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# Drug Development in Japan

## Opportunities and Challenges in Drug Development

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### Abstract

As Japan becomes more integrated into the global market, pharmaceutical research and development (R&D) in the country faces considerable challenges. While global simultaneous drug development including Asian countries has become a common feature for multinational pharmaceutical companies, Japan has also been frequently set aside because of its unique regulatory requirements and provincial clinical trial infrastructure. To counter this, pharmaceutical companies operating in Japan have been working to improve their efficiency. As a result, a gradual but measurable improvement in the clinical trial environment has been witnessed over the past several years – including a reduction in average study duration. Meanwhile, a tremendous number of improvement programmes focussed on the biopharmaceutical industry have been initiated in conjunction with Prime Minister Shinzo Abe's vision of innovation for Japan.

With this increased scrutiny, significant improvements in regulatory process, clinical trial costs and site performance are anticipated over the next few years. At the same time, efforts to promote the field of pharmaceutical medicine in Japan are ongoing. A number of academic institutions have established education and training programmes in drug development and regulatory science. In addition, collaborative initiatives between academia and industry to set standards and establish qualification for the specialists in drug development are continuing with the hope that the number of experts in drug development in Japan will increase. It is hoped that, together, these positive trends will revitalise Japan as a leading global player in pharmaceutical R&D in the Asian region and beyond.

Japan continues to be ranked as the second largest pharmaceutical market in the world. This fact, in combination with increasing development complexity, has led drug development investment for the discovery and development of innovative new pharmaceutical products to new heights in Japan.<sup>[1]</sup>

However, as Japan becomes more integrated into the global market, pharmaceutical research and development (R&D) in the country faces considerable challenges. Most global, R&D-based pharmaceutical companies now aspire to develop new drugs globally and, where possible, launch simultaneously around the world. Under these circumstances, multinational clinical trials have become common and the number of trials that include an Asian country besides Japan has grown rapidly in recent years.<sup>[2]</sup> A provincial and rather inflexible clinical trial infrastructure, com-

binated with unique local regulatory requirements and variations in the interpretation and implementation of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, has served to set Japan apart from other regions.<sup>[3,4]</sup>

Across Asia, various English-speaking, motivated work forces are poised and well-suited to meet the needs of drug development sponsors. To support this, most of the region's leading specialists have received postgraduate medical training in the US or UK. Since per-subject trial costs are significantly lower in some Asian countries than they are in Japan, overall cost savings by including non-Japanese Asian countries in global clinical trials promise to be substantial. For example, one report says that the average per-subject trial cost in Japan was more than \$US20 000, whereas the

equivalent cost in Korea and Taiwan was less than \$US10 000.<sup>[5]</sup> At the same time, positive changes in the regulatory climates combined with continuous and faster improvements to the clinical trial environment under strong government leadership occurred in non-Japanese Asian countries than in Japan have allowed smoother and earlier market access for new drugs in these countries.<sup>[6,7]</sup>

With this trend, other Asian countries have made a concerted effort to support global clinical trials and have surpassed Japan's clinical trial performance. Korea has, for example, developed several very strong clinical sites with best-in-class performance in areas such as number of enrolled patients per trial and number of global protocols. As a result, several significant initiatives to transform and globalise the Japanese pharmaceutical industry have been under serious discussion in Japan.

In this article, the current issues and recent changes influencing Japan's clinical trial landscape are reviewed, and the unique opportunities and future vision for the country's pharmaceutical industry are discussed.

## 1. Recent Changes in the Regulatory and Clinical Trial Environment in Japan

### 1.1 Government Initiatives

Over the course of the last 9 months, the Japanese Prime Minister Shinzo Abe has emphasised that the biopharmaceutical industry is the highest priority focus in his 'Innovation 25' vision for the next 10 years (originally announced on 29 September 2006).<sup>[8]</sup> In accordance with this direction, the Japanese Cabinet, in partnership with various government Ministries, is now undertaking multiple initiatives to dramatically improve the country's stagnant regulatory and clinical trial environment.

The Japanese Ministry of Health, Labour and Welfare (MHLW), the agency primarily responsible for pharmaceutical policy, is leading multiple initiatives to promote improvements in the pharmaceutical environment. These include the *New 5-Year Plan for Clinical Trial Activation (2007–2012)*,<sup>[9]</sup> the *Vision for the Pharmaceutical Industry*,<sup>[10]</sup> and the *Vision to Improve the Environment for Vaccines Research, Development and Production in Japan*.<sup>[11]</sup>

As a result of previous improvements, the Pharmaceutical and Medical Device Agency (PMDA), which is responsible for the review of New Drug Applications (NDAs) in Japan, was formed in 2003 through the merger of the Pharmaceuticals and Medical Devices Evaluation Center and the Organization for Pharmaceutical Safety and Research. Following its formation, the PMDA has

come under criticism because of its slow review process. This is partly due to the backlog of NDAs that accumulated during the merger process. However, the PMDA has recently begun to demonstrate signs of improvement; the backlog of NDAs has been dramatically reduced over the past year. Meanwhile, to the applause of long-time experts on the Japanese pharmaceutical industry, the PMDA has started to encourage Japanese participation in global and Asian regional studies, as well as to accept global and Asian data as core data in NDAs.<sup>[12]</sup> RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and Tolterodine Japan-Korea studies were the first multinational and Asian studies, respectively, to be accepted as core NDA data – with both NDAs approved in April 2006.<sup>[13–15]</sup>

In addition, the PMDA is committed to hiring 236 new reviewers to reach a total of 582 employees by March 2010 with the aim of improving the current shortage of reviewers.<sup>[16,17]</sup> It is also working hard to become more of a partner than an adversary to NDA applicants by helping them find the best solutions to meet regulatory requirements for the approval of new drugs and to establish a transparent and scientific regulatory process.<sup>[18]</sup>

Meanwhile, in support of Prime Minister Abe's vision, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of Economy, Trade and Industry (METI) also appear to be strongly interested in improving the clinical trial environment. This is evidenced by the fact that the MEXT is jointly leading the *New 5-Year Plan for Clinical Trial Activation (2007–2012)*<sup>[9]</sup> with the MHLW, and that MEXT, together with MHLW and METI, is playing an important role as a member of the *Government-Industry Dialogue for Development of Innovative Medicine*, which was initiated in April 2007.<sup>[19]</sup>

### 1.2 Clinical Trial Environment

Since the implementation of ICH guidelines, especially E5 (*Ethnic Factors in the Acceptability of Foreign Clinical Data*)<sup>[20]</sup> and E6 (the consolidated guidelines on Good Clinical Practice [GCP])<sup>[21]</sup> in 1998 and 1997, respectively, many research experts acknowledge that the clinical trial environment in Japan has gradually but measurably improved. In addition to the recent government initiatives described in the previous section, pharmaceutical companies are, on their own initiative, investing resources and money to improve efficiency in clinical trials and to reduce the gap in trial efficiency between Japan and the rest of the world. As one example, a 2006 survey conducted by a group of pharmaceutical companies in Japan demonstrated that the average duration of clinical trials has declined while the use of Clinical Research

Coordinators (CRC) and the number of patients enrolled per site have both increased.<sup>[5]</sup>

Based on changes in the clinical trial environment such as those outlined previously, many pharmaceutical companies in Japan are now conducting – or planning to conduct – an increasing number of global and Asian regional studies. As a result, PMDA officials have announced that the number of consultations regarding global/Asian studies is increasing.<sup>[15]</sup> In addition, the PMDA and MHLW have recently circulated *A Draft Basic of Policy on International Collaborative Clinical Trials for Public Comment*, and it is now under revision based on these comments.<sup>[22]</sup> This guidance will facilitate the conduct of multinational and Asian regional studies for drug development in Japan.

To conduct multinational trials successfully – and to include a Japanese cohort – a well designed development strategy is crucial. There have been a variety of efforts to integrate and align drug development in Japan with the timelines for global simultaneous development. For example, many companies conduct their first studies with Japanese subjects outside Japan – in places such as the US, Canada or Australia. Also, it has been proposed that multiregional dose response trials might serve as an alternative option to running completely parallel or joint programmes for simultaneous development.<sup>[23]</sup> Joint clinical trials with other Asian countries to ensure rapid patient enrolment are becoming an increasingly common feature of drug development in Japan.

### 1.3 Challenges in the Clinical Trial Environment in Japan

Despite improvements in the clinical trial environment, the high cost of clinical trials, low productivity of field monitoring and low performance of trial sites remains significant issues in Japan.

#### 1.3.1 High Cost of Clinical Trials

As already described in the previous section, it is well documented that the cost of drug development is very high in Japan compared with other Asian countries. The costs vary depending on therapeutic areas, company operations and how the costs are calculated. The most recent data available show that the average per-subject costs of a clinical trial in Japan are between 3.3- and 5.6-times higher than those in other Asian countries.<sup>[24]</sup>

The causes of this high cost are multiple and complicated. Several issues have been identified as possible causes, including:<sup>[5]</sup>

- payments to nonperforming investigational sites;
- inconsistent cost calculation among sites by using ‘point tables for clinical study costs’;
- no reimbursement of pre-paid costs to the underperforming investigational sites.

These payment issues originate from Japanese historical and cultural practices that were formalised into the rules when the guidelines were first written. As such, it is not easy to solve these issues. Various discussions are ongoing to form a more transparent payment system to improve costs; however, one key driver of cost is the efficiency of monitoring.

#### 1.3.2 Low Productivity of Field Monitoring

The lower number of clinical trial sites handled by an average field monitor in Japan has been recognised as a significant issue. It is reported that a field monitor in Japan is in charge of six sites (40 subjects) on average, whereas the figures are 22.5 sites (180 subjects) per monitor in the US, and 16 sites (96 subjects) per monitor in the EU.<sup>[25]</sup> This is a major contributor to the high manpower costs, and subsequently higher costs in general, associated with performing clinical trials in Japan.

In order to improve monitoring productivity in Japan, several issues need to be resolved. These can only be mitigated through collaboration between trial sponsors and the trial sites, as well as through positive changes in the regulatory requirement. Specifically, there seem to be five key drivers of inefficiency:

1. the scope of work for field monitoring is considered to be broader than most other countries, and this requires a larger workload for Japanese field monitors. It is generally expected that Japanese field monitors give great consideration to investigator and CRCs workload, and provide on site support for trial sites. For example, field monitors are often expected to assist CRCs and investigators perform the complicated study procedures as defined at the site. This significantly increases the resources pharmaceutical companies need to dedicate to trials;
2. the level of quality required for monitoring is higher than necessary, often termed ‘over-quality’. While many of the reasons behind this (and issue 1) are historical and cultural, creative solutions are needed to rationalise these practices;
3. the workload for documentation is significant. Usually 100% monitoring of worksheets and CRFs are expected, and the number of essential documents that need to be maintained during the clinical trial (as required by Japanese GCP) is reported to be excessive and the handling cumbersome;<sup>[9]</sup>
4. various elements of the clinical trial system are also inefficient. For example, it has been pointed out that utilising a centralised institutional review board (IRB) system would provide more efficient review by more experienced boards. This would benefit patient safety, especially at smaller private clinics or inexperienced trial sites, and would improve field monitoring productivity.<sup>[15]</sup> Not surprisingly, the more flexible use of centralised IRBs

was proposed in the discussion of networking core clinical trial centres in the MHLW's *New 5-Year Plan for Clinical Trial Activation*.<sup>[9]</sup>

### 1.3.3 Low Performance of Trial Sites

Improvement in the performance of clinical trial sites is one of the key factors for the future of drug development in Japan. The Pharmaceutical Research and Manufacturers of America's (PhRMA) Japan Clinical Trial Environment team conducted a site performance survey on the 75 sites that were considered to be the best sites in Japan (as designated by the 14 participating companies).<sup>[26]</sup> The results demonstrated that several positive key practices are present at these sites, including experience with electronic data capture (EDC), participation in global clinical trials and English language capability. However, some factors, including the enrolment of only a small number of patients per site and the slow administrative procedures, were identified as areas that need significant improvement.<sup>[26]</sup>

Transforming these 'best' trial sites into 'Centres of Excellence' would be an important step towards dramatically improving overall clinical trial performance in Japan.

An increasing number of universities and regional core hospitals have launched clinical trial centres in their facilities – either under their own initiative or through support from the MHLW.<sup>[19]</sup> This trend is still at a very early stage; however, significant improvements in the clinical trial performance in the areas including patient enrolment and administrative processes in the near future are anticipated because of the enthusiasm observed at many of these sites. Similar initiatives have already been instituted in other Asian countries. In Korea, for example, nine institutions have been identified as Centres of Excellence and the number of clinical trials, including multinational trials, being undertaken at these centres has dramatically increased.<sup>[21]</sup>

To be able to conduct clinical trials even more efficiently in the future, it is important to form clinical trial networks by placing these Centres of Excellence as the hub and linking them to other research institutions. In addition, collaboration among these centres themselves, as well as partnerships with other Asian Centre of Excellence sites, will be critically important to conduct large pan-Asian clinical trials with rapid patient enrolment.

The Center for Clinical Trials of the Japan Medical Association (JMACCT) is undertaking the Large-Scale Clinical Trial Network (LCN) Project. This was launched in October 2003, to create a country-wide clinical trial network.<sup>[27]</sup> This project also aims to help trial sites gain clinical trial knowledge and skills, including compliance with GCP standards.

In addition to transforming Japan's clinical trial infrastructure, it will be important for companies to undertake novel trial designs<sup>[28]</sup> to optimise Japan's participation in global and Asian trials. The introduction of emerging new technologies such as EDC will further reduce cost, accelerate drug development and increase productivity. For example, the use of EDC in clinical trials has been increasing rapidly in the country,<sup>[29]</sup> and a variety of innovative options for new technologies in clinical trials are expected to become available in the near future.

## 2. Clinical Trial Specialists and Reviewers

Continuous increase of clinical trial standards demands higher levels of expertise in the drug development arena. Shortfalls in the number of clinical trial specialists and reviewers have been identified as an important issue in many countries,<sup>[30]</sup> including Japan. Not surprisingly, this is another key aspect that needs improvement in Japan's clinical trial environment – to develop people with expertise in global drug development.

### 2.1 Drug Development Education and Training

Various opportunities and methods exist to develop the expertise needed to execute an effective drug development project. Unfortunately, such programmes and courses are rather isolated and efforts are segmented. No clear criteria exist regarding the level of knowledge, skills and experience required for individuals to be recognised as 'experts' in the field of drug development and/or to become high-quality reviewers. This lack of clear criteria could lead to inconsistencies in the quality of clinical trials and the evaluation of clinical trial results from those studies.

In order to develop experts in drug development in industry, academia and regulatory agencies – that is, those who are capable of leading high quality drug development with scientific and regulatory rigor – a well established education and training system involving a wide scope of drug development is essential. Fortunately, an increasing number of initiatives to establish these education/training courses are ongoing at this time.

In regard to regulators, the PMDA has recognised the need for training to produce high-quality reviewers, as it plans to hire additional reviewers over the next 3 years, who may not have enough experience to review the data for drug development. As a result, the PMDA is committed to implementing a new, comprehensive programme including technical training, on-the-job training, communication and language training<sup>[16]</sup> in the second half of 2007, and to send the reviewers to workshops and conferences to

help them gain expertise on a par with their European and US counterparts.<sup>[31]</sup>

For industry, the Japanese Association of Pharmaceutical Medicine (JAPhMed), a group of physicians mostly working in the pharmaceutical industry, has been undertaking activities to establish an education/training system for pharmaceutical medicine. The outline of the JAPhMed programme is shown in table I. Training and lectures are given by experienced senior JAPhMed members and/or invited speakers who are experts in each field. Currently, training modules are provided only to members of the JAPhMed.<sup>[32]</sup>

Training for academia is described in more detail in the following sections; some academic institutions have established educational courses in the field of drug development and regulatory science.

## 2.2 Pharmaceutical Medicine as a Solution

Pharmaceutical medicine is a medical scientific specialty covering the discovery, development, evaluation, registration, monitoring and medical aspects of the marketing of medicines for the benefit of patients and public health – as defined by the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of the UK.<sup>[33]</sup> This breadth of disciplines has been an important contributor to the development of consistent quality of clinical trial specialists and reviewers in both the EU and US.

JAPhMed has been working with a number of Japanese institutions to assist in developing appropriate programmes for training

**Table I.** Outline of pharmaceutical medicine programme proposed by the Japanese Association of Pharmaceutical Medicine

### Scope of the programme

Accreditation system compatible with the Council for Education in Pharmaceutical Medicine of IFAPP  
Curriculum with practical case studies  
Appraisal of the qualification by an external accredited body  
Structured continuing education throughout a pharmaceutical physician's career  
Globally harmonised with IFAPP standard

### Programme content

1. Basic programme
  - Principally covers the core curriculum of the IFAPP syllabus in pharmaceutical medicine
  - Suitable for entry class investigators who will conduct clinical trials
2. Advanced programme
  - Workshop with case studies by the trainers with practical experiences

**IFAPP** = International Federation of Associations of Pharmaceutical Physicians.

and education in pharmaceutical medicine. Much of this work focuses on coordinating and harmonising the existing opportunities available in Japan. To date, several Japanese institutions have initiated educational programmes or training courses for drug development and clinical research (as shown in table II).

Given the global and cross-professional aspects of pharmaceutical medicine, the harmonisation of the various related programmes is critical to ensure a consistency of quality to global standards. In 2001, the Council for Education in Pharmaceutical Medicine (CEPM) was created under the auspices of the International Federation of Associations of Pharmaceutical Physicians (IFAPP), and undertook the task of harmonising the existing postgraduate courses in pharmaceutical medicine.<sup>[34]</sup> JAPhMed is also working to align its own educational programme with the global scope of CEPM.

## 2.3 Foundation of Japanese Center of Pharmaceutical Medicine

JAPhMed, in collaboration with the R&D Heads Club (an industry group that includes 20 domestic and multinational pharmaceutical companies operating in Japan), has founded the Japanese Center of Pharmaceutical Medicine (JCPM), a nonprofit organisation, to help advance pharmaceutical medicine for broader professionals including physicians, pharmacists, nurses and other medical staff in academia, industry and regulatory agencies in Japan. JCPM has the following specific objectives:

- to promote pharmaceutical medicine as a specialty in medical science in order to achieve broader recognition of its importance among industry, academic and government stakeholders;
- to develop and expand pharmaceutical medicine training programmes – in collaboration with JAPhMed – broadly to those who need to develop drug development expertise; and
- to set standards in Japan for pharmaceutical medicine specialists and establish qualification for such specialists.

It is hoped that the activities of JCPM will serve to increase the number of local drug development experts in Japan. This organisation should also help to improve and maintain the quality of drug development as well as the transparent evaluation of trial results.

Figure 1 shows the overall structure of the pharmaceutical medicine education/training system, which JCPM is championing. Establishing a qualification for pharmaceutical medicine professionals will significantly improve Japan's standards for drug development. In addition, this will greatly facilitate the employability of those qualified as experts.

**Table II.** Academic programmes for drug development and clinical research

Institute	Name of the department, programme, or course
University of Tokyo	Laboratory of Pharmaceutical Regulatory Science in Graduate School of Pharmaceutical Science
Kitasato University	Division of Pharmaceutical Medicine in School of Pharmaceutical Sciences
Oita University	Department of Pharmaceutical Medicine in Faculty of Medicine
Nagasaki University	Diploma Course on Research & Development of Products to Meet Public Health Needs in Institute of Tropical Medicine
University of Health and Welfare	Department of Clinical Trial Management, Graduate School Master's Programme in Health and Welfare, and Health Service Management
Kyoto University	Master of Clinical Research in School of Public Health
Yokohama City University	Clinical Research Leadership Development Program

### 3. Conclusion

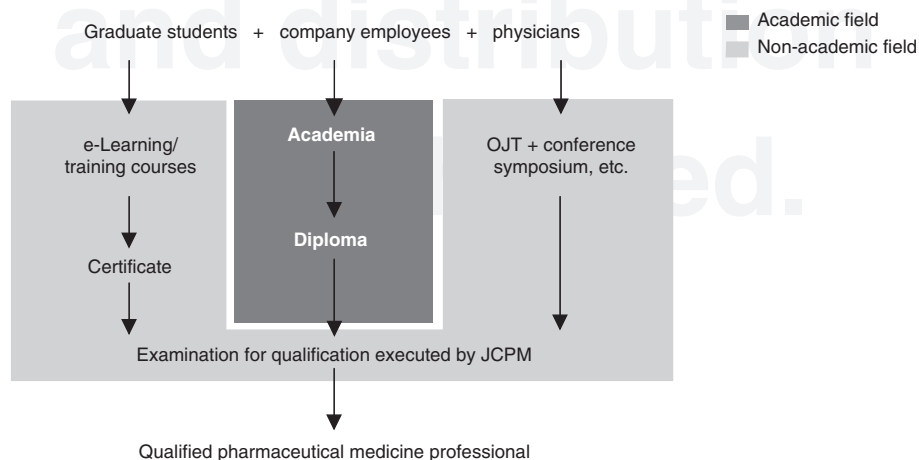
One of the top priorities of the pharmaceutical industry in Japan should be to expand the value that the industry provides to the future of Japan. This should be in the form of providing breakthrough drugs to Japanese patients at the same time as they are provided to patients around the world and, in so doing, adding to the economic growth of the country.

The regulatory requirements for collecting Japanese clinical data for the approval of new drugs are certainly a burden for pharmaceutical companies. In fact, it is the primary cause of the 'drug lag' in Japan. On the other hand, the availability of Japanese clinical data appear to be quite valuable for practicing physicians in the country and is advantageous from a Japanese marketing point of view as well. Therefore, an ideal scenario for Japan over the next 10 years would be for the pharmaceutical R&D industry operating in the country to deliver innovative drugs for the Japa-

nese market simultaneously with the rest of the world with solid Japanese clinical data produced from cost efficient and scientifically rigorous clinical trials. This is quite a challenging situation for Japan, and poses a unique opportunity for the industry and country.

To achieve this goal, globalisation of pharmaceutical R&D in Japan is absolutely imperative, and dramatic changes in many areas must be implemented. These include:

- establishing a transparent and scientific regulatory process with open and collaborative communication between regulators and applicants;
- attaining significant improvement in the country's clinical trial infrastructure and establishing networks of clinical trial sites;
- encouraging clinical trial centres to become true 'Centres of Excellence' in clinical research;



**Fig. 1.** Proposed structure for pharmaceutical medicine in Japan by the Japanese Center of Pharmaceutical Medicine (JCPM). There are three ways of obtaining a professional qualification in pharmaceutical medicine. Academia includes the programmes listed in table II. Non-academic training programmes include the course provided by the Japanese Association of Pharmaceutical Medicine (JAPhMed). On-the-job training (OJT) is actual work-based experience within the industry, academia and government, for a certain time period.

- adopting new methods for effectively conducting global and Asian clinical trials; and
- establishing education and training systems for drug development, such as pharmaceutical medicine programmes.

Any of these changes is challenging and requires intensive efforts from all the key players involved in drug development. Fortunately, Japan has significant advantages over many other countries with its rich resources in life sciences, including a large number of world class scientists, technology experts, and advanced academic institutions. A true partnership forged among these scientific and technological stakeholders, together with government agencies and experienced industry experts, will potentially boost the rate of change and will, hopefully, revitalise Japan as a true leader in pharmaceutical R&D in the Asian region and beyond.

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Dr Takahashi is the president of the Japanese Association of Pharmaceutical Medicine (JAPhMed) and the vice president of the Japanese Centre of Pharmaceutical Medicine (JCPM).

### References

- Office of Pharmaceutical Industry Research report. 2005 Nov [in Japanese; online]. Available from URL: <http://www.jpma.or.jp/opir/single/souyakunoba.pdf> [Accessed 2007 Jul 9]
- Ishibashi K. Office of Pharmaceutical Industry Research news. 2006 Oct 18-21 no. 21 [in Japanese; online]. Available from URL: <http://www.jpma.or.jp/opir/news/news-21.pdf> [Accessed 2007 Jul 9]
- Ebihara A, Takahashi K, Ikemoto F, et al. Clinical pharmacology and clinical trials in Japan. *J Mol Med* 1996 Aug; 74 (8): 479-86
- McCurry J. Japan unveils 5-year plan to boost clinical research. *Lancet* 2007 Apr 21; 369: 1333-6
- Shimatani K. International competitiveness of the Japanese clinical trials on cost and performance [in Japanese]. Session 1: performance of new drug research and development in Japan and its international competitiveness. In: Takeuchi M, Lagakos SW, editors. Development, evaluation and approval of new drugs-partnership between regulatory agencies, industry and academia. Tokyo: Rinsho Hyoka Kankoukai, 2006: 45-58
- Varawalla N. Conducting clinical trial in Asia. *Appl Clin Trial* 2006 Jun 1 [online]. Available from URL: <http://www.actmagazine.com/appliedclinicaltrials/Clinical+Trials/Conducting-Clinical-Trials-in-Asia/ArticleStandard/Article/detail/334577>
- Gross A, Hirose M. Conducting clinical trials in Asia. *Pacific Bridge Medical* 2007 Mar [online]. Available from URL: <http://www.pacificbridgemedical.com/publications/html/AsiaClinicalTrials2007.htm> [Accessed 2007 Jul 9]
- Policy Speech by Prime Minister Shinzo Abe to the 165th session of the diet. 2006 Sep 29 [online]. Available from URL: [http://www.kantei.go.jp/foreign/abespeech/2006/09/29speech\\_e.html](http://www.kantei.go.jp/foreign/abespeech/2006/09/29speech_e.html) [Accessed 2007 Jul 9]
- New 5-yearly clinical trial activation plan [in Japanese; online]. Available from URL: <http://www.mhlw.go.jp/shingi/2007/03/dl/s0330-5a.pdf> [Accessed 2007 Aug 22]
- A draft of vision for the pharmaceutical industry [in Japanese; online]. Available from URL: <http://search.e-gov.go.jp/servlet/Public?CLASSNAME=Pcm1010& BID=495070080&OBJCD=100495&GROUP=> [Accessed 2007 Aug 22]
- Vision to improve the environment for vaccines research, development and production in Japan [in Japanese; online]. Available from URL: <http://www.mhlw.go.jp/shingi/2007/03/dl/s0322-13d.pdf> [Accessed 2007 Aug 22]
- Miyajima A. Role of Japan and Asia in countries in global pharmaceutical development. 2006 Symposium of Asia Pacific Economic Conference (APEC) Network. 2006 Oct 12 [online]. Available from URL: <http://www.pmda.go.jp/apec2006ph/presen/1012/03.pdf> [Accessed 2007 Jul 9]
- Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861-9
- de Koning Gans HJ. Revolution in Asian drug development: a Korea and Japan experience. In: Experience of a Japan/Korea regional trial. Fourth Kitasato University-Harvard School of Public Health Symposium [online]. Available from URL: <http://www.pharm.kitasato-u.ac.jp/biostatiskhsympo2002.html> [Accessed 2007 Jul 9]
- Mori K. Global development: Japanese efforts and views. 2006 Symposium of Asia Pacific Economic Conference (APEC) Network. 2006 Oct 13 [online]. Available from URL: <http://www.pmda.go.jp/apec2006ph/presen/1013/12.pdf> [Accessed 2007 Jul 9]
- Key items of 2007 PMDA business plan [in Japanese; online]. Available from URL: [http://www.pmda.go.jp/guide/hyougikai/19/h190622gijishidai/file/h190622\\_siryos3.pdf](http://www.pmda.go.jp/guide/hyougikai/19/h190622gijishidai/file/h190622_siryos3.pdf) [Accessed 2007 Aug 22]
- The minutes from "2006 PMDA business hyougikai" [in Japanese; online]. Available from URL: <http://www.pmda.go.jp/guide/hyougikai/18/H190306gijishidai/file/h190306gijiroku.pdf> [Accessed 2007 Aug 22]
- Uyama Y. Current status and future perspectives of clinical trial consultation and NDA review performance. Sixth Kitasato University-Harvard School of Public Health Symposium [online]. Available from URL: [http://www.pharm.kitasato-u.ac.jp/biostatiskhsympo2005/Khsympo\\_program\\_2005.html](http://www.pharm.kitasato-u.ac.jp/biostatiskhsympo2005/Khsympo_program_2005.html) [Accessed 2007 Jul 9]
- JPMA News Letter 2007; 119 (5) [in Japanese; online]. Available from URL: [http://www.jpma-newsletter.net/PDF/2007\\_119\\_02.pdf](http://www.jpma-newsletter.net/PDF/2007_119_02.pdf) [Accessed 2007 Aug 22]
- ICH harmonized tripartite guideline. Ethnic factors in the acceptability of foreign clinical data: E5 (R1) [online]. Available from URL: <http://www.ich.org/LOB/media/MEDIA481.pdf> [Accessed 2007 Aug 22]
- ICH harmonized tripartite guideline. Guideline for good clinical practice: E6 (R1) [online]. Available from URL: <http://www.ich.org/LOB/media/MEDIA482.pdf> [Accessed 2007 Aug 22]
- A draft of basic policy on international collaborative clinical trials for public comment [in Japanese; online]. Available from URL: <http://www.pmda.go.jp/guide/hyougikai/19/h190608gijishidai/file/shiryos8.pdf> [Accessed 2007 Aug 22]
- E5: ethnic factors in the acceptability of foreign clinical data: questions & answers (R1) [online]. Available from URL: <http://www.ich.org/cache/comp/276-254-1.html> [Accessed 2007 Sep 6]
- Shimatani K. Clinical trial performance and cost survey [in Japanese]. Session 2-1: Japan's critical path opportunities - 1. Reforming the clinical trial process for trial conduct: environment and infrastructure of clinical research and trials. In: Takeuchi M, Lagakos SW, editors. Japan's critical path opportunities. Tokyo: Rinsho Hyoka Kankoukai, 2007: 139-54
- Umehara S. Field Monitor's scope of work is too broad [in Japanese]. *Nikkan Yakugyo* 2006 Nov 20
- Taniguchi T. Improvement in Japan's clinical trial environment: a prospective of global companies: are you ready to use Japanese sites for your global clinical trials? Seventh Kitasato University-Harvard School of Public Health Symposium [in Japanese; online]. Available from URL: <http://www.pharm.kitasato-u.ac.jp/> [Accessed 2007 Jul 9]

27. Uchida T, Kobayashi F, Kiko Tanaka K, et al. Promoting clinical trials in Japan. *Applied Clinical Trials* 2007 Mar 1 [online]. Available from URL: <http://www.actmagazine.com/appliedclinicaltrials/Feature+Article/Promoting-Clinical-Trials-in-Japan/ArticleStandard/Article/detail/410606> [Accessed 2007 Jul 9]
28. Califf RM. Issues facing clinical trial of the future. *J Intern Med* 2003; 254: 426-33
29. Sekine E. Survey results: current status of EDC use in Japan. Session 2-1. Japan's critical path opportunities – 1. Reforming the clinical trial process for trial conduct: environmental and infrastructure of clinical research and trials. In: Takahashi M, Lagakos SW, editors. *Japan's critical path opportunities*. Tokyo: Rinsho Hyoka Kankoukai, 131-8
30. Clemens N. Shortfalls of qualified persons in pharmaceutical medicine. *IFAPP World I* 2007 Apr [online]. Available from URL: [http://www.dgpharmed.de/01\\_public/pressemitteilungen/PDFs/IFAPPworld\\_I\\_2007.pdf](http://www.dgpharmed.de/01_public/pressemitteilungen/PDFs/IFAPPworld_I_2007.pdf) [Accessed 2007 Jul 9]
31. Mayer A. A window of opportunity: the cooperative efforts of government agencies, pharmaceutical manufacturers and academic researchers are helping to modernize Japan's drug development climate. *Envisage* 2007 Jul; 1 (3): e1 [online]. Available from URL: <http://www.envisagemag.com/article.cfm?articleid=57> [Accessed 2007 Aug 22]
32. Takahashi K. Training of clinical trial specialists and reviewers [in Japanese]. Session 4: Review System and Discussion on Good Review Practice (GRP). In: Takeuchi M, Lagakos SW, editors. *Global development strategies of new drugs: achievement and future direction*. Tokyo: Rinsho Hyoka Kankoukai, 2005: 295-9
33. Summers K. The pharmaceutical physician. In: Burley DM, Clarke JM, Lasagna L, editors. *Pharmaceutical medicine*. 2nd ed. London: Edward Arnold, 1993: 290-319
34. Postgraduate courses in pharmaceutical medicine in Europe: a pilot survey. *Int J Pharm Med* 2001; 15 (6): 293-9 [online]. Available from URL: [http://www.uni-due.de/pressestelle/webredaktion/pharmaceutical\\_medicine/ifapp.pdf](http://www.uni-due.de/pressestelle/webredaktion/pharmaceutical_medicine/ifapp.pdf) [Accessed 2007 Jul 9]

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