Pre-consultation system at the authority for clinical trials and NDA in Japan

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Pharmaceuticals and Medical Devices Agency (PMDA)

The 6th Seminar Joint Taiwan and Japan
November 22, 2011, Taipei
Research and Development of Medicinal Products

Development State

Basic Research, etc. → Non-Clinical → Clinical Studies/ Clinical Trials → NDA → Review → Approval → Post-Marketing

Success Rate*

1 / 652,336 compounds
1 / 3,213 203 compounds
1 / 8,698 75 compounds
1 / 25,090 26 compounds
1 / 31,064 21 compounds

Documents for NDA

CMC Data → Toxicity Data → Pharmacology Data → ADME → Clinical Data → Common Technical Document (CTD)

Approval Review and GCP/GLP inspection and conformity audit at PMDA

Marketing Authorisation by Minister of Health, Labour and Welfare

Listing of Drug Price List

Post-marketing surveillance and Re-examination and Re-evaluation

Most important stage for NDA

*Source: JPMA DATA BOOK 2011

Research and Development of Medicinal Products

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*Source: JPMA DATA BOOK 2011
History of Consultation
Background

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

1. Reinforcement of consultation/guidance for Clinical trials
2. Reinforcement of approval review
3. Strengthening of post-marketing measures
4. Others
The change of the enforcement system of IND and Consultation


- Establishment of PMDEC at NIHS
- OPCS (KIKO)
- Equivalence review for generic drugs
- GCP Inspection
- Compliance audit
- Approval review
- Clinical trial notifications / review
- Clinical Trial Consultation
- Approval review
- Clinical trial notifications / review
- Clinical Trial Consultation
- Others

Clinical Trial Consultation started on April 1997
System of Consultation
Purpose of Pre-consultations

By implementation of consultation in development stage

- **Solve the issues in clinical development**
  - Secure the safety of human subjects in clinical trials
  - Shortening of the time before the application / cost reduction

- Avoid finding any critical issues on NDA review
Pre-consultation System at PMDA

IND

Non-clinical
- Healthy volunteer
- Safety
- Toxicity study
- CMC study

Pre-PI Study
- Additional

Pre-PII Study
- Additional

PIII Study
- Additional

End-of-PII
- Additional

Pre-Application
- Additional

GLP/GCP Compliance

Safety
- Additional
  (Consultation only for Toxicity and Pharmacology)

Quality
- Additional
  (Consultation only for CMC)

Procedure
  (Consultation for Pharmaceutical Affairs Procedures)

Bioequivalence testing

Document maintenance of Cell-and tissue-based products

PGx/ Biomarker

Prior Assessment Consultation
- Patients (few)
- POC
- Patients (many)
- Dose finding etc.
- Patients (many)
- RCT etc.
- Verification of Efficacy and Safety

Attached the Consultation Minutes

MHLW

April 2011

NDA

Non-clinical
- Healthy volunteer
- Safety
- Toxicity study
- CMC study
Contents of Pre-consultations

- 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

+30day
-2m
-5w
-4day
+30day
Composition of Consultation Team

**Office Director***

![Diagram showing the composition of the consultation team.](diagram)

* PMDA has 5 office for New Drug Review and 2 office for Biologic product evaluation
Scene of Face-to-face Meeting

PMDA member

Consulter’s member
### Consultation Fee

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Fee (JPY)</th>
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<tr>
<td>Consultation <strong>Pre-phase I study</strong> for drugs</td>
<td>4,239,400 (Orphan 3,186,100)</td>
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<td><strong>Pre-application</strong> consultations</td>
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Note: 1 TWD = approx. 2.7 JPY
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* : including a withdrawal
New Challenge for R & D
For Speed up of Review time

Prior Assessment Consultation
(July 2011～)

For Innovation, New Technology

Pharmaceutical Affairs Consultation on Research and Development Strategy
(April 2011～)
For Speed up of Review time

Prior Assessment Consultation
(July 2011～)

For Innovation, New Technology

Pharmaceutical Affairs Consultation on Research and Development Strategy
(April 2011～)
**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
Implementation status of prior-assessment consultation

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※Data: the end of January 2011
For Speed up of Review time

Prior Assessment Consultation
(July 2011～)

For Innovation, New Technology

Pharmaceutical Affairs Consultation on Research and Development Strategy
(April 2011～)
Policies

- New Growth Strategy (Cabinet decision in June 2010)
  (2) Health power strategy through “Life Innovation”

  Promoting research and development of innovative pharmaceuticals and medical and nursing care technologies from Japan

  We will promote research and development of highly safe, superior, and innovative pharmaceuticals and medical and nursing care technologies from Japan. We will promote unified approaches among industry, government, and academia, foster drug development ventures, and promote research, development, and application in a number of fields. These include new drugs, regenerative medicine and other state-of-the-art medical technologies, remote medical treatment systems making full use of information and communications technologies, use of manufacturing technologies to improve personal mobility for the elderly, and medical and nursing care robots. To this end, we will work to resolve the urgent drug and device lag issue, improve the clinical testing environment, and expedite drug approval decisions.
Pharmaceutical Affairs Consultation on R&D Strategy

-To accelerate the development of Japan-originated medical products-

Basic Research → Seeds Search → Seeds Improvement → Clinical Trial → Apply for product approval

(PMDA)

NEW

Pharmaceutical Affairs Consultation on R&D Strategy

Consultation on conducting clinical trials (in operation)

Necessary CTs / Drug formulation / Efficacy / Validity
The consultation fee for ventures and academia can be reduced by subsidies from GoJ

◆ Shorten duration of collecting data for application
◆ Improve the success rate

◆ Creation of innovative medical product

Accelerate the development for Japan-originated medical products
再生医療用iPS細胞バンク構築に向けた薬事戦略相談を開始

京都大学iPS細胞研究所（CiRA）は、再生医療用iPS細胞バンクの構築準備を進めていますが、規制科学部門の木村啓文教授、青井哲之教授と篠原伸太郎研究員が中心になり、このほど、医薬品医療機器総合機構（PMDA）（注1）との薬事戦略相談（注2）における対面助言を開始し、iPS細胞バンク構築に向けた規制的課題を克服するための第1歩を踏み出しました。

CiRAは、細胞移植治療に用いることのできるiPS細胞バンクの構築を目指し、細胞のHLA型（注3）のうち、他のHLA型との相関反応が低い3種（HLA-A、HLA-B、HLA-DR）ホモ接合型を持つ人からのiPS細胞をバンク化する計画を進めています。このように様々な移植適応型が希望の細胞から作製した「再生医療用iPS細胞バンク」を構築することにより、品質の保証されたiPS細胞及びiPS細胞から作製した移植用細胞をあらかじめ準備しておくことができ、個々の患者さんからiPS細胞を製造する必要がなくなります。これによって、移植細胞を準備する期間の大幅な短縮や、患者さん1人あたりにかかる費用の削減に貢献し、より多くの難治性疾患や急性期の傷病の治療に対する再生医療を実現することが可能となります。
Targets: To reduce the “drug lag” by a total of 2.5 years

**Measures by PMDA for eliminating drug lag**

### Targets (by 2011)
- 1.5 year reduction of development time
- 1.0 year reduction of approval review time

### Measures for development time

**Expansion of the Consulting Service**
- Increase the number of staff 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 the pre-application consultations

**Clarify the review criteria**
- Further promote Global Clinical Trials
- Draft a guideline on cutting-edge technologies

### Measures for approval review time

**Expansion of the Review System**
- Increase the number of staff
- Give adequate training

**Enhancement and improvement of the Review System**
- **Introduce a prior assessment**, and reduce applicant workload.
- Improve productivity of reviews through measures such as the standardization and Streamlining of the review process

**Liaise more closely with the FDA and other overseas regulatory authorities**
PMDA website

<English version>
http://www.pmda.go.jp/english/service/outline_s.html

<Japanese version>
http://www.pmda.go.jp/operations/shonin/info/consult/iyakuheitaimen.html
Thank you for your attention!