Role of Japan and Asian Countries in the Global Pharmaceutical Development

Pharmaceuticals and Medical Devices Agency (PMDA)
Akira Miyajima

Oct. 12, 2006
WHAT’S
3 major Operations

Review and Audit for Drugs/ Medical Devices Efficacy and Safety
- Clinical Trial Consultation
- Review of Efficacy and Safety
- Conformity Audit for Application Materials of GLP, GCP and GMP

Post-marketing Safety Operations for Drugs/ Medical Devices
- Reinforced Safety Information (Database)
- Scientific Review and Research for Safety Information
- Information Provision (via the Internet), Pharmaceutical Consultation for Consumers

Relief Service for ADR and Other Infectious Disease
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients
## Comparison of Number of Reviewer, Fees, etc.

<table>
<thead>
<tr>
<th></th>
<th>Japan 2003</th>
<th>Japan 2008 (prospect)</th>
<th>US (Drugs only)</th>
<th>UK</th>
<th>France</th>
<th>EMEA</th>
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<tbody>
<tr>
<td>Number of reviewer</td>
<td>183</td>
<td>292</td>
<td>2,600</td>
<td>436</td>
<td>950</td>
<td>248</td>
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<td>IAA inspection</td>
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<td>Safety operation</td>
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<tr>
<td>Application fee, etc</td>
<td>3.4</td>
<td>7.3**</td>
<td>32</td>
<td>6.6</td>
<td>6.7</td>
<td>10.2</td>
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<tr>
<td>Public Charged/</td>
<td>36%*</td>
<td>21%*</td>
<td>46%</td>
<td>0%</td>
<td>34%</td>
<td>36%</td>
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<tr>
<td>Total Expenses</td>
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<td></td>
<td></td>
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<tr>
<td>Fees /Gross Proceeds</td>
<td>0.05%</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.12%</td>
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</table>

* Total of MHLW HQ, PMDA, ** Total of Application fee and contribution

<table>
<thead>
<tr>
<th>US FDA</th>
<th>Covered Activities</th>
<th>Japan</th>
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</thead>
<tbody>
<tr>
<td>Application Fee</td>
<td>Review Process</td>
<td>Application Fee</td>
</tr>
<tr>
<td>Product Fee</td>
<td>Stabilizing Review System</td>
<td>Contribution</td>
</tr>
<tr>
<td>Registration Fee</td>
<td>Guidance on Post-Marketing Surveillance (Based on Product risk)</td>
<td></td>
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<tr>
<td></td>
<td>Safety Information</td>
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</tbody>
</table>
Our Mission

To Ensure **Faster** Accessibility to **More Effective** and **Safer**
Drugs/ Devices for the Public

Improving Public Health
“More Effective” Drugs/Devices

Biotech Drugs
Plasmid Vector for Protein Expression
E. Coli
Cell Line
Useful Protein

Animal Factory
Recombinant Vector
Egg Cells or Early Embryos of Animals
Transgenic Animals
Useful Protein

Gene Therapy
Vector Integration
Adjustment of Therapeutic Vector
Gene Therapeutic Drugs

Cellular Therapy
Sorting
Processing
Proliferation
Cells for Cell Therapy

Human
Transgenic Animals
cDNA of Useful Protein

Human
Biotech-related Patents

Source ('00 -): PATOLIS
To Ensure “Faster” Access to Drugs/Devices for the public
Our New Review System ~ For Faster Approval ~

1. Early clarification of review policy tailored to each product (Cooperation with Post-marketing Vigilance)
2. Integrated organization to perform NDA reviews in consistency with pre-NDA (clinical trial) consultation
3. Early detection and prompt problem solving through the use of pre-NDA consultation
4. Introduction of “Fast Track System” and expansion of the scope for priority reviews
5. More transparency in review process (Improvement in Predictability)
6. Development of appeal system
Comparison of Time for New Drug Approval Between Japan and The U.S. (Median)

【Normal Review Products】

【Products for Priority Review】

Note1: Review Time for Reviewers means in total review process, actual time for reviewers to review. It does not include time for applicants to submit additional documents on review’s request.

Note2: Japan: Number is on a fiscal year basis. The U.S: Number is on a calendar year basis.
Comparison of Total Review Time for New Drug Approval Between Japan and EU

Japan: Median / EU: Average number of phase

Ref: JPMA-Institute of Pharmaceutical Industry Policy
Number of Application and Actual Operation of Clinical Trial Consultations

Note: 20–30% of applicants are those who applied before
For “Safer” Drugs/Devices

Inseparable Pair

Early-phase Post-marketing Vigilance

Phase I
- Healthy Subjects
- Limited Number of Patients
- About 20

Phase II
- Large Number of Patients
- More than 100

Phase III
- Various cases undetected even by doctors

ADR and Infectious Disease Report System

Review and Approval

Reexamination and Reevaluation

Post-marketing Surveillance

Early-phase Post-marketing Vigilance

Reinforce Risk Management

Safety

Inseparable Pair

= Risk Unknown

= Risk Known

Various cases undetected even by doctors

About 50

More than 100

ADR and Infectious Disease Report System
Reported ADR Cases

Note: Foreign reports by drug makers are not included in and before FY03'.
Our New Safety Measure (Precautionary Principle)

Receipt of ADR/Infection Reports

Compiling Reports

DATA BASE

Grasp of All Information

Extracting Urgent & Significant Information

Advisory committee (PFSC)

Scientific/ Objective Research
  * Analysis of Accumulative Information (Expert Consultation, Company interviews)

Administrative Consideration

Analysis Report

Safety Measure Implementation

Information Provision System (via the Internet)

Medical Professionals, Public and Companies

Information Provision

Real-time Notification

PMDA

Companies

Medical Institutions

MHLW
Reform of Safety Measures

Safety Measures Based on a Series of Cases

Case 1
Case 2
Case 1
...

A Series of Cases

Prospective/Preventive Safety Measures

PMDA
ADR Information etc

Sentinel Medical Institution Network (In Specific Area)

Data Mining Technique
Risk Extraction
Scientific Analysis/Evaluation

MHLW Implementation of Safety Measures

MHLW Implementation of Safety Measures
Sentinel Medical Institution Network
(In FY 05’ ‘the Actual Situation of combined therapies of anti-cancer drugs’ was conducted.)

Sentinel Institution A
Follow-up survey for a year
- Grasping Number of Conducted Therapies and Actual Situation of using those.
- Grasping Serious DRs related to the Treatment.

Inform/Request
Academic Societies

Provide Information

Request of Cooperation for review

Cooperation

PMDA
Analysis and Evaluation of Accumulated information
Grasping actual situation of prescriptions, and occurrence rates of ADRs.

Inform/Analysis Request etc.

Investigation of ADRs

Liaison

Relevant Companies
Detailed Investigation & Case Analysis

Case Report

Feedback of Analysis Request etc,

- In Investigation of ADRs
- Grasping Serious DRs related to the Treatment.

Inform/Request
Institution B

Institution C

Institution D

Institution E

Follow-up survey for a year
- Grasping Number of Conducted Therapies and Actual Situation of using those.
- Grasping Serious DRs related to the Treatment.
Drug Risk & Relief

Non-clinical study
- Risk
- Benefit

Clinical Trial

Review

Post-marketing

Social Risk
- Impossible to prevent risks completely even with benefit of Revolutionary technology

Social Relief System

Relief Fund
- Contribution
- Relocation Benefits
- Medical Cost
- Disability Pension

Pharmaceutical Manufacturers, etc

* Infectious Disease Relief
  Launched in April 2004
ADR Relief System

*Infectious Disease relief system started in Apr.04’

**Financial Resources**

1. Contributions collected from pharmaceutical manufactures, etc
   - General Contributions: Certain rate of total shipment (0.3/1000 at current rate)
   - Additional Contributions: 25% form manufactures of main cause
2. 50% of administrative fees at government expenses

**Diagram**

- Health Minister
- PAFSC
- MHLW
- Victims of ADR
- Hospital, clinic and pharmacy
- PMDA
- Drug Manufacturers etc.
- Financial Resources

- Request for Benefit
- Request for Decision
- Inquiry
- Report
- Notification of Decision
- Subscription
- General Contribution
- Additional Contribution
- Administrative fee
- Inhouse prescription
- Prescription
- Payment of benefit
- Distribution
Safety Triangle
- Total Risk Management through Three Operations -

Review
Risk Containment

General Public
Continuous Risk Reduction

Safety

Relief
Relief for ADR
Two disadvantages

1. Patients = No benefit from leading edge medical treatment
2. Manufactures = Inaccessible to Japanese market
Number of products waiting for marketing
Among World’s top 88 selling-products in 2004

IMS Lifecycle, All rights reserved
How soon to release a product?

Asian (including Japan) Current Issue
="THE DLUG LAG"

Two disadvantages
1. Patients=No benefit of leading-edge medical treatment
2. Manufacture=inaccessible to Asian market
Delayed Drug Application to Japan

Situation of 28 popular products

- Undeveloped
- Under Clinical Trial
- Applied for Authorization

Length from world first release to application in Japan (about 15 products under application)

Years on average

- 1990~94 (4 products)
- 1995~99 (8 products)
- 2000~ (2 products)

IMS Lifecycle, All rights reserved
Clinical trial sites of Japanese drug companies

In Japan ahead or Only in Japan
In Japan and overseas at a time
In overseas ahead or only in overseas

<table>
<thead>
<tr>
<th>Year</th>
<th>In Japan ahead or Only in Japan</th>
<th>In Japan and overseas at a time</th>
<th>In overseas ahead or only in overseas</th>
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<tr>
<td>1993</td>
<td>18.3%</td>
<td>46%</td>
<td>43.2%</td>
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<td>2000</td>
<td>20.4%</td>
<td>36.4%</td>
<td>43.2%</td>
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Clinical Study Package of Bridging Studies

Japan
Phase I
   II
   III
USA/EU
Phase I
   II
   III

The “DRUG LAG”
Involvement in Global Clinical Study

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Review and approval processes for clinical studies in Japan and USA/EU, with phases I, II, and III.
Number of Notified Clinical Trials

Initial CT Notification

Year

New GCP promulgation

New GCP Enforcement

Larger Acceptance of Foreign Clinical Data

3-year CT activation plan

(Source: MHLW)
1. Reinforcement of CT Operation for Medical Institution
   - 1170 Medical Institutions registered in large-scale CT network

2. Cultivation of Staff
   - 4524 staffs completed CRD training

3. Promotion of participation in CT
   - Illuminating measures and information supplement (Clinical Study Registration System)

4. Promotion for Drug Maker
   - Introduction of IT and adoption of fixed format

5. Promotion of Product Research and Development
   - 3-year CT activation plan (2003-2005) (the Health Policy Bureau)

1. Summary
   - Participation in Global Clinical Trial and Promotion of Concurrent Application
   - Development of CT Environment of Asia

2. Clinical Trial System
   - Reform of CT procedure
   - Operation of GCP ordinance for Globalization
   - Improvement of Quality and Function of IRB including consideration of Central IRB
   - Rationalization of call for subject
   - GCP operation under consideration of Medical Devices
   - Compensation program

3. Review and approval system
   - Improvement of Review system in PMDA
   - Modification of approval system for Medical Devices (PFSB)
**Clinical Trial Environment**

*Comparison of period of CT*

- **2003**: 555 days on average
- **2004**: 526 days on average

*Comparison of average days (form application to case report)*

- **2004**: 622 days
- **2005**: 558 days

*Comparison of cost for Medical Institution (Including R&D expenses, CRC expenses, SMO expenses)*

- **2004**: 1.95 m yen
- **2005**: 1.678 m yen (on average)

Source: JPMA

Source: Research on Clinical Cost / R&D Head Club cost research working group
1. Appraisal of Necessary Clinical Trial Data and Evaluation Methods in Review
   1) To Promote Japan’s Participation in Global Development and International Clinical Study
   2) To Consider Positioning of Japanese Domestic Data among International Clinical Study Data obtained in Other Asian Countries
   3) To Introduce Evaluation Methods focusing on Cutting-edge Technologies such as Pharmacogenomics
   4) To Strengthen Risk Management by Reinforcement of Post-marketing Safety Measures Coordinated with Pre-market Review in Introduction of International Clinical Study and Cutting-edge Technologies

2. To Assist Improvement of Clinical Trial Environment by reinforcing On-site GCP Audit

3. Active Support of Development of Cutting-edge Biotechnologies through Clinical Trial Consultations and Other Measures

4. Increase number of experts and developing their ability
Our Efforts toward Global Clinical Trial

Global Clinical Trial

Bridging Studies
- Clinical Trial Consultation
- Review/Approval

Post-Marketing Survey

Global Clinical Trial

Clinical Trial Consultation

Post-marketing Survey

Japan

Asia

Japan
Global Clinical Trial
To Achieve Tripartite Simultaneous Development and Approval

CT Data

Europe
EU

Asia
Japan

N.America
U.S.

S.America

Africa
Development of International Harmonization in review operation

「International Conference on Harmonization (ICH)」(Founded in 1991)

MHLW/ FDA/ EU/EMEA/ JPMA/ PhRMA / EFPIA (obs.) WHO/Canada/ EFTA

ICH

Common Requirements on new drug application
(More than 50 guidelines)

Goal＝Simultaneous Submission & Approval In the World

(Reference) ”The Global Harmonization Task Force (GHTF)”since 1992
Growth of Clinical Development in Asia

Year

Patients Recruited


- Phase I & II
- Phase IV
- Phase III
- Total

ICH-GCP, 1996

Source: Quintiles Translational

From JPMA Report of Asian CT Study Team
Asia in Global Development

-To ensure faster access to superior drugs for Asian people-

Asian Collaboration Network

People

Information

Technology
Thank you for your attention.

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