Measures for enhancing new drug development by Ministry of Health, Labour and Welfare

Hiroshi Chimura

Research and Development Division, Ministry of Health, Labour & Welfare
Japan’s Potential
Japanese pharmaceutical R&D ability

Origins of the medicine that ranked within world top 100


2004

USA 39
Japan 13
UK 14
Switzerland 12
France 5
Germany 3
Denmark 3
Sweden 3
Others 3

2007

USA 41
Japan 11
UK 12
Switzerland 7
French 5
Germany 5
Denmark 3
Sweden 2
Belgium 2
Others 2

Japanese R&D ability is the 3rd in the world!!

Source: Office of Pharmaceutical Industry Research (OPIR), based on the data from IMS LifeCycle (IMS Health) and Pharmaprojects
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## Trend of medical research

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>USA</td>
<td>1st</td>
<td>3097</td>
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<tr>
<td></td>
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<td>3314</td>
</tr>
<tr>
<td>UK</td>
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<td>365</td>
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<tr>
<td></td>
<td>2nd</td>
<td>920</td>
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<tr>
<td>Germany</td>
<td>2nd</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>511</td>
</tr>
<tr>
<td>Japan</td>
<td>6th</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>122</td>
</tr>
<tr>
<td>South Korea</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>China</td>
<td>—</td>
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<tr>
<td></td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Source: OPIR News No.25 (2008)*
Increasing trend of excellence in basic medical science.

Time to promote clinical application more!

Source: NISTEP
Clinical Trial Trends
Trend of dependency on foreign clinical trials

(Japanese company sponsor basis)

Japan Priority
Japan/Foreign
Foreign Priority

OPIR News No.22 (2007)
Volume of ongoing clinical trials in Asia Pacific region


Data provided by Dr M.L. Chu, CDE, Taipei
Number of IND notifications

Source: MHLW

- First IND Notification
- IND Notification

New GCP publication
New GCP enforcement
ICH E5

- 3-Years Clinical Trial Activation Plan (prolonged 1 year)
- New 5-Years Clinical Trial Activation Plan

Number of IND notifications:

<table>
<thead>
<tr>
<th>Year</th>
<th>First IND</th>
<th>IND</th>
</tr>
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<tbody>
<tr>
<td>2000</td>
<td>722</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>406</td>
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<tr>
<td>2003</td>
<td>391</td>
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<tr>
<td>2004</td>
<td>463</td>
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<tr>
<td>2005</td>
<td>424</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>414</td>
<td></td>
</tr>
</tbody>
</table>

- FY 1996: 95
- FY 1997: 71
- FY 1998: 54
- FY 1999: 52
- FY 2000: 63
- FY 2001: 43
- FY 2002: 60
- FY 2003: 60
- FY 2004: 56
- FY 2005: 96
- FY 2006: 105
- FY 2007: 107
- FY 2008: 109
Increasing trend toward multi-regional trials

PMDA’s trial consultation basis

As of Apr. 27, 2009
(The figure in FY2008 is not fixed.)

Source: PMDA
<table>
<thead>
<tr>
<th></th>
<th>① Total INDs (first time + n times)</th>
<th>② INDs of multi-regional trials</th>
<th>③ Ratio (②/①)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2007</td>
<td>508</td>
<td>38</td>
<td>7.5%</td>
</tr>
<tr>
<td>FY 2008</td>
<td>525</td>
<td>82</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

Tend to be a lot of notifications in oncology
Increasing trend toward multi-regional trials

**EFPIA data**

- **2004**
  - Multi-regional trials: 3
  - Domestic trials: 56

- **2005**
  - Multi-regional trials: 5
  - Domestic trials: 45

- **2007**
  - Multi-regional trials: 11
  - Domestic trials: 56

**PhRMA data**

- **2006.5**
  - Finished: 3
  - In trial: 3
  - Under consideration: 5

- **2006.9**
  - Finished: 4
  - In trial: 6
  - Under consideration: 10

- **2007.4**
  - Finished: 4
  - In trial: 12
  - Under consideration: 17

- **2007.11**
  - Finished: 9
  - In trial: 17
  - Under consideration: 27
# Ranking of number of multi-regional trial sites

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country / Region</th>
<th>Rank</th>
<th>Country / Region</th>
<th>Rank</th>
<th>Country / Region</th>
<th>Rank</th>
<th>Country / Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
<td>16</td>
<td>Hungary</td>
<td>31</td>
<td>Slovakia</td>
<td>46</td>
<td>Estonia</td>
</tr>
<tr>
<td>2</td>
<td>Germany</td>
<td>17</td>
<td>India</td>
<td>32</td>
<td>Greece</td>
<td>47</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>3</td>
<td>Canada</td>
<td>18</td>
<td>Mexico</td>
<td>33</td>
<td>Switzerland</td>
<td>48</td>
<td>Latvia</td>
</tr>
<tr>
<td>4</td>
<td>France</td>
<td>19</td>
<td>South Africa</td>
<td>34</td>
<td>Japan</td>
<td>49</td>
<td>Malaysia</td>
</tr>
<tr>
<td>5</td>
<td>Spain</td>
<td>20</td>
<td>Sweden</td>
<td>35</td>
<td>Portugal</td>
<td>50</td>
<td>Ireland</td>
</tr>
<tr>
<td>6</td>
<td>Italy</td>
<td>21</td>
<td>Denmark</td>
<td>36</td>
<td>Bulgaria</td>
<td>51</td>
<td>Singapore</td>
</tr>
<tr>
<td>7</td>
<td>UK</td>
<td>22</td>
<td>Austria</td>
<td>37</td>
<td>Chile</td>
<td>52</td>
<td>Croatia</td>
</tr>
<tr>
<td>8</td>
<td>Poland</td>
<td>23</td>
<td>Ukraine</td>
<td>38</td>
<td>Turkey</td>
<td>53</td>
<td>Slovene</td>
</tr>
<tr>
<td>9</td>
<td>Australia</td>
<td>24</td>
<td>Finland</td>
<td>39</td>
<td>Philippines</td>
<td>54</td>
<td>Costa Rica</td>
</tr>
<tr>
<td>10</td>
<td>Russia</td>
<td>25</td>
<td>Norway</td>
<td>40</td>
<td>Puerto Rico</td>
<td>55</td>
<td>Indonesia</td>
</tr>
<tr>
<td>11</td>
<td>Belgium</td>
<td>26</td>
<td>Israel</td>
<td>41</td>
<td>Peru</td>
<td>56</td>
<td>Pakistan</td>
</tr>
<tr>
<td>12</td>
<td>Holland</td>
<td>27</td>
<td>Korea</td>
<td>42</td>
<td>Lithuania</td>
<td>57</td>
<td>Serbia</td>
</tr>
<tr>
<td>13</td>
<td>Argentina</td>
<td>28</td>
<td>China</td>
<td>43</td>
<td>Colombia</td>
<td>58</td>
<td>Guatemala</td>
</tr>
<tr>
<td>14</td>
<td>Czech</td>
<td>29</td>
<td>Taiwan</td>
<td>44</td>
<td>New Zealand</td>
<td>59</td>
<td>Venezuela</td>
</tr>
<tr>
<td>15</td>
<td>Brazil</td>
<td>30</td>
<td>Romania</td>
<td>45</td>
<td>Thailand</td>
<td>60</td>
<td>Tunisia</td>
</tr>
</tbody>
</table>

Source: OPIR News No.26 (2008)
When to start international multi-regional trials?

- As early as possible in the clinical development to see ethnic similarity/difference
Roles of academic research organisation

1. International core research center of innovative medicine

2. International core center to support innovation
   - Manage international trials
   - Develop scientific method to evaluate efficacy & safety
   - Put clinical trial infrastructure in place

3. Collaboration to develop guidance
   - Regulatory scientific development with industry and regulators
   - Expert advice to company and regulator

4. Training provision
   - Human resource development for clinical trials
   - Human resource development for regulation, such as for PMDA
Where are we in multi-regional trial environment?

Intra-Asian network and inter-regional network model
Japan’s Policies
MHLW started the Ministers–Industry meeting for promoting communication for creation of innovative drugs and medical devices between public and private sectors.

Participants:

The Minister of Cabinet Office
The Minister of Education, Culture, Sports, Science and Technology
The Minister of Health, Labour and Welfare
The Minister of Economy, Trade and Industry

Pharmaceutical Industry CEOs
Medical Device Industry CEOs

Presidents of Medical Universities and Medical Institutions
Outline of 5-year Strategy for Creating Innovative Medicines and Medical Devices

Cabinet Office / MEXT / MHLW / METI

- Intensive research funding
- Venture enterprises promotion
- Improve clinical research/trial environment
- Asian cooperation
- Improve review
- Appropriate evaluation of innovation
- Public-private dialogue

Provide public with medicine and medical devices of the highest global standards
Pharmaceutical and medical device industry as an engine for Japan's growth
Strategic group for advanced development in Japan and Japanese participation in simultaneous global development

Strengthen cooperation among related ministries, research institutes and industry
Budget in FY2009 for the 5-year Strategy

(1) Intensive research funding
69.73B¥ (69.64B¥)
- MEXT 43.44B¥ (43.67B¥)
- MHLW 16.89B¥ (16.36B¥)
- METI 9.40B¥ (96.1B¥)

(2) Venture enterprises promotion
4.81B¥ (4.50B¥)
- MHLW 1.51B¥ (1.90B¥)
- METI 3.30B¥ (2.60B¥)

(3) Improve clinical research/trial environment
15.62B¥ (14.52B¥)
- MEXT 4.59B¥ (3.66B¥)
- MHLW 7.73B¥ (8.26B¥)
- METI 3.30B¥ (2.60B¥)

(4) Asian cooperation
0.23B¥ (0.05B¥)
- MHLW 0.23B¥ (0.05B¥)

(5) Improve review
0.75B¥ (0.85B¥)
- MHLW 0.70B¥ (0.79B¥)
- METI 0.05B¥ (0.06B¥)

(6) Appropriate evaluation of innovation

(7) Public-private dialogue

Budget in FY 2009 : 87.9 B¥ approx. 879 M$
(FY 2008 : 87.0B¥ / approx. 870M$)
Super Special Consortia
for Supporting Development of Cutting-edge Medical Care

Promotes efficient developments of relevant researches by connecting researchers
Coverage: iPS cell applications, regenerative medicines, innovative medical devices, innovative bio-tech. pharmaceuticals, other concerns

Effective use of funds
Promotion of research and development
Consultation with regulatory authorities in early phase

Provides cutting-edge medical care to the public rapidly

5-year Strategy for Creating Innovative Medicines and Medical Devices
Suggested by the Council on Economic and Fiscal Policy in March 2008

24 projects are adopted in Nov. 2008
# New 5-Years Clinical Trial Activation Plan

**MEXT / MHLW**  
March 2007

<table>
<thead>
<tr>
<th>(1) Clinical Research Infrastructure Building</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ 10 core clinical research centers that are able to plan and manage multi-centered trials</td>
</tr>
<tr>
<td>➢ 30 major clinical trial institutions that are able to perform trials smoothly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(2) Human Resource Development for Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Training provision for MDs, CRCs, Bio-statisticians, Data managers, etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(3) Facilitate Patients’ Participation in Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Provide public with relevant information</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(4) Improve Efficiency in Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Harmonize format of administrative documents</td>
</tr>
<tr>
<td>➢ Streamline administrative work share between hospitals and sponsors</td>
</tr>
<tr>
<td>➢ Improve transparency of hospitals’ research capacity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(5) Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Review GCP Ordinance and Clinical Research Guideline for international harmonization and patient protection</td>
</tr>
</tbody>
</table>
Expected goals of the 5-years plan

① Improve **cost, speed and quality** of clinical trials

② Improve **number of multi-regional trials**

③ Secure provision of high quality innovative medicine and **enable patients to enroll trials safely**
Assign 10 core clinical research centers (Cores) and 30 majors clinical trial institutions (Majors) to intensify technologies and to train staff.

In collaboration with 9 TR centers designated by MEXT, create nation wide network to perform trials efficiently and rapidly.

Assess performances to evaluate improvement in performances over 5 years period (examples)

- Period of administrative procedure
- Cost to be paid based on contract
- IT platform for CRF
- Common Document format introduction
- Number of clinical papers
- Number of visit required for sponsor to contract
Network of clinical research centers

Institutional reinforcement of staff and IT environment to support trials

Build site networking to accumulate subjects → cost down and speed-up

Alliance with related trial sites and accumulate trial subjects

10 Core clinical research centers

Total 1,000MY / year (approx. 10M$ / year)

- Train human resources in-house and in the institutions in the network
- Strengthen IRB capacity
- Consolidate data management system
- Plan, Do, Assess clinical research

30 Major clinical trial institutions

Total 750MY / year (approx. 7.5M$ / year)

- Secure Recruiting CRCs and other trial supporting staff
- Support promotion of common IT plat home

Expeditie trial performance

Ensure timely access to new drug from clinical trial stage (satisfy unmet needs)

Promote innovation of new drug

Infrastructure improvement
Nationwide network of Cores, Majors and TR centers

Core is able to plan and manage multi-centered trials (MHLW)

- Core clinical research centers [10]
- Major clinical trial institutions [30]
- TR centers [9]

Major is a core center to perform trials smoothly (MHLW)

TR center is to translate basic medical research to clinical trial (MEXT)

Local-area clinical trial network
Global core research center for clinical trial

[Goal]
Reinforcement of clinical trial institutions in Japan and promotion of simultaneous global development of innovative drugs

Function
- Management of international trials
- Central IRB
- Planning and analysis of international trials
- Human resource
- Training of doctors and CRC
- Data management

Budget in FY 2009: 400M¥ (approx. 4M$)
Progress of New 5-Years Clinical Trial Activation Plan
August 1, 2009

(1) Clinical Research Infrastructure Building
- Designated cores and majors. Set up the Conference of Clinical Research Institutions to promote communication and consolidation among cores, majors and other related organizations. Conducted the survey on performance of cores and majors in 2007, etc.

(2) Human Resource Development for Clinical Research
- Provided training programs for CRCs (basic, advanced), Local Data Managers and IRB Members, etc.

(3) Facilitate Patients’ Participation in Trials
- Started operation of Japan Clinical Trial Information Registry Search Portal Site http://rctportal.niph.go.jp/
- Japan Primary Registries Network has been approved as a WHO Primary Registry.
- JPMA’s campaign on clinical trial promotion: “Good Communication ’08-’09”, etc.

(4) Improve Efficiency in Clinical Research
- Developed common format of administrative documents
- Working team of IT on clinical trials to be formed, etc.

(5) Others
- Amended GCP Ordinance has been enforced on Apr. 2008 and Apr. 2009
- Amended Clinical Research Ethical Guideline has been enforced on Apr. 2009, etc.
## Training programs (FY 2008)

<table>
<thead>
<tr>
<th>Course</th>
<th>Term</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRCs (basic)</td>
<td>Lecture (one week) + practical training (one or three weeks) 97 students (in Tokyo)</td>
<td>Pharmaceutical Affairs Law (GCP), basic knowledge on clinical trials, informed consent, etc.</td>
</tr>
<tr>
<td>Local data manager</td>
<td>Lecture (two days): added on the basic CRCs course. 65 students (in Tokyo)</td>
<td>Function, Practice, Basic knowledge of biostatistics, Management tools (incl. practical training), etc.</td>
</tr>
<tr>
<td>CRCs (senior)</td>
<td>Lecture (two days) 45 students (in Osaka) 64 students (in Tokyo)</td>
<td>Latest GCP regulation, multi-regional trials, investigator initiated trials Education etc. (incl. group discussion)</td>
</tr>
<tr>
<td>IRB members</td>
<td>Lecture (one day) 93 students (in Tokyo)</td>
<td>Board member's function, review points, mock IRB training, etc.</td>
</tr>
</tbody>
</table>
Provision of information

MHLW clinical trials website

Portal site of clinical trials registration
1. Keep public well informed
2. Avoid publication bias
3. Utilize negative data
4. Promote subject recruitment

Since Oct. 2007

Public

MHLW

UMIN Clinical Trial Registry

JMA Center for Clinical Trials

JAPIC Trial Information System

Investigator or company

Portal site management
Promotion
Coordination of 3 sites
Coordination with WHO

http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/

http://www.umin.ac.jp/ctr/index-j.htm

https://dbcence2.jmacct.med.or.jp/ctrialr/

http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/

http://www.clinicaltrials.jp/

Japan Primary Registries Network as a WHO primary registry

http://www.umin.ac.jp/ctr/index-j.htm

https://dbcence2.jmacct.med.or.jp/ctrialr/

http://www.clinicaltrials.jp/

http://www.umin.ac.jp/ctr/index-j.htm

https://dbcence2.jmacct.med.or.jp/ctrialr/

http://www.clinicaltrials.jp/

http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/

http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/

http://www.clinicaltrials.jp/
JPRN approved as a primary registry by WHO

Press Release on October 16, 2008

<table>
<thead>
<tr>
<th>Registry Network</th>
<th>View Profile</th>
<th>Go to Website</th>
</tr>
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<tbody>
<tr>
<td>Japan Primary Registries Network</td>
<td>View Profile</td>
<td>Go to Website (in Japanese)</td>
</tr>
<tr>
<td>Network members:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go to UMIN Website</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go to JapnICCTI Website</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go to JMACCT Website</td>
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</tr>
</tbody>
</table>

WHO Primary Registries meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. WHO Primary Registries meet the requirements of the ICMJE.
Intending schedule of the 5-years plan

FY 2007
1st year
Adopted Cores and Majors
Set up Conference of Cores, Majors and TR centers
Baseline surveillance

FY 2008
2nd year
Surveillance of performances (on FY 2007 action)

FY 2009
3rd year (midterm)
Surveillance of performances (on FY 2008 action)

FY 2010
4th year

FY 2011
5th year (final year)
Objective
Establish nation wide framework that is able to facilitate clinical trials.

Midterm Review
Midterm review of the 5-years plan

Visualization of the final goal

① Improve **cost, speed and quality** of clinical trials

② Improve **number of multi-regional trials**

③ Secure provision of high quality innovative medicine and **enable patient to enroll a trial safely**

(Identifying problems and bringing them to the foreground)