Quality of Clinical Trials
-PMDA’s Point of View-

Tomoko OSAWA, Ph.D.
Director for GCP Inspection
Office of Conformity Audit
PMDA, Japan

The views presented in this presentation are those of the author and should not be understood or quoted as being made on behalf of Pharmaceuticals and Medical Devices Agency (PMDA).
Contents

1. Current Trend around Clinical Trials
2. To Ensure the Quality of Clinical Trials
3. Current Trend of GCP Inspection conducted by PMDA
4. To the Future
1. Current Trend around Clinical Trials
2. To Ensure the Quality of Clinical Trials
3. Current Trend of GCP Inspection conducted by PMDA
4. To the Future
Trend in Notified CTs in Japan

Initial CT Notification (NCEs only)
CT notification

J-GCP

3-year clinical trial activation plan (extended 1 year)

The New 5-year Clinical trial Activation Plan

5-Year Plan for Activation of Clinical research and Clinical Trial 2012

Initial CT Notification


0 50 100 150 200 250 300


0 200 400 600 800

The New 5-year Clinical trial Activation Plan

5-Year Plan for Activation of Clinical research and Clinical Trial 2012

J-GCP
Trend in Notified Global CTs

Number %

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of CTs other than Initial Notification</th>
<th>Number of CTs of Initial Notification</th>
<th>Ratio of global CTs ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY’07</td>
<td>35</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>FY’08</td>
<td>73</td>
<td>15.6</td>
<td>15.6</td>
</tr>
<tr>
<td>FY’09</td>
<td>98</td>
<td>20.2</td>
<td>20.2</td>
</tr>
<tr>
<td>FY’10</td>
<td>106</td>
<td>21.2</td>
<td>21.2</td>
</tr>
<tr>
<td>FY’11</td>
<td>98</td>
<td>17.6</td>
<td>17.6</td>
</tr>
</tbody>
</table>
Current Trend

- 24th October 2011
  Revision of the GCP Notification
- 7th March 2012
  Revision of Notification ‘Uniform Forms Regarding Clinical Trial Applications, etc.
- 30th March 2012
  5-Year Clinical Trials Vitalization Plan 2012
- 6th June 2012
  5-Year Strategy for Medical Innovation
- 31st July 2012
  The Strategy for Rebirth of Japan
- 28th December 2012
  Revision of Ministerial Ordinance on GCP and GCP Notification
Purpose of these Revisions

- To ensure the reliability of the data more
- To promote harmonization of J-GCP and ICH-GCP
- To streamline clinical trial (CT) procedures, saving unnecessary procedures
- To activate CTs led by investigators
- To clarify that Notification is just one form of guidance or an option and not the only way to implement GCP
What to do

- Vigorous Participation in Global Clinical Trials
- Promotion of Early-phase Exploratory Trials for Creation of Innovative Pharmaceuticals and Medical Devices from Japan

Implementation of High-Quality Clinical Trials
1. Current Trend around Clinical Trials
2. To Ensure the Quality of Clinical Trials
3. Current Trend of GCP Inspection conducted by PMDA
4. To the Future
High-Quality Clinical Trials Are • • •

- Ethical, of course.
- Capable to introduce clear-cut conclusion to the hypothesis set in the protocol. (Scientific)

⇒ Compliance with Good Clinical Practice (GCP)
Compliance with GCP provides

**public assurance** that

- The rights, safety and well-being of trial subjects are protected.
- The clinical data are credible.
GCP and Quality

- Quality assurance
- Quality control
Major factors influencing the Quality of Clinical Trials

☑ Protocol

What kind of data should be collected, and from whom? From when to when? How?

☑ Implementation system

Are the clinical trials conducted adequately?
Key to Ensure the Quality

- Capture the problems on conducting clinical trials (e.g., interpretation of inclusion criteria, exclusion criteria, etc.) as early as possible.
- Feed back the solutions to all related sites.

- • • • Monitoring: Initiation, Intervals, Items, etc.

How to monitor is important!
1. Current Trend around Clinical Trials
2. To Ensure the Quality of Clinical Trials
3. Current Trend of GCP Inspection conducted by PMDA
4. To the Future
Trend in Document-based Conformity Inspection for New Drug

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Number</th>
<th>PMDA visited the site</th>
<th>Oversea inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY’07</td>
<td>145</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>FY’08</td>
<td>159</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>FY’09</td>
<td>92</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>FY’10</td>
<td>106</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>FY’11</td>
<td>100</td>
<td>76</td>
<td>2</td>
</tr>
</tbody>
</table>
Trend in GCP On-site Inspection for New Drug

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Number</th>
<th>Oversea inspection</th>
<th>Document-based conformity inspection conducted at the same time</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY'07</td>
<td>80</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>FY'08</td>
<td>100</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>FY'09</td>
<td>84</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>FY'10</td>
<td>84</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>FY'11</td>
<td>83</td>
<td>83</td>
<td>7</td>
</tr>
</tbody>
</table>
# Trend in GCP On-site Inspection

<table>
<thead>
<tr>
<th></th>
<th>FY '07</th>
<th>FY '08</th>
<th>FY '09</th>
<th>FY '10</th>
<th>FY '11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drugs (NMEs)</td>
<td>80 (0)</td>
<td>100 (3)</td>
<td>84 (6)</td>
<td>84 (7)</td>
<td>83 (7)</td>
</tr>
<tr>
<td>Number of sponsors</td>
<td>80 (0)</td>
<td>100 (4)</td>
<td>80 (6)</td>
<td>78 (7)</td>
<td>87 (7)</td>
</tr>
<tr>
<td>Number of medical institutions</td>
<td>167 (0)</td>
<td>216 (6)</td>
<td>180 (13)</td>
<td>188 (14)</td>
<td>181 (13)</td>
</tr>
</tbody>
</table>

( ): The number of inspections in overseas
### Detail of GCP On-site Inspection in Overseas

<table>
<thead>
<tr>
<th>Sponsors (28)</th>
<th>Countries</th>
<th>Number of GCP Inspection</th>
<th>Countries</th>
<th>Number of GCP Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>7</td>
<td>Netherlands</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>3</td>
<td>China</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>3</td>
<td>Korea</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>1</td>
<td>Taiwan</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>Philippines</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical institutions (46)</th>
<th>Countries</th>
<th>Number of GCP Inspection</th>
<th>Countries</th>
<th>Number of GCP Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>11</td>
<td>Belgium</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
<td>Netherlands</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>4</td>
<td>China</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2</td>
<td>Korea</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>2</td>
<td>Taiwan</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>2</td>
<td>Philippines</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

1) Notices of results issued from April 2007 to March 2012,  
2) Including the number of CRO  
3) 4 cases are GCP on-site inspection and document-based conformity inspection
Findings for Sponsors in JAPAN (FY2009 - FY2011)

Monitor’s responsibility
124 cases

Safety information reporting
59 cases

Others
10 cases

(N=193 cases)

Details of findings for monitor’s responsibility

Informed consent
10 cases

IRB’s review
41 cases

CRF
38 cases

Protocol deviation
27 cases

Others
8 cases

(N=124 cases)
Findings for Sponsors in Overseas (FY2009 - FY2011)

Monitor's responsibility: 20 cases

CRF: 8 cases

Protocol deviation: 7 cases

Subinvestigators-designate: 3 cases

Others: 2 cases

Others: 3 cases

(N=23 cases)
General Findings for Medical Institutions (FY2009 - FY2011)

**JAPAN**

- IRB’s review: 59 cases
- Investigational product control: 16 cases
- Outsourcing duties: 28 cases
- Subinvestigators-designate: 2 cases
- Others: 5 cases

(N=110 cases)

**Overseas**

- Clinical trial contract: 1 case
- Investigational product control: 2 cases
- Outsourcing duties: 1 case
- Subinvestigators-designate: 3 cases

(N=7 cases)
Findings for Individual Subjects
-Medical Institutions- (FY2009 - FY2011)

(J=293 cases)

- Protocol deviations
- 146 cases
- Selection of subjects
- 31 cases
- CRF
- 57 cases
- Informed consent
- 35 cases
- Others
- 1 case

Overseas

(N=38 cases)

- Protocol deviations
- 17 cases
- CRF
- 11 cases
- Informed consent
- 5 cases
- Selection of subjects
- 2 cases
- Others
- 3 cases
Ratio of Medical Institutions with Findings (FY2009 - FY2011)

JAPAN

42 %
(N= 549 cases)

Overseas

67 %
(N= 39 cases)
In view of recent inspection results in Japan and overseas, the Quality level of CTs in Japan is ...

The earnestness of Japanese could contribute to ...

Sometimes some people try to prepare too good-looking document, without error or correction, in the manner against the spirit of so-called ALCOA.

ALCOA : attributable, legible, contemporaneous, original, accurate
1. Current Trend around Clinical Trials
2. To Ensure the Quality of Clinical Trials
3. Current Trend of GCP Inspection conducted by PMDA
4. To the Future
Quality of Clinical Trials Conducted in Japan

- Quality of implementation system of uninspected sites
  - • • • unknown
- Limited information on CTs conducted in overseas
- Role of Principal investigator to raise the quality level of CTs conducted in Japan
- Smooth communication between sponsors and clinical sites
- Compliance with the protocol
Japanese Identity and Quality of Clinical Trials

- Earnestness and carefulness of Japanese would continuously be the key to establish and/or raise the quality of clinical trials.
- Excessive consideration for making good looking documents could be harmful for compliance with the standard of reliability
Every person involved in clinical trials should carry out his/her own duty.

Teamwork
Every unit ⇒ All Japan
Thank you for your attention!