Clinical Trial Environment in Japan

Expectations of sponsors to medical institutions

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Agenda

◆ Current status of new drug development in Japan.
✓ Drug lag and steps for its reduction
◆ Diagnosis of strengths and weaknesses of clinical trial implementation environment in Japan
✓ The R&D Head Club Survey on performance and costs of clinical trials
◆ Expectations and recommendations from sponsors to clinical trial sites for improvement of environment for clinical trials
Drug lag in Japan

Drug lag = delay of initiation of clinical trials + difference of development periods + difference of approval periods

<table>
<thead>
<tr>
<th>Difference of Starting Clinical Periods</th>
<th>Domestic Period of Clinical Development</th>
<th>Drug Lag</th>
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<tbody>
<tr>
<td>US: 1.9 years (0.5, 4.2)</td>
<td>Domestic approval: 1.8 years (1.2-2.3)</td>
<td>The US/Europe period of clinical development</td>
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<tr>
<td>Europe: 2.7 years (1.4, 4.9)</td>
<td></td>
<td>3.8 years (2.0, 6.3)</td>
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</tbody>
</table>

- The US: 4.5 years (2.8, 7.0) 1.1 year (0.8, 1.9) 3.8 years (2.0, 6.3)
- Europe: 5.3 years (3.7, 6.8) 1.1 year (0.7, 1.4) 4.3 years (2.6, 6.3)

→ Market Introduction to Japan is delayed 4 years vs. Europe and US

Steps for reduction of drug lag

Report" Discussion for rapid market introduction of effective and safe drugs”-July 27 2007

Reduction of 2.5 years between the period of development and approval of new drug (drug lag becomes reduced to the same level as Europe and the US)

Implementation of appropriate clinical trials and approval tests for each drug

①Steps for early initiation of clinical trials
②Steps to reduce implementation period of clinical trials
③Steps to reduce the approval period

- Promotion of global clinical trials, consultation of cooperative clinical trials between Japan and US regulators, use of Asian clinical trials
- Revision of regulation regarding clinical trials such as GCP
- Disclosure of information related to clinical trials
Engagement of MHLW-Five year action plan for revitalization of clinical trials

Expectation for revitalization of clinical trials

◆ Goals:
✓ Provide high quality, cutting-edge health care
✓ Ensure the effective structure of clinical research and trials for medicines and devices which will be the foundation of international competitiveness.

◆ Expectation of clinical trials and research enforced by five years plan
✓ Improved cost, speed, and quality of clinical trials to the level of US and Europe
✓ Larger number of simultaneous clinical trials, like in other Asian countries
✓ Establishment of quality health care and the structure for the safe conduction of clinical trials and research.
Internal activities of pharmaceutical companies to promote global clinical trials

- Changes in Organization of process and structure
  - Process for portfolio review and development strategy
  - R & R between different countries and groups
  - Use of global SOPs and standard tools (IVRS, eDC, Central-Lab, Clinical database, Tracking system)
  - Improvement of efficiency and flexibility
  - Consider implications for post-marketing phase.
- Improvement of skills
  - Training of staff for global simultaneous trials and overseas experience.
  - English language skills and project management skills
- Mindset change of employees
  - Motivation for change management of employees
  - Understanding and acceptance of diversity
Diagnosis of strengths and weaknesses of clinical trial implementation environment in Japan

– The R&D Head Club Survey on performance and costs of clinical trials
R&D Head Club Cost Survey
-Survey for performance and costs of clinical trials in Japan

- **Participants:** 18 pharmaceutical companies
- **Survey period:** Every year from 2004
- **Subject:** Phase 2 and 3 trials which have been completed on the previous year
- **Elements of survey:** Information of clinical trials, cycle time, speed, costs, and monitoring
- **2007 survey:** Included an analysis of all trials in the database, according to their start date (99-01, 02-03, 04-05)
- **2008 survey:** Preliminary results available
Conclusions from 2007 RDHC Survey

R&D Heads Club 2007. Comparison of trials started in 3 periods (99-01, 02-03, 04-05)

<table>
<thead>
<tr>
<th>RDHC cost survey factors</th>
<th>change from previous year</th>
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<tbody>
<tr>
<td>Speed: Cycle time</td>
<td>Reduce</td>
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<tr>
<td>Enrollment of subjects:</td>
<td>Improved</td>
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<tr>
<td>Registration rate</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Number of cases per site</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Costs of clinical trials: Total trial costs, SMO costs</td>
<td>Unchanged</td>
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<tr>
<td>Monitoring productivity:</td>
<td>Number of sites and cases per monitor</td>
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What shall be improved in Japan to successfully implement simultaneous clinical trials?

Important actions
Enrollment of subjects
Conclusions from 2007 Survey

R&D Heads Club 2007. Comparison of trials started in 3 periods (99-01, 02-03, 04-05)

◆ Number of enrolled subjects per site
  • Total average 7.6 → 7.4 → 9.8 cases
  • Number at Clinics increased 10.2 → 12.8 → 14.8
  • Average number at Public and University Hospitals is 5 and at Private Hospitals is 9 (no change)
  • Average number of cases per site is smaller than in Asia, the US and Europe.

◆ Achievement rate (comparing with the first contract cases):
  • Implementation rate remains around 70 % regardless of type of site and period
2008 Survey: Number of Enrolled Patients by the Type of Site

2008

- National/Public U. (84)
  - Contracted: 6.1
  - Enrolled: 4.6
  - Entered: 3.7

- Private U. (78)
  - Contracted: 7.3
  - Enrolled: 6.3
  - Entered: 4.6

- National HP (58)
  - Contracted: 8.2
  - Enrolled: 7.5
  - Entered: 6.5

- Public HP (107)
  - Contracted: 8.0
  - Enrolled: 7.7
  - Entered: 6.5

- Private HP (327)
  - Contracted: 9.0
  - Enrolled: 8.2
  - Entered: 6.6

- Clinic (452)
  - Contracted: 10.6
  - Enrolled: 8.1
  - Entered: 6.8

- ALL (1106)
  - Contracted: 10.3
  - Enrolled: 8.5
  - Entered: 6.8

(# of sites)

Average patients

- Contracted
- Enrolled
- Entered
Cycle time and efficiency
Conclusions from 2007 Survey

R&D Heads Club 2007. Comparison of trials started in 3 periods (99-01, 02-03, 04-05)

◆ Period from “Trial application-FPI” has been reduced more than 40 days
◆ Period from “LPV-Data lock” has been reduced 3 months
◆ The speed in these periods is now generally competitive with global standards
◆ Number of sites per monitor is reduced to 3.9→2.5→2.4
◆ Number of cases per monitor is reduced to 31.5→18.9→22.9 every year.
◆ While the speed has improved, efficiency of monitoring has decreased.

**2007**
- **Non EDC** (700)
  - Protocol fix - Trial application: 58
  - Trial application - IRB: 2018
  - IRB - Contract: 30
  - Contract - Drug setting: 57
  - Drug setting - FPI: 183
  - FPI - LPI: 86

- **EDC** (23)
  - Protocol fix - Trial application: 321
  - Trial application - IRB: 11
  - IRB - Contract: 132
  - Contract - Drug setting: 134
  - Drug setting - FPI: 268
  - FPI - LPI: 52

**2008**
- **Non EDC** (669)
  - Protocol fix - Trial application: 58
  - Trial application - IRB: 1716
  - IRB - Contract: 31
  - Contract - Drug setting: 40
  - Drug setting - FPI: 145
  - FPI - LPI: 83

- **EDC** (251)
  - Protocol fix - Trial application: 66
  - Trial application - IRB: 131
  - IRB - Contract: 69
  - Contract - Drug setting: 36
  - Drug setting - FPI: 137
  - FPI - LPI: 59
Clinical trials costs
Conclusions from 2007 Survey

◆ The average cost at sites supported by CRC from SMO is 3.3 million yen per case.
◆ This cost is higher by one million yen than the sites fully supported by SMO and the sites not supported by SMO.
◆ The sites with achievement rate lower than 50% have twice the cost than the sites with higher than 80% achievement.
◆ The proportion of sites which require R&D costs in advance / no refund is 27.3%, which is slightly higher than the previous year.
◆ National Universities and Public Hospitals have not introduced the system of milestone payment yet.

MHLW baseline research report at clinical trial core sites. January 2008
◆ The proportion of the core hospitals which have “contract per year” is 27%.
◆ The proportion of “advance payment/ no refund” is 31%.
◆ The core hospitals requiring SDV costs is 25%. Average costs is 45,000 yen (11,000 yen/per hour)
Payment method by type of site (2007 vs. 2008)

**[2007]**
- National/Public U. (131): 87.0% No refund, 3.8% Partially refund, 9.2% Performance based
- Private U. (84): 40.5% No refund, 14.3% Partially refund, 45.2% Performance based
- National HP (90): 37.8% No refund, 11% Partially refund, 61.1% Performance based
- Public HP (117): 43.6% No refund, 3.4% Partially refund, 53.0% Performance based
- Private HP (208): 10.1% No refund, 3.4% Partially refund, 86.5% Performance based
- Clinic (299): 0.0% No refund, 10.1% Partially refund, 89.0% Performance based
- ALL (929): 27.3% No refund, 3.4% Partially refund, 69.2% Performance based

**[2008]**
- National/Public U. (80): 67.5% No refund, 12.5% Partially refund, 20.0% Performance based
- Private U. (77): 42.9% No refund, 7.8% Partially refund, 49.4% Performance based
- National HP (54): 31.5% No refund, 8% Partially refund, 68.5% Performance based
- Public HP (106): 28.3% No refund, 9.4% Partially refund, 62.3% Performance based
- Private HP (328): 9.8% No refund, 2% Partially refund, 89.0% Performance based
- Clinic (460): 12.2% No refund, 0% Partially refund, 87.8% Performance based
- ALL (1105): 20.1% No refund, 2.7% Partially refund, 77.2% Performance based
2008 Survey: Cost per patient with presence or absence of SMO support

![Chart showing cost per patient with different levels of SMO support](chart.png)
Expectation of sponsors to medical Institutions

◆ Enhancement of capability for enrollment
◆ Improvement of clinical trial speed and productivity by standardizing clinical trial administration and operation
◆ Develop an adequate cost structure for clinical trials
Enhancement of capability for enrollment

◆ Increase access to potential study subjects
  • Information disclosure for patients about clinical trials
  • Establish networks of hospitals and with clinics and the local community
  • Education of the local community on clinical trials and its value to society
  • Information disclosure for potential sponsors
Enhancement of capability for enrollment

- Improvement of infrastructure of clinical trial implementation
  - Establishment of clinical research structure and enhancement of administrative control.
  - Increase awareness of the value of clinical trials among hospital administrators.
  - Increase of number of clinical investigators and allow for time for clinical research.
  - Training of staff and establishment of a career path for CRCs and research nurses.
  - Improvement of incentives and motivation of staff. Greater recognition of clinical research activity.
Standardization of operation

◆ Help in reduction of burden for monitors
  • Establishment of clinical trial office to coordinate different hospital departments
  • Proactive use of common IRB
  • Introduction of IT system, including eDC
  • Adaptation to global standards (ICH GCP)

◆ Clarification of role and responsibilities between medical institutions and clinical trials sponsors
  • Standardization of role and responsibilities. Train staff in their GCP responsibilities
  • Engagement in reduction of burden, over-quality, excessive attention to detail and site-specific requirements
  • Ensure training of CRCs and other supporting staff
Adequate structure of trial costs

◆ Improvement of achievement rate and introduction of a system of milestone payment
◆ Employment of full time CRCs working on multiple protocols.
◆ Adjustment of actual costs such as IRB costs and SDV costs
Establishment of structure which enables simultaneous clinical trials with global standards

- Collaboration between medical institutions and sponsors
- Early start of clinical trials
- Promotion of simultaneous international clinical trials

Increased number of international clinical trials

Simultaneous development and market introduction

Realization of quality, cutting-edge health care and benefits for patients and their families
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