking the opinion of the PAFSC, as requiring proper management due to their significant potential risk to human life and health in the event of a malfunction or side effect occurring

"General Medical Device" – Medical devices other than Specially Controlled Medical Devices and Controlled Medical Devices that are designated and controlled by the Minister, after seeking the opinion of the PAFSC, as posing a somewhat significant potential risk to human life and health in the event of a malfunction or side effect occurring

Article 2, Pharmaceutical Affairs Law



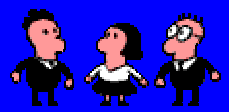
Three Posts *(san-yaku)*

QUALIFICATION
- Pharmacist license for Classes I and II (drugs)
- Pharmacist license or Pharmacy / chemistry major at university, *etc*. for Classes II (medical device) & III

General Manufacturing & Marketing Manager

QUALIFICATION
minimum 3 years of QC experience

Safety Manager



Quality Assurance Manager

QUALIFICATION
minimum 3 years of experience of GPMSP, *etc*. for Class I

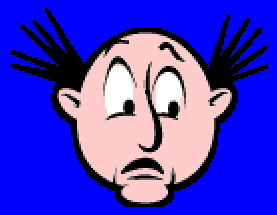
GVP

GQP

How many companies will be granted licenses by the Tokyo Metropolitan Government?

About 3,700 (licenses)

- **Drugs: 700 (Class I:– 300; Class II: – 400)**
- **Quasi-drugs: 400**
- **Cosmetics: 1,100**
- **Medical devices: 1,500**



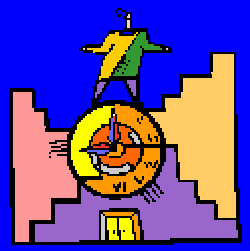
Data: Tokyo Metropolitan Government

Outline of JPAL Revision (1)

- Most significant modification in 10 years -

• "Manufacturing/Marketing Business License" is approximately equivalent in concept to ICH's "Marketing Authorisation Holder".

• This license was issued by prefectural governments under the authority of the MHLW.



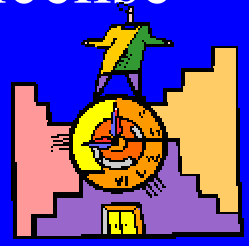
• This license is separate from Product Approval.

• Drug production can be outsourced to a company holding a new manufacturing license. Some pharmacovigilance tasks can also be outsourced.

Outline of JPAL Revision (2)

- Most significant modification in 10 years -

•The license holder is responsible for manufacturing and marketing (the company must have the specified 3 managers (“Three Posts”) as a prerequisite for the license being granted).



• The company may be required to establish an organization such as a Reliability Assurance HQ/Center that incorporates the “Three Posts”.

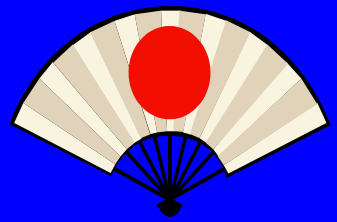
• License must be renewed every 5 years and the license holder must satisfy the conformity certification criteria (inspection by prefectural government).

Impact of JPAL Revision

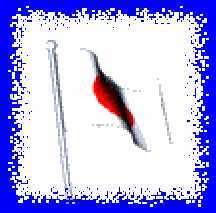
- **Some pharmacovigilance tasks can be outsourced** (no sub-contracting allowed).
  - Collection of safety information such as literature search
  - Analyses
  - Measures implemented as a result of assessment of safety information
  - Storage of collected safety information documents
- **New organizations** (such as a Reliability Assurance HQ/Center **may be required.**
- **New SOPs and manuals were required.**

- **How can a company's global pharmacovigilance and global safety evaluation system be integrated?**

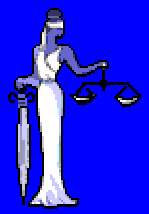
Do you know?

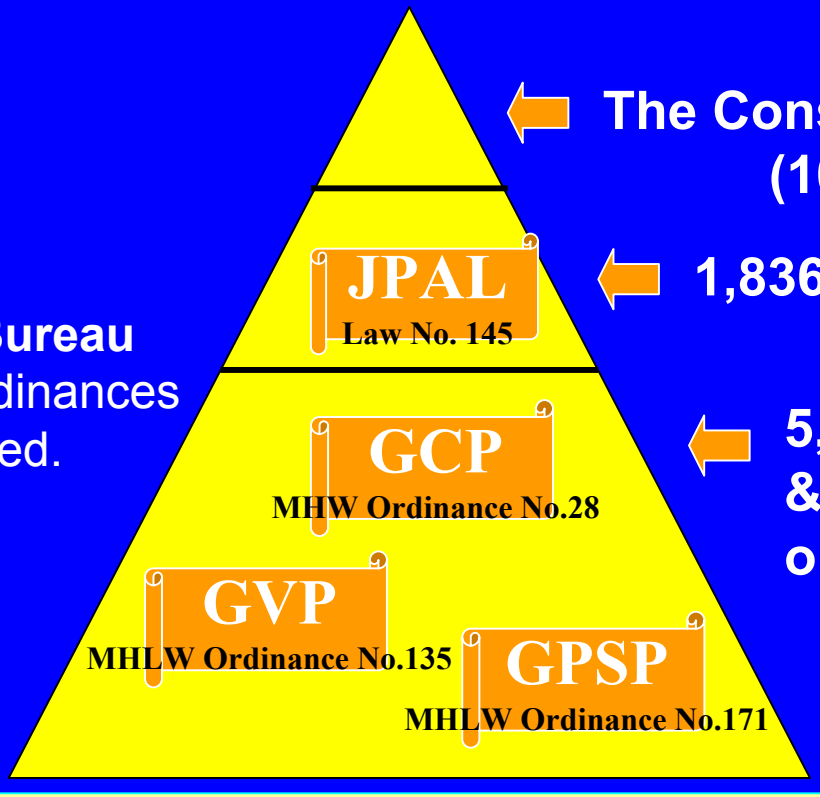


Structure of Laws in Japan



Cabinet Legislation Bureau reviews the orders / ordinances before they are approved.





The Constitution of Japan (103 articles)

1,836 laws

5,379 cabinet orders & ministerial/imperial ordinances

as of March 4, 2005

Data: http:/law.e-gov.go.jp/announce.html (April/2005)

Number of Physicians/Pharmacists in Japan

7,568 passed the national examination in 2005 (89.1%)

Japanese Association of Pharmaceutical Medicine has only 167 members (as of March 2005)

300,000 (people)

200,000

100,000

262,687 physicians*

229,744 pharmacists*

8,653 passed the national examination in 2004 (78.3%)

97 universities have a faculty of law (a total of 47,000 students) and 68 universities have law schools in Japan (there will be 74 law schools with a total quotas of 5,825 students in April 2005)

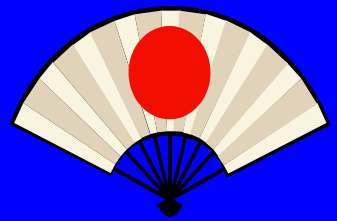
20,263 lawyers**

* reported to the MHLW in 2002

** as of 2003

Data: http://www.mhlw.go.jp/toukei/saikin/hw/ishi/02/tou2.html. (Dec/2004)
http://www.sankei.co.jp/kyoiku/law/new-colum-1.htm (Dec/2004)
http://www.japhmed.org/ (Dec/2004), *The Nikkei* Nov.25, 2004

Revision of Safety Reporting
MHLW Ordinance No. 30
Issued on March 17, 2005



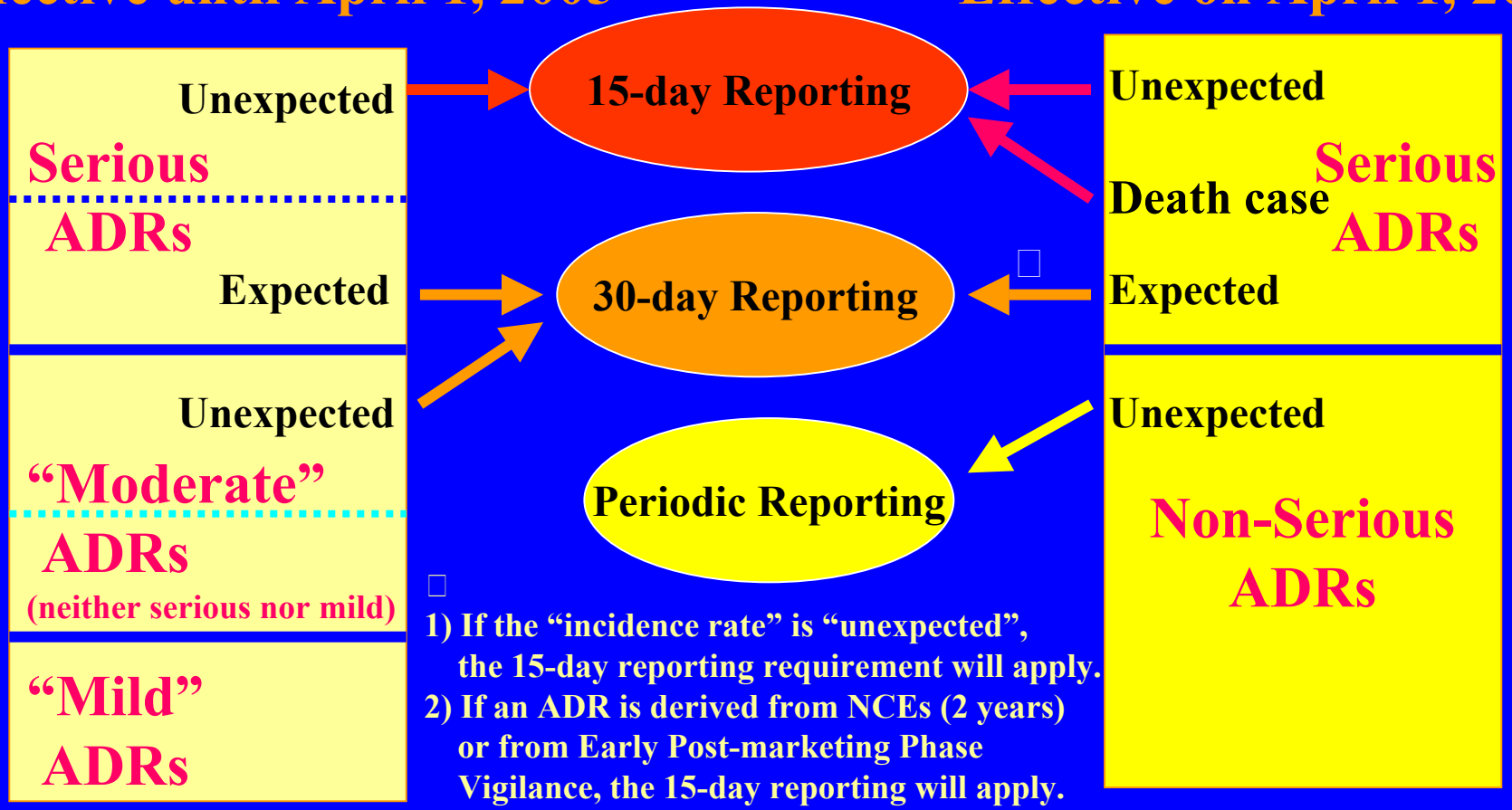
Effective April 1, 2005

Outline of Revision

- Reinforcement of drug safety by prioritizing most frequently emergent cases
- Reinforcement of drug safety through international harmonization
- Consistent reporting standards for pharmaceuticals and medical devices

Simplified ?

Pharmaceuticals – Domestic Cases



1) If the "incidence rate" is "unexpected", the 15-day reporting requirement will apply.
2) If an ADR is derived from NCEs (2 years) or from Early Post-marketing Phase Vigilance, the 15-day reporting will apply.

("Severity" grading criteria: Notification #80 issued by MHW on June 29, 1992)

If an ADR from a foreign country is serious and unexpected, the 15-day reporting will apply.

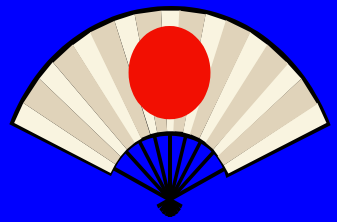
"Unexpectedness"

If the incidence rate of an event is "unexpected", the 15-day reporting requirement will apply.

However, clear definitions are required, including:

1) **Counting from what timepoint? (Clearly defined reporting period)**
2) **Calculation of rate at which new cases occur in the exposed population (incidence rate)**
3) **Time frame of 15-day reporting**
4) **Handling of "mined reports" due to an alert, such as a "Dear Doctor letter"**

ICH E2D
- Guideline -



Effective April 1, 2005

ICH E2D

Notification (#0328007) issued by MHLW's Safety Division on March 28, 2005

- Effective April 1, 2005
- Guideline
- Translation of ICH E2D
  1. Introduction
  2. Definitions and terminology associated with post-approval drug safety experience
  3. Sources of individual case safety reports
  4. Standards of expedited reporting
  5. Good case management practices

ICH E2D
- Japanese variation -

2.2 Adverse Drug Reaction

"Adverse drug reactions, as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product." In Japan the definition is "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions."

Source: Notification (#0328007) issued by MHLW's Safety Division on March 28, 2005

ICH E2D
- Japanese variation -

4.3 Reporting Time Frames

"In general reporting of serious and unexpected ADRs is required soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH." In Japan the MAH is interpreted as the "Manufacturing and Marketing Business License Holder".

***i.e.* in Japan ... arts when the company in Japan receives the information.**

Consumer Reports ?

Adoption of ICH E2D (effective April 1, 2005)

- **"Implied causality" in spontaneous reporting**
- **"Unsolicited sources" include spontaneous reporting, literature searches, and the internet.**
- **"Consumer reports" should be treated as spontaneous reports.** *(MHLW's comments regarding opinions from the public, issued on April 4, 2005)*

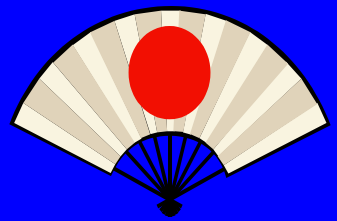
However, a regulation (such as GVP) mandating "consumer reports" has not yet been established ...

ICH E2D

How have we implemented?

- **Unsolicited sources** ("Consumer adverse reaction reports should be handled as spontaneous reports irrespective of any subsequent 'medical confirmation'.")
- **Literature** ("The frequency of the literature search should be according to local requirements or at least every two weeks." "If the product source, brand, or trade name is not specified, the MAH should assume that it was its product, although the report should indicate that the specific brand was not identified.")
- **Internet** ("MAHs should regularly screen websites under their management or responsibility for potential ADR case reports.")
- **Other sources** ("If an MAH becomes aware of a case report from non-medical sources, e.g. the lay press or other media, it should be handled as a spontaneous report".)
- **Overdose** ("The MAH should collect any available information on overdose related to its products.")

PMDA ?



Effective April 1, 2004

What is IAA?
What is PMDA?

Effective April 1st 2004, KIKO (Organization for Pharmaceutical Safety and Research (OPSR) was re-organized as **the Pharmaceuticals and Medical Devices Agency (PMDA)**, an **Incorporated Administrative Agency**. (In Japanese, "*dokuritsu gyouseihoujin iyakuhin iryoukiki sougoukikou*")

What is Incorporated Administrative Agency (IAA)?

An "IAA" is an organization that is engaged in work separate from the GOJ (Government of Japan) in order to provide a high quality of administrative service in a more flexible manner than previously.

PMDA, consolidated new agency

Evaluation Center (PMDEC)

(Pharmaceuticals and Medical Devices Evaluation Center)

(old) KIKO (OPSR)

(Organization for Pharmaceutical Safety and Research)

JAAME

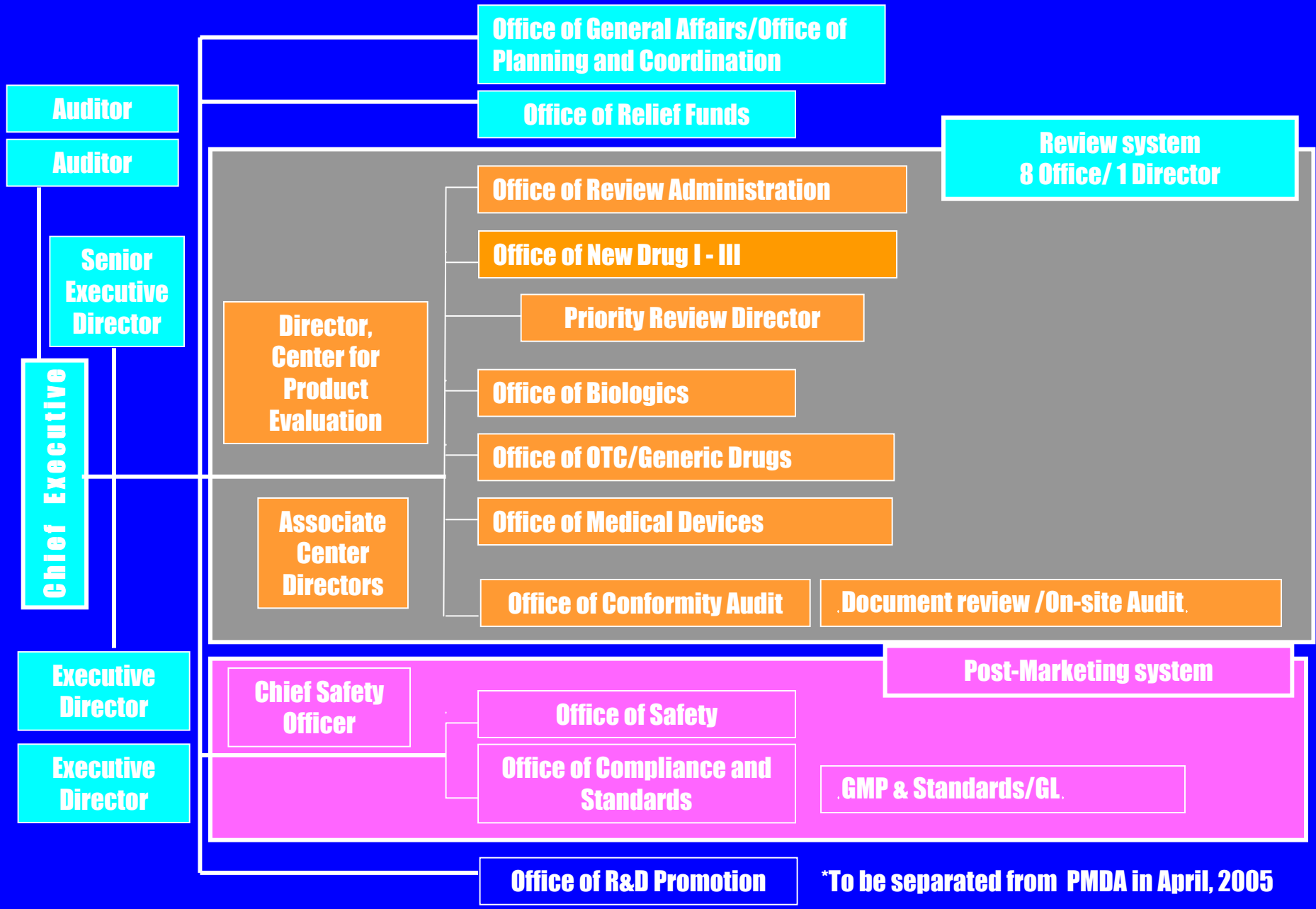
(Japan Association for the Advancement of Medical Equipment)

Effective April 1, 2004

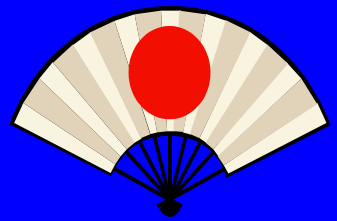
PMDA

Pharmaceuticals & Medical Devices Agency

PMDA Organizational Structure



Medical Representatives in Japan



Role of Medical Representatives

- In Japan there are 52,206 medical representatives* ("MRs").
- Since 1997, the **MR Education and Accreditation Center** has been providing training and administering examinations to **"accredited MRs"**. (Exams include diseases & therapy, pharmacology, biopharmaceutical science, professional ethics & pharmaceutical regulations, **PMS**, and package insert terminology)
- PV training for MRs is mandatory at drug companies.
- More than 80%** of all safety information is reported by drug companies (safety information is mostly obtained by the MRs) .

Data: * as of January 2005
http://www.mre.or.jp/ (April/2005, in Japanese)
http://www.chikennavi.net/data/mr-number.htm (April/2005, in Japanese)
** M. Yamazaki, et. al, Drug Informatics (Japanese), 1998; 44

PV Regulations in Selected Asian and Arab Countries

Selected Asian and Arab Countries

- **Egypt:** There is no obligation to report AEs in Egypt. The regulations regarding safety information may be changed within the next few years to adopt ICH guidelines.

- **China:** A safety monitoring system has been in place at designated hospitals and pharmaceutical companies since March 2004. Companies are required to provide a report to the Center for Adverse Reactions Monitoring upon request. After 5 years from market launch, only serious/unexpected (infrequent) events are required to be submitted (no need for quarterly reporting)..There are 185 hospitals that have passed the requirements of the SFDA for conducting clinical trials. Several major pharmaceutical companies including one European company have successfully conducted global trials in China. The SFDA conducts inspections for clinical trials. As yet, there are no inspections by the SFDA regarding spontaneous safety reporting in China.

- **Indonesia:** Some companies voluntarily submit spontaneous ADRs to the regulatory authorities.

Data: Otsuka affiliates

Selected Asian and Arab Countries (cont.)

- **Korea:** During the PMS period (6 years for a new drug, 4 years for additional indication), companies usually submit expedited reports to the regulatory authorities. After the PMS period, AE reports are rarely submitted to the authorities. There is no "early post-marketing phase vigilance" in Korea.

- **Pakistan:** Although there are reporting regulations, it seems that few companies actually report adverse events to the regulatory authorities. Regarding the post-marketing investigation, it is required to take a similar action in Pakistan as well, as taken in the country of origin such as the USA, the UK or Japan.

- **Philippines:** Post-marketing surveillance is conducted on ALL new drugs for 3 years starting immediately after market launch. ALL newly approved new drugs are being registered under Monitored Release. PMS reports are required to be submitted every 15th of January. A Post-Marketing Surveillance Report must be submitted within 3 years after market launch or upon completion of investigation. If the target number of patients has not been reached in 3 years, PMS may be extended for another year.

Data: Otsuka affiliates

Selected Asian and Arab Countries (cont.)

- **Taiwan:** Expedited submission is strictly conducted in compliance with the regulations. A PSUR (Taiwan version) is also submitted to the regulatory authorities. According to DOH announcement #8246232 dated July 7, 1993, periodic safety reports are to be prepared for newly approved medicinal products. During the period of post-marketing surveillance, the company that holds the license for the new drug is required to provide updated reports of adverse reactions occurring either in Taiwan or overseas to the DOH every 6 months for 7 years after approval. Since the revised PAL went into effect on September 9, 2004, DOH announced that PSUR should be submitted for newly approved medicinal products for 5 years, every 6 months for the first 2 years , and then once a year for the next 3 years. Companies can opt to choose to follow either the old regulation or the new one.

- **Thailand:** A safety monitoring system has been in place at designated hospitals since 1983. AE information reported from the hospitals is pooled by the regulatory authorities. An SMP (Safety Monitoring Program) is required to be conducted for 2 years or longer after market launch of newly approved medicinal products, and the SMP report needs to be submitted to obtain safety validation and obtain UNCONDITIONAL APPROVAL. The product can then be sold in drug stores.

Data: Otsuka affiliates

PV Reporting Requirements in Selected Asian and Arab Countries

	Clinical Trials		Spontaneous Reporting	
	Domestic	Foreign	Domestic	Foreign
Egypt	NR	NR	NR	NR
China	**24 hrs**	**(Encouraged to report)**	**15 days (5 yrs)**	NR
Hong Kong	NR	NR	**NR***	**NR***
Indonesia	**15 days**	**15 days**	NR	NR
Korea	**15 days**	NR	**15 days (PMS)**	**Annual Report**
Pakistan	**Immediately**	**Immediately/15 days**	**30 days**	**30 days**
Philippines	**3 days/15 days**	NR	**14 days**	NR
Taiwan	**7 days/15 days**	**7 days/15 days**	**15 days**	**PSUR****
Thailand	**48 hrs/15 days**	NR	**48 hrs/15 days (2 yrs)**	NR

NR: Not Required

* The 15-day reporting requirement is being adopted.

** Taiwanese PSUR: every 6 months for 7 years

Data: Otsuka affiliates

Points to Consider

Where are we going?

Japan:

. The ratio of E2B/M implementation is the highest in the world

. ICH guidelines such as E2D are adopted, but there are also local specific regulations/requirements, with more guidelines/guidances to come. E2E is being implemented.

. Japan's "lost decade" is over. Increased M&A activity.

Asia:

. They are ICH-oriented, but in varying stages of implementation of ICH guidelines.

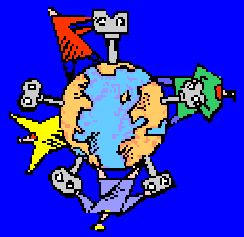
. Expanding drug market

Global:

. PV is becoming increasingly more regulated and more complicated.

. A local issue is a global issue.

. The challenges of risk management



Acknowledgements:

I'd like to thank the following Otsuka people:

S. Ahmed, M. Aslam, J. Chen, M. Hikita, M. Hui, K. Hwang, Y. Ike, R. Jimenez, E Jonosewojo, H. Kim, H. Kurokawa, S. Morita, B. Onishi, T. Onoda, S. Talha Raza, S. Win, P. Yen, K. Zhao

Thank you for staying awake!

Arigato gozaimashita!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Reference

- http://www.jpma.or.jp/12english/publications/index.html JPMA Newsletter (English)
- http://www.mhlw.go.jp/english/index.html MHLW website (English)
- http://www.pmda.go.jp/index-e.html PMDA website (English)