The challenge about the research and development for medical innovation

国際シンポジウム
「医療分野における研究開発に関する
新たな取り組み」

August 18th, 2015

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Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
1. Current situation of New Drug Development

2. Regulatory Authorities’ Challenge for Medical Innovation (EMA, FDA, PMDA)

3. MHLW’s Measures for Medical Innovation
   1) SAKIGAKE Designation
   2) CIN(Clinical Innovation Network)
   3) RSI(Regulatory Science Initiative)
When Pfizer announced that it was halting clinical testing of its new cholesterol drug, torcetrapib, the company’s market value fell by $21 billion overnight. Ten thousand job cuts followed. The ongoing promise of nearly $3 billion in annual sales vanished when Merck pulled Vioxx (rofecoxib) from the shelves, and the company’s market value fell by $25 billion. For decades, blockbuster drugs have nourished Big Pharma, but it is increasingly uncertain whether they can be counted on to support the industry in the future.
A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.


Comments open through March 4, 2015

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015

President Obama has long expressed a strong conviction that science offers great potential for improving health. Now, the President has announced a research initiative that aims to accelerate progress toward a new era of precision medicine (www.whitehouse.gov/precisionmedicine). We believe that the time is right for this visionary initiative, and the National
Cost of Developing a New Drug

November 18, 2014

The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is:

$2,558 million
The most expensive step in creating a new drug is conducting clinical trials. Conducting a trial costs $25,000 or more per patient studied, and phase 3 trial programs consume more than 40% of a sponsoring company’s expenditures.

Unfortunately, every patient is not equally valuable when it comes to clinical trials, and many clinical development programs are economically inefficient in that they are excessively large relative to the amount of information they yield, especially in light of the information-technology breakthroughs that have lowered the cost of data acquisition and analysis over the past 20 years.
The randomized registry trial represents a disruptive technology, a technology that transforms existing standards, procedures, and cost structures.
**Surprising low-cost clinical research!!**

The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was $300,000, or $50 for each participant who underwent randomization.

PMDA’s challenge and performance
New drug approvals in ICH countries 2005 – 2014

R&D Briefing 57, July 2015, © Centre for Innovation in Regulatory Science, Ltd.

New active substance (NAS) approval time by approval year

Note: The EMA approval time includes the EU Commission time.

High performance in amount of business

Figure 1: Number of NASs approved by ICH agencies by approval year

High performance at review speed

Figure 2: Median approval time for NASs approved by ICH agencies by approval year

Note: The EMA approval time includes the EU Commission time

Advanced Review with Electronic Data

Analysis by PMDA
- Giving additional scientific value to submitted data

Cooperation with Academia
- More rational & effective evaluation process for regulatory decision

Regulatory Science

Practical use of Innovative Medical Products
- More rational & effective evaluation process for regulatory decision

Sophisticated review
- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis
- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - Disease model
  - Objective B/R assessment
  - Identifying AE-related factors etc.

Sophisticated Consultation
- More evidence-based consultation

More effective and high quality Review
- More predictable efficacy/safety after approval
- Reduction of applicant’s workload
- More scientific regulatory decision

More efficient and Successful Development
- Epoch-making proposal leading the world
- Proactive publication of guideline
MHLW’s Measures for Innovation
SAKIGAKE Designation
SAKIGAKE Designation System

**SAKIGAKE** is a strategy to put innovative medicines/medical devices/regenerative medicines into practice.

### Designation Criteria

Medical products for diseases in dire need of innovative therapy and satisfies the following two conditions:

1. Applied for approvals firstly in Japan or simultaneously in Japan and other countries (desirable to have PMDA consultation from the beginning of R&D)
2. Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action from non-clinical study and early phase of clinical trials (phase I to II)

### Designation Advantage

<table>
<thead>
<tr>
<th>① Prioritized Consultation</th>
<th>② Substantial Pre-application Consultation</th>
<th>③ Prioritized Review</th>
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<tbody>
<tr>
<td>[Waiting time: 2 months → 1 month]</td>
<td>[de facto review before application]</td>
<td>[12 months → 6 months]</td>
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<tr>
<td>Shortening a waiting time for a clinical trial consultation from the submission of materials.</td>
<td>Accepting materials in English</td>
<td>Striving to conclude review within 6 months</td>
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<tr>
<td>* Accept the result of phase III study after the application on a case-by-case basis to shorten the time from R&amp;D to approval</td>
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<tr>
<th>④ Review Partner</th>
<th>⑤ Substantial Post-Marketing Safety Measures</th>
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<tr>
<td>[PMDA manager as a concierge]</td>
<td>[Extension of re-examination period]</td>
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<tr>
<td>Assign a manager as a concierge to take on overall management for the whole process toward approval including conformity assurance, quality management, safety measures, and review</td>
<td>Strengthening post-marketing safety measures such as extension of re-examination period as well as facilitating coalition with scientific societies, and transmission of information globally.</td>
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### Designation Procedure

1. **Initiation by applicant**: Application is to be submitted to the Evaluation and Licensing Division (ELD) and to be reviewed at the PMDA. The result is to be notified within 60 days.
2. **Initiation by the ELD**: the ELD is to approach a potential applicant. The result is to be notified within 30 days after the submission, if agreed by the applicant.
Notification about Sakigake (No. 0401-6, April 1, 2015)

薬食審査発 0401 第 6 号
平成 27 年 4 月 1 日

各都道府県衛生主管部（局）長 殿

厚生労働省薬食品局審査管理課長
（公印 省略）

先駆け審査指定制度の試行的実施について

先駆け審査指定制度については、「日本再興戦略」改訂 2014（平成 26 年 6 月 24 日閣議決定）及び「先駆けパッケージ戦略」（平成 26 年 6 月 17 日厚生労働省取りまとめ）において、世界に先駆けて、革新的医薬品・医療機器・再生医療等製品を日本で早期に実用化すべく、その開発を促進するため、「既存の治療法より大幅な改善が期待されるものを指定し、相談・審査における優先的な取扱いの対象とすることで更なる迅速な実用化を目指す」こととしたところであるが、本日より、試行的運用として、まずは医薬品について下記の通り実施することとしたので貴管下関係業者に対して周知願いたい。
The notification is made public to the start in 2015 fiscal year, and it advertises for the candidate products after a well-known period of about one month.

**Step 1: Trial operation beginning and public advertisement**

- The Evaluation and Licensing Division conducts hearing on the candidate products to be applied, and the potential candidates meeting specified criteria are selected as candidates of the preparatory phase.

**Step 2: Hearing and preliminary selection on candidate products**

- The New Drug Review Division of PMDA evaluates the applied products on each area in charge, and it sets priorities. Especially, the products judged to be excellent are selected.

**Step 3: Evaluation and prioritization**

- Excellent products are specified as SAKIGAKE designated products based on the evaluation results, and the designation results are made public. The MHLW promptly reports the designation results to the Pharmaceutical Affairs and Food Sanitation Council.
Clinical Innovation Network (CIN)
Clinical Innovation Network (CIN)  
(Improvement of Infrastructure for Clinical Study with Disease Registry)

**[Background]**
- Cost of developing a new drug or other medical products is rising over the world, especially in Japan compared to other countries.
- Recently, new approaches for clinical study with disease registry has been highly interesting.

**Brief overview of CIN**
- The clinical study infrastructure in Japan is improved so that cost effective clinical studies are performed with disease registries, based on Regulatory Science. The improvement will accelerate clinical studies in Japan by entities in the world, which would result in the contribution to healthy life expectancy for people.
- CIN will also support for marketing in Asia of medical products developed in Japan.

- Acceleration of global clinical trials
- Asian Regulatory Training center
- Development of registries for patients with intractable diseases
- Rare diseases drug development Gateway
- Development of disease registries
- Foundation of a clinical trial consortium, acceleration of clinical studies
- Advancement of regenerative medicine clinical studies
- Establishment of a Clinical Trial Cooperation Office

**National Center, Clinical Research Core Hospital**
- Demographics
- Therapy
- Complication
- Adverse effect
- Prognosis
- Research for method to utilize disease registry in clinical study (Regulatory Science)

**PMDA**
- Jurisdiction: MHLW

**AMED**
- Jurisdiction: CAO, MEXT, MHLW, METI

**Industry**
- Utilizes data in clinical studies
- Performs clinical studies quickly and cost-effectively
- Support for R&D
- Human resource cultivation in the clinical research and trial field

**CIN Promotion Conference**
- Composed of stakeholders, including National Centers, Industries and Japanese Government; and promotes the CIN project.
Regulatory Science Initiative (RSI)
### Regulatory Science Initiative (RSI)

#### Objective
- Actively contribute to the international regulatory harmonization and cooperation by introducing Japan’s knowledge on Pharmaceutical Regulations (Regulatory Science) to Asia and to the world
- Contribute to improving health and sanitation among the international society for solving the drug/device lag in the world
- Activate pharmaceutical and medical device industry by attracting investment in Japan and increasing export of superior products

Development of “Harmonization Strategy on International Pharmaceutical Regulation” which clarifies mid-long term vision and priority of its measures on international regulatory harmonization and cooperation

#### Current Status in Japan

**Advantages**
- National health insurance system: Prompt reimbursement, High possibility of clinical data collection
- Improvement of PMDA structure: Improvement of the predictability and speed of product approval
- World’s highest level of medical technology and science: Technological basis to accelerate first-in-the-world development of pharmaceuticals and medical devices

**Issues**
- Low incentives of investment in product development due to smaller market size than in US (Japan holds only 10% of world market while US holds 40%) and higher cost of clinical trials resulting from smaller size of hospitals
- Low capacity of information provision on Japanese pharmaceutical regulations, know-how, and techniques, and weak system of MHLW and PMDA to deal with international affairs

#### Possible Measures

- **In Japan**
  - Proactively promote regulatory science in order to approve innovative pharmaceuticals and medical devices first-in-the-world in Japan.
  - Establish the “Training center for pharmaceuticals and medical devices regulatory affairs” within PMDA

- **In overseas**
  - Clarify the priority of future measures from the following viewpoints:
    - Characteristics of each product (pharmaceuticals, medical devices, cellular and tissue-based products)
    - Framework of international harmonization and current status of bi-lateral cooperation in each area, etc
Thank you for your attention!