Clinical trial notifications and scientific consultation system in Japan

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Contents

① Outline of clinical trial notifications for drugs and consultation system

② Clinical trial notifications for drugs

③ Clinical trial consultation and prior assessment consultation
Background

1. Reinforcement of consultation/guidance for Clinical trials
2. Reinforcement of approval review
3. Strengthening of post-marketing measures
4. Others

October, 1994
Increase in the number of drugs which have potent pharmacological effects.
→ Needs for improving drug safety

Strengthening of the role of pharmaceutical companies
Taking comprehensive measure for pharmaceuticals

June, 1996 Publication of the revised Pharmaceutical Affairs Law
April, 1997 Enforcement of the revised Pharmaceutical Affairs Law
The change of the enforcement system of IND and Consultation

- 1980: Establishment of PMDEC at NIHS
- 2004: Establishment of PMDA

- MHW: Grant approval, Approval review, Clinical trial notifications
- ★PMDEC/NIHS: Approval review, Clinical trial notifications / review
- ★OPSР (KIKO): Clinical Trial Consultation, Equivalence review for generic drugs, GCP Inspection, Compliance audit
- ★MHLW: Approval review, Clinical trial notifications / review, Clinical Trial Consultation, Others
- PMDA: Approval review, Clinical trial notifications / review, Clinical Trial Consultation, Others
Consultations according to individual needs

April 1997
Organization for Pharmaceutical Safety and Research (OPSR/Kiko)

- Consultation before IND
- Consultation after completion of phase II study for drug
- Pre-application consultations
- Individual consultation

Expansion of the consultation category

April, 2011
PMDA

1. Consultation before start of phase I study for drugs
2. Consultation before start of early phase II study for drugs
3. Consultation before start of late phase II study for drugs
4. Consultation after completion of phase II study for drugs
5. Pre-application consultation
6. Consultation on the protocols of clinical trials for reevaluation and re-examination of drugs
7. Consultation at completion of clinical trials for reevaluation and re-examination of drugs
8. Additional consultation

Application procedure consultation
Consultation on bioequivalence testing, etc. for drugs
Safety consultation
Quality consultation
GLP/GCP compliance (for priority review)

Prior assessment consultation for drugs
1. Quality
2. Non-clinical: toxicity
3. Non-clinical: pharmacology
4. Non-clinical: pharmacokinetics
5. Phase I study
6. Phase II study

As a pilot
Why did we introduce “Prior Assessment Consultation”? 

Measure to eliminate drug lag?

About 2.5 years

Measures by PMDA for eliminating drug lag

**Targets:** To reduce the “drug lag” by a total of 2.5 years

- 1.5 year reduction of development time
- 1.0 year reduction of approval review time

**Measures**

**Expansion of the Consulting Service**
- Increase the number of staff about 236 approximately in 3 years
- Give adequate training
- Improve the quality and quantity of consultations
- Advise on overall development strategy to improve development time
- Reduce the application preparation time through stepping up pre-application consultations
- Clarify the review criteria
- Further promote Global Clinical Trials
- Draft a guideline on cutting-edge technologies

**Expansion of the Review System**
- Increase the number of staff
- Give adequate training
- Introduce a prior assessment, and reduce applicant workload.
- Improve productivity of reviews through measures such as standardization and streamlining of the review process
- Liaise more closely with the FDA and other overseas regulatory authorities
Submission of the Clinical trial notification
(Pharmaceutical Affairs Law)

(Handling of Clinical Trials)

Article 80-2 Sponsors of clinical trials must conduct in accordance with standards specified in MHLW Ordinance.

2 Sponsors of clinical trials must submit the clinical trial protocol to the Minister beforehand as specified in MHLW Ordinance.

3 Persons submitting protocols, shall not sponsor the clinical trial until after of 30 days has passed from the submission date. In such cases, the Minister shall undertake a review of the clinical trial protocol to prevent from jeopardizing public health and hygiene.
Drugs requiring submission of CT notifications(1)

① Drugs with **active ingredients differing** from that of approved drugs.

② Drugs with active ingredients that are **same** but **the route of admission differing** from approved drugs.

③ Drugs **differing** from **combination ratio** of active ingredients, or **indications** or **dosage and administration** of approved drugs.

④ Drugs with active ingredients that are **same ingredient which had approved** as new molecular entity, but that **reexamination period has not expired**.

⑤ Drugs expected to be as **biological products**.

⑥ Drugs manufactured using **recombinant technology**.

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 268
No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008,
No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.
The person who has submitted a clinical trial notification must inform [●●] when the contents of the notification were changed.

- [The Minister]
  - Notifications of changes in clinical trial protocol and completion or discontinuation of the clinical trial.

- [Director of Evaluation and Licensing Division]
  - Notifications of discontinuation of the development
Documents which is required to be attached to the clinical trial notifications

1. Statement regarding the reason why the sponsoring of the proposed clinical trial is scientifically justified.
2. A protocol of the proposed clinical trial
3. An explanation document used for informed consent and consent form
4. Sample of Case Report Form
5. Current investigator’s brochure

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 269
No. 0815001 of Director of Evaluation and Licensing Division dated August 15, 2008.
No. 0815005 of Director of Evaluation and Licensing Division dated August 15, 2008.
Timing of submission of clinical trial notifications

① The first notifications of regarding trial drugs must be submitted **at least more than 31 days before** the day of planning on contract with the medical institutions.

② Notifications other than those specified in ① above shall be submitted **at least around 2 weeks before** the day of planning on contract with the medical institutions.

The Pharmaceutical Affairs Law, Enforcement Regulations: Article 269
No. 0815001 of Director of Evaluation and Licensing Division dated August 15 2008.
No. 0815005 of Director of Evaluation and Licensing Division dated August 15 2008.
What kind of drug is needed to submit the 1st notification before at least 31 days of the contract?

1. Drugs with active ingredients differing from that ingredient of approved drugs.
2. Drugs that are the same active ingredients but the route of administration differing from approved drugs.
3. Medical combination drugs excluding similar medical combination agent.
For review of the clinical trial protocol

Flowchart

**PMDA’s Action**
- Accept clinical trial notifications
- Review the contents of the clinical trial protocol
- Inquiry
- Review of contents of sponsor side response
  - confirm the details by phone
  - resend the another inquiry again
- Accept the replacement
- Report of investigation results
- Send the report to MHLW
- ≤ 30day

**Sponsor’s Action**
- Submit clinical trial notifications
- 1day
- Submit the response to inquiry
- ≤ 17day
- Detail description • submit another response again
- ≤ 21day
- Submit the replacement
- ≥ 10day
The change of number of clinical trial notifications

- Initial CT Notification (NME)
- CT Notification

Key Events:
- New GCP Promulgation
- New GCP Enforcement
- Larger Acceptance of Foreign Clinical data
- 3 year CT Activation Plan
- New 5-year CT Activation Plan

Years:
- 1996 to 2010

Notifications:
- Initial CT Notification
- CT Notification

Values:
- 1996: 722
- 1997: 500
- 1998: 406
- 1999: 391
- 2000: 463
- 2001: 424
- 2002: 438
- 2003: 361
- 2004: 414
- 2005: 497
- 2006: 504
- 2007: 530
- 2008: 495
- 2009: 553
- 2010: 616
PMDA’s scientific consultation

Non-Clinical
(Synthesis)
(Preparation)
(Pharmacology)
(Toxicology)
etc

IND

Clinical

Phase I

Phase II

Phase III

Review

NDA

Post-Market

Clinical trial consultations

Pre P-I

Pre P-II

End of P-II

Pre PMC

Pre NDA

End of PMC

Prior assessment consultation

P-I data Assessment

Non-Clinical Assessment

Quality Assessment

P-II data Assessment
Purpose and contents of clinical trial consultations

**Purpose**

By implementation of consultation in development stage
- Solve the issues in clinical development → shortening of the time before the application / cost reduction
- Avoid finding any critical issues on NDA review

**Consultation contents**

- Consultation **before start of phase I study** for drugs
  - The validity of applying the drug to a person for the first time
  - Clinical study design of Phase I etc.

- Consultation **before start of phase II or after completion of phase II study** for drugs
  - Clinical study design of phase II or phase III etc.

- **Pre-application** consultation
  - The way for compiling the application document
  - Sufficiency of the application document
Clinical trial consultations
Flowchart

PMDA’s Action

Accept tentative application
Fix the meeting date
Accept application
Review the questions and documents
Inquiries
PMDA opinion
Face to face meeting
Draft minutes
Fixed minutes

Consulters’ Action

Tentative application
Application
Submit the Questions and Documents
Submit the response to inquiry
Applicant opinion
Amendments

Inquiries
- 8W
- 5W
- 4day
± 30day
# Implementation status of each consultation

## Total number of each IND scientific consultation about the new medical supplies

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>**Total (Storing number) *</td>
<td>215</td>
<td>327</td>
<td>303</td>
<td>337</td>
<td>332</td>
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<td>Consultation before start of phase I study for drugs</td>
<td>42</td>
<td>73</td>
<td>65</td>
<td>48</td>
<td>47</td>
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<td>Consultation before start of early phase II study for drugs</td>
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<td>5</td>
<td>13</td>
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<td>14</td>
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<tr>
<td>Consultation before start of late phase II study for drugs</td>
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<td>Consultation after completion of phase II study for drugs</td>
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<td>63</td>
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<td>109</td>
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<td><strong>Pre-application</strong> consultations</td>
<td>41</td>
<td>42</td>
<td>24</td>
<td>38</td>
<td>34</td>
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<tr>
<td>Additional consultation</td>
<td>31</td>
<td>35</td>
<td>20</td>
<td>28</td>
<td>45</td>
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<td>2</td>
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<td>Application procedure consultation</td>
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<td>16</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Quality consultation</td>
<td>5</td>
<td>8</td>
<td>23</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Safety consultation</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>13</td>
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<tr>
<td>Consultation on bioequivalence testing, etc. for drugs</td>
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<td>4</td>
<td>5</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Consultation on GLP/GCP compliance (for priority reviews)</td>
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<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Consultation on document maintenance of Cell-and-tissue-based products</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
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* : including a withdrawal
The change of the consultation and notification number of GCTs

Basic principles on global Clinical Trials was published on September 28th, 2007 for helping to make a strategy and clinical trial designs for Global Drug Development.

Number of global clinical trial consultations *

Number of global clinical trial consultations/ clinical trial consultations

※ excluding consultation of prior assessment and pharmacogenomics/biomarkers

Number of global clinical trial notification

Purpose and contents of prior assessment consultation

**Purpose**

- By implementation of consultation before formal NDA
  - Shorten NDA review time
    - Identify major discussion points and tasks for NDA submission
    - Help applicant to prepare a good CTD with the inclusion of PMDA’s view points

**Consultation contents**

- Quality, Toxicity (non-clinical), Pharmacology (non-clinical), Pharmacokinetics (non-clinical), Phase I study, Phase II study

- Data evaluation before a formal NDA submission
- PMDA provides a prior-assessment report for the submitted data/study
For Prior assessment consultation

Flowchart

PMDA’s Action
- Accept tentative application
- Inform the availability
- pre-meeting (Informally)
- Accept application
- Review the documents
- Inquiry
- Review response
- Evaluation report writing
- Evaluation report

Consulters’ Action
- Tentative application
- Submit application
- Submit document
- Submit the response to inquiry
- Confirm the evaluation report

*working day

40 day*
15 day*
35 day*
30 day*
120 day*

(6 months)

15 day*
30 day*
40 day*

rough standard
### Implementation status of prior assessment consultation

<table>
<thead>
<tr>
<th>(FY)</th>
<th>Status of acceptance</th>
<th>Status of consultation (Numbers of category)</th>
<th>Status of review (Number of the ingredient)</th>
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<tr>
<td></td>
<td>Total of the ingredient</td>
<td>Total of the acceptance</td>
<td>Before consultation</td>
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<tr>
<td>2009</td>
<td>7</td>
<td>33</td>
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<tr>
<td>2010</td>
<td>9</td>
<td>30</td>
<td>2</td>
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※Data: the end of January 2011
Q: Consultation Items were resolved or cleared?

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<thead>
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<th></th>
<th>Count</th>
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<td>Resolved or Cleared</td>
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<td>Relatively cleared</td>
<td>2</td>
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<tr>
<td>Neither</td>
<td>0</td>
</tr>
<tr>
<td>Relatively Not cleared</td>
<td>0</td>
</tr>
<tr>
<td>Not resolved or Not cleared</td>
<td>0</td>
</tr>
</tbody>
</table>

Q: How can you conclude a value of the consultations?

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very useful</td>
<td>3</td>
</tr>
<tr>
<td>Useful</td>
<td>4</td>
</tr>
<tr>
<td>Neither</td>
<td>0</td>
</tr>
<tr>
<td>Not useful</td>
<td>0</td>
</tr>
</tbody>
</table>

- Generally cleared
- Found the value in the all consultations
<table>
<thead>
<tr>
<th>Q: How frequently should the application opportunity of consultations be available to apply?</th>
<th>Q: Do you think a new category (prior consultation for Phase III data) is necessary?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / year</td>
<td>0</td>
</tr>
<tr>
<td>2 / year</td>
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<td>4 / year</td>
<td>3</td>
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<tr>
<td>6 / year</td>
<td>0</td>
</tr>
<tr>
<td>Every Month</td>
<td>3</td>
</tr>
</tbody>
</table>

- Everybody hopes to increase opportunities of consultation than the present (1/year)
- Recognize a necessity of new category to cover clinical data assessment in later stage
Next steps

Further improvement through the Communicative Process

In FY2011, Prior-assessment consultation will be implemented with following improvement.

- Increased an application opportunity
  ➣ Once/year ➔ Twice/year (March & June)
- Established New Category
  ➣ Phase II/III study consultation
Many projects in PMDA support and encourage drug development for regulatory approval

PMDA would be happy to discuss what strategy/plan is the most appropriate for your drug development

PMDA will continue challenges to improve processes and promote drug development for providing effective and safe drugs quickly to patients.
Thank you for your attention!

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