The recent progress of GCP inspection in Japan

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Deputy Inspection Director,
Office of Non-clinical and Clinical Compliance
1. Introduction of our office
2. Trends of clinical trials and approved drugs utilizing MRCTs
3. GCP inspection procedure in Japan
4. GCP on-site inspection
5. International cooperation
Pharmaceuticals and Medical devices Agency

Date of Establishment: April 2004

Kansai Branch

Tokyo

Major services

- Scientific review for drugs & Medical devices
- GCP, GLP, GMP inspection
- Consultation on clinical trials
- Safety measures
- Relief services
PMDA’s safety triangle

- Consultations
- Drug reviews
- Medical device reviews
- GLP/GCP/GPSP inspections *
- GMP/QMS inspections *
- Standards development

Review
Reduction in risk

Safety
Continuous risk mitigation efforts

Japanese citizens

Relief
Relief measures for health damage caused by risk factors

*GLP: Good Laboratory Practice, GCP: Good Clinical Practice, GPSP: Good Post-marketing Study Practice
GMP: Good Manufacturing Practice, QMS: Quality Management System

2017 Sep 7th-8th 3rd Asia QA Forum Conference in Beijing
Organizational chart of PMDA
Regulatory authority in Japan

MHLW
Pharmaceuticals and Food Safety Bureau, MHLW
- Final authorization of applications
- Publishing guidelines
- Advisory committee
- Supervising PMDA activities

PMDA
Pharmaceuticals and Medical Devices Agency
- Scientific review for drugs & medical devices
- GCP, GMP inspection
- Consultation on clinical trials etc.

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Trends of MRCT-related clinical trial notifications in Japan

![Graph showing trends in MRCT-related clinical trial notifications from FY2007 to FY2015.](image)

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Trends of approved new drugs based on MRCTs in Japan

Number of approved drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>MRCT</th>
<th>Bridging Strategy</th>
<th>% of MRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2007</td>
<td>81</td>
<td>1</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>FY2008</td>
<td>79</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>FY2009</td>
<td>107</td>
<td>4</td>
<td>3.7</td>
<td>0.0</td>
</tr>
<tr>
<td>FY2010</td>
<td>114</td>
<td>7</td>
<td>6.1</td>
<td>0.0</td>
</tr>
<tr>
<td>FY2011</td>
<td>130</td>
<td>12</td>
<td>9.2</td>
<td>0.0</td>
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<tr>
<td>FY2012</td>
<td>134</td>
<td>19</td>
<td>14.2</td>
<td>0.0</td>
</tr>
<tr>
<td>FY2013</td>
<td>138</td>
<td>22</td>
<td>15.9</td>
<td>0.0</td>
</tr>
<tr>
<td>FY2014</td>
<td>119</td>
<td>32</td>
<td>26.9</td>
<td>20.0</td>
</tr>
<tr>
<td>FY2015</td>
<td>115</td>
<td>23</td>
<td>20.0</td>
<td>20.0</td>
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### Approved new drugs based on MRCTs in Japan

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Paclitaxel</td>
<td>Riociguat</td>
<td>Sirolimus</td>
<td>Evolocumab</td>
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<tr>
<td>Aripiprazole</td>
<td>Pregabalin</td>
<td>Tadalafil</td>
<td>Ruxolitinib</td>
<td>Levetiracetam</td>
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<td>Olanzapine</td>
<td>Tofacitinib</td>
<td>Afatinib</td>
<td>Eftrenonacog alfa</td>
<td>Sebelipase alfa</td>
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<tr>
<td>Exenatide</td>
<td>Regorafenib</td>
<td>Turoctocog alfa</td>
<td>Efinaconazole</td>
<td>Asenapine</td>
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<tr>
<td>Crizotinib</td>
<td>Ofatumumab</td>
<td>Ranibizumab</td>
<td>Lamotrigine</td>
<td>Perampanel</td>
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<tr>
<td>Budesonide/</td>
<td>Bevacizumab</td>
<td>Goserelin</td>
<td>Aflibercept (PM)</td>
<td>Mepolizumab</td>
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<tr>
<td>Formoterol</td>
<td>Pertuzumab</td>
<td>Everolimus</td>
<td>Edoxaban (AF)</td>
<td>Ceritinib</td>
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<tr>
<td>Esomeprazole</td>
<td>Lixisenatide</td>
<td>Tolvaptan</td>
<td>Edoxaban (VTE)</td>
<td>Osimertinib</td>
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<td>Formoterol</td>
<td>Ranibizumab</td>
<td>Favipiravir</td>
<td>Bosutinib</td>
<td>Ruroctocog alfa pegol</td>
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<td>Regorafenib</td>
<td>Tapentadol</td>
<td>Suvorexant</td>
<td>Octocog beta</td>
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<tr>
<td>Budesonide/</td>
<td>Indacaterol/</td>
<td>Tofogliflozin</td>
<td>Aflibercept (DME)</td>
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</tr>
<tr>
<td>Formoterol</td>
<td>Glycopyrronium</td>
<td>Alogliptin</td>
<td>Tiotropium</td>
<td></td>
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<tr>
<td>Atomoxetine</td>
<td>Paliperidone</td>
<td>Sorafenib</td>
<td>Darbepoetin alfa</td>
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</tr>
<tr>
<td>Aflibercept</td>
<td>Viulanterol/</td>
<td>Anti-Inhibitor-</td>
<td>Empagliflozin</td>
<td></td>
</tr>
<tr>
<td>Insulin-Degludec</td>
<td>Fluticasone</td>
<td>Coagulant-Complex</td>
<td>Elosulfase alfa</td>
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</tr>
<tr>
<td>Glycopyrronium</td>
<td>Bevacizumab</td>
<td></td>
<td>Secukinumab</td>
<td></td>
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<tr>
<td>Pazopanib</td>
<td>Aflibercept</td>
<td>Umeclidinium/</td>
<td>Insulin glargine (BS1)</td>
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</tr>
<tr>
<td>Everolimus</td>
<td></td>
<td>Vilanterol</td>
<td>Nonacog gamma</td>
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<tr>
<td>Fesoterodine</td>
<td></td>
<td></td>
<td>Efraloctocog alfa</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-degludec+Aspart</td>
<td></td>
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</tr>
</tbody>
</table>

**Red : Asian Trials**

- 123 applications were approved as of March 31, 2016

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Office of Non-clinical and Clinical Compliance

- Director
- Deputy Director

- GCP on-site Inspection
- Document-based Inspection
- Devices Inspection
- GPSP Inspection
- GLP Inspection
Two types of inspection in Japan

Medical Institution

- Implementation system (including IRB and SMO)
- Source documents (medical record, patient diary, etc.)

Sponsor

- Implementation system (including CRO)
- Documents from all medical Institutions and sponsor’s records (case report form, monitoring reports, etc.)

GCP on-site Inspection

We verify conformity of the data of clinical trials in application dossier

Document-based Inspection

New drug application for approval

Source documents (medical record, patient diary, etc.)

Documents from all medical Institutions and sponsor’s records (case report form, monitoring reports, etc.)
Typical flow chart of review and inspection

- **NDA review**
  - PMDA
  - Discussion with review team before the inspection

- **Inspection**
  - **Document-based**
    - Site/study selection
    - Scheduling
  - Sponsor
  - Medical institutions
  - Inspection result

- **GCP on-site**
  - Medical institutions
  - Inspection result

- **Approval**
  - MHLW
  - Pharmaceutical Affairs and Food Sanitation Council

**Simultaneous implementation of document-based and on-site inspection is under way**
GCP on-site inspection
- Overview -
Overview of GCP inspection

CRF: Case Report Form, eCRF: electronic Case Report Form, CSR: Clinical Study Report

On-site inspection

Document-based inspection
Outline of GCP on-site inspection

1. Select medical institutions/clinical trials for inspection
2. Fix inspection schedules of **sponsor** and medical institutions
3. Establish an inspection team
4. Send notifications to **sponsor** and medical institutions
5. Receive pre-submitted documents from **sponsor** and medical institutions
6. Conduct inspections
7. Write an inspection report
8. Evaluate compliance based on GCP at monthly meetings
9. Send notifications of inspection results to **sponsor** and medical institutions
Typical schedule of inspection

1. **NDA**
   - Close communication with applicant* 
   - Pre-submitted documents

2. **Selection** 
   - 0 months

3. **On-site Inspection**
   - 1.5 months
   - 4 months
   - 5-5.5 months

4. **Approval**
   - 7 months
   - 12 months (Months)

- Notification of conducting inspection
- Notification of inspection results

- *Arrangement of inspection schedule, F2F meeting
- **Domestic sites → Foreign sites → Foreign sponsors → domestic sponsors

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Selection of clinical trials and medical institutions to be inspected
(point to consider)

Clinical trials

- Priority in the clinical data package for J-NDA (e.g. pivotal trial, bridging trial)

Medical Institutions

- Sampling number
  - The drugs with new active pharmaceutical ingredients
    (Excluding the drugs of quick/priority review, the orphan drugs)
    → Approximately 4 institutions
  - Others
    → Approximately 2 institutions
- The number of subjects
- Results of previous inspections

- Clinical trials and medical institutions to be inspected are decided on after discussing them with NDA reviewer.
- Additional institutions will be inspected if there are problems identified during review/inspection process.
Selection of clinical trials and medical institutions in oversea inspection

Conduct oversea inspection?

Points to be considered

- (Pivotal trial in the package) was conducted in foreign countries?
- (Product) already approved by foreign authorities?
- (Trial/Institution) already inspected by foreign authorities?
- Others (total ratio/number of subject in Japanese sites, etc.)
Which country/medical institutions to be inspected?

Points to be considered

- Conducted clinical trials at the site
- The number of subjects
- Results of previous inspections
- Future inspection plan
- Inspection of foreign authorities
- Others (security situation, etc.)

Usually 2 medical institutions in 1 country are selected.
Main points in the checklist of medical institution

Outline of clinical trials
Requirement of Medical institute
Control of Clinical Trials

Investigator
Requirement, work information
transfer to the staffs

Subjects
Selection of the subjects
Informed consent

IRB
Organization, Management,
review process to result notification

Control of clinical trials
AE information, Investigational
drugs control, Record keeping

Case report
Consistency to the source
documents, Investigator’s
confirmation

Checklist (Only Japanese) is available in the PMDA website
http://www.pmda.go.jp/files/000205701.doc
Main points in the checklist of sponsor

Clinical trial management
- Protocol, Investigator’s brochure
- Selection of medical institute, Principal investigator

Preparing clinical trials
- Control of IMPs
- Safety information
- Monitoring
- Contract of CT
- Compensation
- Audit
- Record keeping

Checklist (Only Japanese) is available in the PMDA website
http://www.pmda.go.jp/files/000205702.doc
GCP on-site inspection
- Performance -
## Trend in GCP on-site inspection

<table>
<thead>
<tr>
<th></th>
<th>FY’ 11</th>
<th>FY’ 12</th>
<th>FY’ 13</th>
<th>FY’ 14</th>
<th>FY’ 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of drugs</strong></td>
<td>84</td>
<td>99</td>
<td>125</td>
<td>110</td>
<td>106</td>
</tr>
<tr>
<td><strong>Number of sponsors</strong></td>
<td>80 (8)</td>
<td>97 (5)</td>
<td>120 (6)</td>
<td>103 (7)</td>
<td>108 (6)</td>
</tr>
<tr>
<td></td>
<td>Total:88</td>
<td>Total:102</td>
<td>Total:126</td>
<td>Total:110</td>
<td>Total:114</td>
</tr>
<tr>
<td><strong>Number of medical institutions</strong></td>
<td>175 (13)</td>
<td>190 (9)</td>
<td>233 (7)</td>
<td>218 (10)</td>
<td>213 (12)</td>
</tr>
<tr>
<td></td>
<td>Total:188</td>
<td>Total:199</td>
<td>Total:240</td>
<td>Total:228</td>
<td>Total:225</td>
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</tbody>
</table>

( ): The number of inspections in overseas

1) New Molecular Entities, except generic
## Detail of GCP on-site inspection in overseas

<table>
<thead>
<tr>
<th>The number of IPs inspected</th>
<th>Breakdown by nations</th>
</tr>
</thead>
<tbody>
<tr>
<td>68&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>USA 20</td>
</tr>
<tr>
<td></td>
<td>Germany 7</td>
</tr>
<tr>
<td></td>
<td>China 6</td>
</tr>
<tr>
<td></td>
<td>Korea 5</td>
</tr>
<tr>
<td></td>
<td>UK 4</td>
</tr>
<tr>
<td></td>
<td>Taiwan 4</td>
</tr>
<tr>
<td></td>
<td>Austria 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The number of sponsors inspected (including CROs)</th>
<th>Breakdown by nations</th>
</tr>
</thead>
<tbody>
<tr>
<td>66&lt;sup&gt;2)&lt;/sup&gt;</td>
<td>USA 21</td>
</tr>
<tr>
<td></td>
<td>China 12</td>
</tr>
<tr>
<td></td>
<td>Korea 8</td>
</tr>
<tr>
<td></td>
<td>Taiwan 7</td>
</tr>
<tr>
<td></td>
<td>Germany 6</td>
</tr>
<tr>
<td></td>
<td>UK 4</td>
</tr>
<tr>
<td></td>
<td>Spain 4</td>
</tr>
<tr>
<td></td>
<td>Romania 4</td>
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</table>

1) Counted based on the notification published during Apr. 2008～Mar. 2017
2) 9 cases are coincident inspection of GCP on-site inspection and document-based inspection
Result of GCP on-site inspection for new drug (FY2014) 1,2)

1) The products for which the inspection result notification was issued from Apr. 2014 to Mar. 2015.
2) There were no “non-compliance” cases in FY 2014.
3) Number of inspection result notifications issued (per applicant), except sponsor-investigator.

A total of 106 cases 3)

- Compliance (Voluntary actions to improve indicated) 22 cases, 21%
- Compliance (no indication) 82 cases, 77%
- Compliance with condition 2 cases, 2%
Findings for sponsors in Japan (FY2014) ¹)

N=28 cases²)
1) The products for which the inspection result notification was issued from Apr. 2014 to Mar. 2015.
2) Number of findings for sponsors (Except the Sponsors in Overseas, sponsor-investigator)
Findings for sponsors in overseas (FY2014)

(N=32 cases)

Monitor’s responsibility
27 cases

Details of findings for monitor’s responsibility
N=27

Protocol deviation
10 cases

Discrepancy of CRF
9 cases

Deficiency of Subinvestigator’s designate
3 cases

Others
5 cases

Others
5 cases

(N=32 cases)
General findings for medical institutions
(FY2014 for Japan, FY2008 – 2014 for overseas)

Japan

- IRB’s review: 11 cases
- Safety information reporting: 1 cases
- Contract of outsourcing etc: 9 cases
- PI/Sub-PI etc, 2 cases
- Investigational product control: 2 cases
- Insufficient description of contract: 1 case

(N=26 cases)

Overseas

- Investigational product control: 7 cases
- Contract of outsourcing: 1 case
- PI/Sub-PI etc, 6 case
- Informed consent form: 2 cases
- Contract of clinical trial: 1 case

(N=17 cases)
Findings for individual subjects (medical institutions) 
(FY2014 for Japan, FY2008 – 2014 for Overseas)

<table>
<thead>
<tr>
<th>Category</th>
<th>Japan Cases</th>
<th>Overseas Cases</th>
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</thead>
<tbody>
<tr>
<td>Protocol Deviations</td>
<td>35 cases</td>
<td>35 cases</td>
</tr>
<tr>
<td>CRF</td>
<td>4 cases</td>
<td>16 cases</td>
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<tr>
<td>Selection of subjects</td>
<td>4 cases</td>
<td>5 cases</td>
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<tr>
<td>Informed consent</td>
<td>5 cases</td>
<td>7 cases</td>
</tr>
<tr>
<td>Record keeping</td>
<td>3 cases</td>
<td>3 cases</td>
</tr>
</tbody>
</table>

(N=51 cases) (N=71 cases)
International cooperation in GCP area
Globalization challenges

• Increasing number of MRCTs
• Resource challenges, Inspection coverage
• Need for synergies and avoidance of duplication

Regulatory authorities should work closely to secure the quality of the result of clinical trial and protection of subject all over the world

• Promote confidence building with other regulatory authorities
  - Mutual understanding on GCP regulation in each region
  - Confirmation on the practical GCP inspection level
• Make a platform to exchange information of GCP inspection
Recent communication with foreign regulatory agency

- Participate in the inspection of Japanese site by foreign inspectors
- Sharing information of inspection etc. with FDA and EMA
- Acceptance of foreign regulators as trainees for inspector training by PMDA
- Asia training center (ATC)
Training seminar for inspectors from foreign regulatory agencies

PMDA-ATC MRCT Seminar 2017

Pharmaceuticals and Medical Devices Agency (PMDA) recently completed the PMDA-Asia Translational Center for Pharmaceuticals and Medical Devices Regulatory Affairs (ATC) Multi-Regional Clinical Trial (MRCT) Seminar 2017 on January 23-26, 2017, as a Center of Excellence (CoE) Pilot Workshop, the MRCT/Good Clinical Practice (GCP) Inspection Priority Work Area in the Asia-Pacific Economic Cooperation. Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (LSIF-RHSC). This seminar was designed for officials from overseas regulatory agencies who are engaged or interested in the area of MRCT. Total of 32 regulators from 14 economies (Brazil, China, Chinese Taipei, Indonesia, Malaysia, Mexico, Myanmar, Nepal, Papua New Guinea, Peru, Philippines, Sri Lanka, Tanzania, and Thailand) joined the seminar.

The seminar opened with remarks by Dr. Jun'ichi Sato, Office Director of Office of International Cooperation and Dr. Yoshikazu Uyama, International Senior Training Coordinator as well as Office Director of Office of Medical Informatics and Epidemiology, followed by the keynote speech by Tatsuya Kondo, Chief Executive of PMDA. Subsequent lectures and the case studies were presented by
Reference

• PMDA website

• Information of GLP / GCP / GPSP Compliance Assessments
  (English)
  http://www.pmda.go.jp/english/review-services/glp-gcp-gpsp/0001.html
  (Japanese)
  http://www.pmda.go.jp/review-services/inspections/0001.html

• International activities

Thank you for your attention.