— **Review** —

Clinical Trials and Good Clinical Practice

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To analyze the quality of clinical trials in Japan for new applications of pharmaceuticals, compliance with the Good Clinical Practice (GCP) inspection was studied using Review Reports for approvals from fiscal year (FY)1999 to FY2008. Guidelines for GCP in Japan were harmonized with those of other countries at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Both to protect human rights, safety and welfare and to perform clinical trials scientifically and ethically, ensuring conformity with GCP is necessary when evaluating the safety and efficacy of the clinical data in common technical documents (CTD). In the conformity audit service of the Office of Conformity Audit of Pharmaceuticals and Medical Devices Agency (PMDA), the conformity of the studies and the documents between application materials of CTD attached to application forms for approval and case report forms (CRFs) is reviewed by document-based conformity inspection, and the conformity between medical records and CRFs is reviewed by on-site GCP inspection including oversea inspection. The GCP inspection includes both the on-site GCP inspection and the document-based conformity inspection. The importance of the GCP inspection by the Office of Conformity Audit to protect human rights, safety and welfare is summarized in this study. In conclusion, GCP inspection is conducted in accordance with the latest GCP, and the quality of clinical trials in Japan meets the Review Process by PMDA for marketing authorization. I hope that the GCP inspection protects human rights and improves the GCP conformity of clinical trials in Japan.

Key words —— Good Clinical Practice, clinical trial, human subject protection, Inspection, Pharmaceuticals and Medical Devices Agency

INTRODUCTION

Good Clinical Practice (GCP) is one of the basic sets of rules for hospitals, researchers and pharmaceutical companies engaged in clinical trials. Guidelines for GCP in Japan are in The Ministry of Health, Labor and Welfare (MHLW) Ministerial Ordinance No. 28 dated March 27, 1997 and No. 24 dated February 29, 2008,[1] and these were harmonized with those of other countries at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[2] In Japan, the Declaration of Helsinki[3] and GCP are important to protect human rights during clinical trials. Both to protect human rights, safety and welfare and to perform clinical trials scientifically and ethically, ensuring conformity with GCP is necessary when evaluating the safety and efficacy of the clinical data in common technical documents (CTD). As GCP was established on the basis of the Declaration of Helsinki, the principles of ICH-GCP show that clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements.

Although GCP was harmonized internationally by the ICH, the inspection program or review systems that ensure the conformity of the studies and the documentation from source documents to CTD are slightly different among U.S.A., European Union (EU) and Japan. In Japan, before Mar. 2004, staff of the Organization for Pharmaceutical Safety and Research (OPSR/KIKO) and the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC) performed a document-based conformity

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inspection and on-site GCP inspection, respectively, and MHLW evaluated the conformity and published a GCP inspection report. This was a very difficult procedure given that the number of GCP inspections and GCP inspection reports were limited. After April 2004, The Office of Conformity Audit of Pharmaceuticals and Medical Devices Agency (PMDA) evaluated conformity of the studies and the documents to application materials of CTD by a combination of on-site GCP inspection including oversea inspection and document-based conformity inspection.[4] The numbers of GCP inspection reports of new drugs in fiscal year (FY)2006, FY2007 and FY2008 were 120, 137, 122 and 182, respectively.[5] Because of an increase in operational efficacy and in the number of GCP inspectors, the ability to undertake GCP inspections is increasing. By conducting GCP inspection and publishing review articles in scientific journals, GCP inspectors contribute to improving the clinical trial environment in Japan.[6–10] I previously reported on methods to improve clinical trials from the findings of a GCP inspection of the Office of Conformity Audit.[6,7] The quality of clinical trials of new drugs is classified into 2 classes of Compliance Classification for the source document: NAI (No Action Indicated) and OAI (Official Action Indicated). Before approval of the pharmaceuticals, public access of GCP inspection reports is completely restricted, because the information concerning GCP compliance would affect the New Drug Review Process. On the other hand, after approval of marketing authorization, the summary of the results of the conformity review concerning the documents appended to the New Drug Application and the conclusion of PMDA is freely accessible on the website of PMDA.[11,12]

In this study, therefore, the compliance of the GCP inspection from the Review Reports for recently approved new drugs was studied, and clinical trials in Japan were analyzed. The efforts of GCP inspectors seem to improve the quality of clinical trials in Japan.

MATERIALS AND METHODS

From the website of PMDA and to some extent from Japan Pharmaceutical Information Center, Review Reports are provided in Japanese.[11,13] Recently, English Review Reports have also become available.[12] Therefore, in this study, the Japanese Review Reports discussed at the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) from FY1999 (from September) to FY2008 were analyzed. The Review Reports reported to PAFSC were not analyzed. Before FY2000, some approved pharmaceuticals were not accompanied by a Review Report. The quality of the clinical trials was classified into 3 types for on-site GCP inspection and 3 types for document-based conformity inspection in this study as follows.

Classes of On-site GCP Inspection

Class 1: NAI and/or VAI (Voluntary Action Indicated): As no findings had been made or the findings indicated no violation of GCP in the clinical trials, there should be no problem in conducting the regulatory review based on the application dossier submitted.

Class 2: At some study sites, there were inappropriate cases. PMDA asks the applicants to withdraw the cases from the dossier or exclude these cases from efficacy evaluation. The revised dossier should be acceptable.

Class 3: OAI: Human rights are not protected in all clinical trials for approval, and PMDA recommends that the applicants withdraw the application of the product.

Before Mar. 2004, MHLW instead of PMDA made recommendations to the applicants.

Classes of Document-based Conformity Inspection

Class 4: There should be no problem in conducting the regulatory review based on the application dossier submitted.

Class 5: PMDA asks the applicants to revise the dossier submitted. There should be no problem with conducting the regulatory review based on the revised dossier.

Class 6: PMDA asks the applicants to reexamine the non-clinical and clinical studies.

The document-based conformity inspection does not include the proofreading of CTD Module 2. Before Mar. 2004, OPSR instead of PMDA made recommendations to the applicants.

The results of on-site GCP inspection and document-based conformity inspection are analyzed. PMDA was established in FY2004 (April), and at that time the audit systems in Japan were changed as described previously. The qualities of clinical trials of the GCP inspection are compared before and after PMDA establishment.

Moreover, typical deviations from the GCP inspection in English Review Reports of ten new drugs are summarized.

Table 1. The Results of the On-site GCP Inspection and PMDA's Conclusion

FY	No. of New Drugs	No. of Review Reports	No. of on-site GCP inspections	Class 1	Class 2	Class 3
1999	39	19	16	62.5% (10/ 16)	37.5% (6/ 16)	0.0% (0/ 16)
2000	45	42	37	75.7% (28/ 37)	24.3% (9/ 37)	0.0% (0/ 37)
2001	50	50	42	83.3% (35/ 42)	16.7% (7/ 42)	0.0% (0/ 42)
2002	35	35	32	81.3% (26/ 32)	18.8% (6/ 32)	0.0% (0/ 32)
2003	31	31	28	82.1% (23/ 28)	17.9% (5/ 28)	0.0% (0/ 28)
2004	27	27	18	88.9% (16/ 18)	11.1% (2/ 18)	0.0% (0/ 18)
2005	36	36	36	75.0% (27/ 36)	25.0% (9/ 36)	0.0% (0/ 36)
2006	62	62	58	86.2% (50/ 58)	13.8% (8/ 58)	0.0% (0/ 58)
2007	53	53	48	81.2% (39/ 48)	18.8% (9/ 48)	0.0% (0/ 48)
2008	56	56	50	92.0% (46/ 50)	8.0% (4/ 50)	0.0% (0/ 50)
Average				82.2% (300/365)	17.8% (65/365)	0.0% (0/365)
Total	434	401	365			

The quality of clinical trials was classified into 3 types as follows.

Class 1: NAI and/or VAI: As no findings had been made or the findings indicated no violation of GCP in the clinical trials, there should be no problem in conducting the regulatory review based on the application dossier submitted.

Class 2: At some study sites, there were inappropriate cases. PMDA asks the applicants to withdraw the cases from the dossier or exclude these cases from efficacy evaluation. The revised dossier should be acceptable for new drug application.

Class 3: OAI: Human rights are not protected in all clinical trials for approval, and PMDA recommends that the applicants withdraw the new drug application.

RESULTS

The Results of the On-site GCP Inspection and PMDA's Conclusion

Classification of on-site GCP inspection of the pharmaceuticals approved from FY1999 (from September) to FY2008 is shown in Table 1.

In FY1999, Class 2 was the most common. From FY2001 to FY2007, the frequency of Class 2 classification ranged from 11 to 19%, except for FY2005. In FY2008, the frequency of Class 2 classification was less than 10%. The OAI application was withdrawn. Therefore, there were no Class 3 classifications, as shown in Table 1.

The quality of clinical trials of the new approved drugs is compared before and after PMDA establishment. It seems that there were no substantial differences between the periods before and after PMDA establishment. The number of Class 2 products from FY1999 to FY2003 was 33, and that from FY2004 to FY 2008 was 32. These were drugs mainly used for treating cardiovascular diseases, the central nervous system, asthma, autoimmune diseases, dyslipidemia, osteoporosis and hepatitis (data not shown).

The Results of Document-based Conformity Inspection and PMDA's Conclusion

The results of document-based conformity inspection are shown in Table 2. The average frequency of Class 4 classification was more than 90%, and that of Class 5 was less than 5%. In FY2001 and FY2005, there were some Class 6 classifications. Staff involved in document-based conformity

Table 2. The Results of Document-based Conformity Inspection and PMDA's Conclusion

FY	No. of New Drugs	No. of Review Reports	No. of document-based conformity inspections	Class 4	Class 5	Class 6
1999	39	19	17	100.0% (17/ 17)	0.0% (0/ 17)	0.0% (0/ 17)
2000	45	42	33	90.9% (30/ 33)	9.1% (3/ 33)	0.0% (0/ 33)
2001	50	50	39	89.7% (35/ 39)	7.6% (3/ 39)	2.6% (1/ 39)
2002	35	35	33	97.0% (32/ 33)	3.0% (1/ 33)	0.0% (0/ 33)
2003	31	31	31	93.5% (29/ 31)	6.5% (2/ 31)	0.0% (0/ 31)
2004	27	27	25	96.0% (24/ 25)	4.0% (1/ 25)	0.0% (0/ 25)
2005	36	36	36	86.1% (31/ 36)	8.3% (3/ 36)	5.6% (2/ 36)
2006	62	62	62	95.2% (59/ 62)	4.8% (3/ 62)	0.0% (0/ 62)
2007	53	53	53	94.3% (50/ 53)	5.7% (3/ 53)	0.0% (0/ 53)
2008	56	56	55	100.0% (55/ 55)	0.0% (0/ 55)	0.0% (0/ 55)
Average				94.3% (362/384)	4.9% (19/384)	0.8% (3/384)
Total	434	401	384			

The quality of clinical trials was classified into 3 types as follows.

Class 4: There should be no problem in conducting the regulatory review based on the application dossier submitted.

Class 5: PMDA asks the applicants to revise the dossier submitted. There should be no problem with conducting the regulatory review based on the revised dossier.

Class 6: PMDA asks applicants to reexamine the non-clinical and clinical studies. In FY2001 and FY2005, it was asked that the non-clinical studies be reexamined.

inspection asked these applicants to reexamine their non-clinical studies. There were no products for which more clinical trials were requested because of a violation of GCP. In 2008, there were no Class 5 or Class 6 non-clinical or clinical studies for a new drug application.

Typical Deviations from GCP Inspection in the Clinical Trials of Recently Approved Products

PMDA provides English Review Reports on its website. The English Review Reports are selected and translated among the new drugs and the new medical devices that recently received marketing approval. As of 10th Dec. 2009, these include ten pharmaceuticals: pirfenidone, thalidomide, tocilizumabu (genetic recombination), adsorbed influenza vaccine (H5N1) "HOKKEN," adsorbed influenza vaccine (H5N1) "BIKEN," topiramate, garenoxacin mesilate hydrate, ezetimibe, alglucosidase alfa (genetic recombination) and bevacizumab (genetic recombination). As the PMDA indicates that the Japanese original version shall prevail, the quality of these drugs is confirmed as Class 1 and Class 4 of GCP on-site inspection and conformity document review, respectively, from the Review Report in Japanese. Table 3 shows the typical findings written in the English Review Reports. These show deviations at some medical institutions. PMDA asked the sponsors and the medical institutes to improve the level of GCP, and PMDA will evaluate the improvement at the next inspection of the sponsors and the institutes.

DISCUSSION

The constitution of Japan indicates that "In all spheres of life, the State shall use its endeavors

Table 3. Typical Findings of GCP Issues in the Clinical Trials of Recently Approved Drugs

Deviations	Issues
Findings in on-site GCP inspection	
Inappropriate management of the IRB or Deficiencies concerning management of IRB	A failure to consult the IRB on whether the study should be continued or not in relation to reports notified by the sponsor on unexpected serious adverse drug reaction
	Audit report and monitoring report
	A review conducted by the IRB in the absence of doctors
Deviation from the protocol	A failure to conduct a patient examination upon study
	Discontinuation
	Exclusion criteria
	Dose escalation
	Preparation of the clinical study reports
	Non-compliance with the procedure
	Failure to perform tests
	Inappropriate description in the CRF
A failure to submit the audit protocol	Not to submit to the head of the study site
Monitoring	Sponsor did not appropriately monitor activities in these cases in accordance with the SOP
	Inappropriate or inadequate monitoring activities
Transcribing data from the source document to the CRF	Errors and omission *etc*.
Findings in document-based conformity inspection	
Failure of the principal investigator	Affix the name and seal on CRF
	Noncompliance with the administration method or treatment duration
	Missing follow-up of adverse events

PMDA concluded that there should be no problem in conducting regulatory reviews based on the application dossier. CRF: Case Report Form. IRB: Institutional Review Board. SOP: Standard Operationg Procedure.

for the promotion and extension of social welfare and security, and of public health." The Declaration of Helsinki indicates that medical progress is based on research that ultimately must rest in part on medical research involving human subjects. Medical progress means, in part, the development of new drugs and new devices. Clinical investigators should perform medical research involving human subjects for new drugs and new device applications in conformity with the Declaration of Helsinki and GCP. In Japan, PMDA audits the GCP compliance of clinical trials to ensure human subject protection and credible clinical trial data. The application materials for New Drug Application are reviewed by PMDA in accordance with GCP and the reliability criteria in the Pharmaceutical Affairs Law.

The significance of the GCP inspection by PMDA is to ensure the rights, safety and wellbeing of trial subjects, to allow third parties to check the adequacy of past judgments retroactively and to assist in the verification of the adequacy and reliability of data.

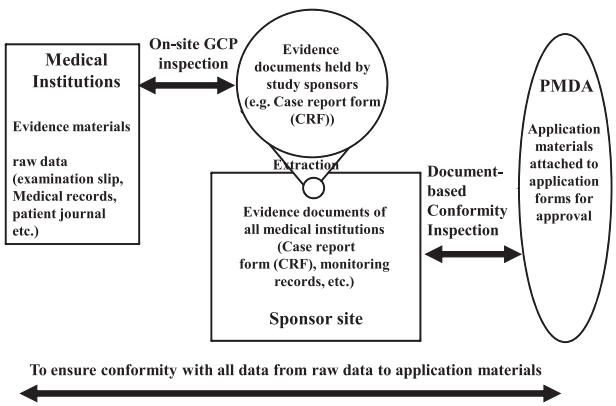

Fig. 1. GCP Inspections in Japan

Under the current system, there are 2 kinds of inspections in GCP inspection in Japan (Fig. 1), on-site GCP inspection and document-based conformity inspection. The conformity between medical records, examination slips, patient journals *etc*. as raw data and case report forms (CRFs) as evidence materials are assessed through on-site GCP inspec-

tion performed at specified medical institutions. In addition, the reliability and conformity with GCP between CRFs and monitoring records *etc*. as evidence materials and application materials are currently confirmed by document-based conformity inspection, which is conducted for all medical institutions where pivotal clinical trials are performed.

The important issues raised by the on-site GCP inspection and document-based conformity inspection were previously summarized,[8, 10] suggesting the importance of monitoring to find protocol deviation and to highlight investigational product safety for the protection of human rights. I also previously reported on the quality of clinical trials in Japan;[6, 7] the quality of clinical trials in Japan from FY2001 to FY2006 was not the highest but was sufficient for the New Drug Review Process. It is noteworthy that the average frequencies of Class 1 and Class 4 classifications of the approved drugs were more than 80% and 90%, respectively. In FY2008, the quality of clinical trials was the highest, suggesting that the increased frequency of on-site GCP inspection by PMDA promoted the principles of GCP effectively in clinical trial environments. Violation of GCP is likely to occur in clinical trials performed by pharmaceutical companies that do not have sufficient experience as was the case for statins for dyslipidemia, interferons and their analogues for hepatitis and vitamin D analogues for osteoporosis. The number of violations of GCP for these drugs is decreasing with the decrease in the number of new applications for these new drugs. Instead of these drugs, the number of Class 2 anti-cancer drugs has increased, suggesting that the development of anticancer drugs is increasing. In clinical trials of drugs used for cardiovascular diseases, for the central nervous system, for asthma and for autoimmune diseases, violations of GCP were repeatedly found by GCP inspection, suggesting that the investigators, clinical research coordinators, other clinical professionals and monitors involved in these clinical trials should not overlook the principles of GCP to protect human subjects.

There were small deviations from GCP in clinical trials. However, PMDA concluded that these were too trivial to prevent continued evaluation of the new drugs. For improvement of the quality of clinical trials in Japan, it is important that the findings concerning violation or deviation are reported by PMDA. Review Reports of PMDA indicate the differences between violations and deviations of GCP compliance of clinical trials. In violation cases, it is indicated that PMDA requests action from the pharmaceutical company in question, such as the exclusion of clinical data from the clinical data package of the CTD. In Japan, clinical trial staff and monitors often tend to focus on maximizing the quality of documents for the new drug application rather than considering the rights of human subjects. This is one of the reasons for certain responses of monitors and clinical research coordinators in clinical trial environments. Unfortunately, sometimes these individuals hide human errors illegally. In the GCP inspection service, preventing the violation of GCP seems to be more important than finding violations and requesting appropriate actions by sponsors and medical institutions. PMDA evaluates benefits, risks, indications and usage of new drugs for public health in Japan. In the decision-making process for marketing authorization, maintenance of the transparency and traceability of clinical trials is important. Moreover, the rights, safety and wellbeing of the trial subjects are the most important considerations and should prevail over interests of science and society.

Saito *et al.* reported that protocol deviations are a compelling issue for quality improvement,[14] and GCP inspectors of PMDA reported the importance of monitoring.[8, 10] In this study, details of protocol deviations and the failure of monitoring are shown in Table 3. To perform clinical trials under correct scientific protocol is to protect human subjects. Moreover, information on adverse events is important for safety. Regulators do not demand complete and perfect compliance with GCP by sponsors and medical institutions. However, human subject protection including the provision of informed consent is essential in clinical trials. Recently, U.S. Food and Drug Administration (FDA) issued guidance for industry in the document "Investigator responsibilities—protecting the rights, safety, and welfare of study subjects."[15] Clinical research investigators should not overlook the responsibilities to protect human subjects both in the U.S.A. and Japan. PMDA began the voluntary registration of institutional review boards (IRB) and found more than 1000 IRBs dealing with pharmaceutical and medical device clinical trials in Japan.[16] The number of registered IRBs is increasing.

MHLW has promoted clinical trials in Japan, and the proportion of global clinical trials performed in the country is increasing. To participate in global clinical trials and for FDA or European Medicines Agency (EMEA) to evaluate the

data from clinical trials performed in Japan favorably, the quality of the clinical trials for new drug applications must be kept as high as that in the other regions. As the number of global clinical trials outside the U.S.A. and EU is increasing, the FDA and EMEA have agreed to launch an EMEA-FDA GCP initiative.[17] To assure that more clinical trials that are submitted to both FDA and EMEA are of the highest quality, the FDA and EMEA will collaborate with GCP inspections and share information on the interpretation of GCP.[18] The Office of Conformity Audit performs oversea GCP inspection, but it is not clear whether PMDA will join the collaborative GCP inspections with FDA and EMEA. Under the PMDA International Strategic Plan in 2009,[19] PMDA will strengthen cooperation with foreign countries with respect to inspections and audits conducted to ensure compliance with Good Laboratory Practice (GLP), GCP, Good Manufacturing Practice (GMP) and Quality Management System (QMS). OECD began collaborative GLP inspection, and PMDA has experienced the collaborative GLP inspection.[20] As such, it does not seem too difficult for PMDA to join the collaborative GCP inspection. I hope that PMDA performs appropriate GCP inspections of sponsors and medical institutions to continue to improve the quality of clinical trials in Japan.

Disclaimer This is not official PMDA guidance or an official policy statement.

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