Comparing GCP Requirements for Medical Device Clinical Trials in the US and Japan

By Harmonization-by-Doing Working Group 4

Introduction

The convergence of US and Japanese medical device regulations and practices provides an opportunity to accelerate delivery of innovative medical devices to patients in need of medical treatment. Reciprocal acceptance of Good Clinical Practices (GCPs) would facilitate multinational studies and promote the use of clinical data to support regulatory submissions in multiple countries. The process of regulatory convergence involves first recognizing differences between the regulations and practices of the governments or governing organizations involved.

Previous reports and regulatory discussions have suggested differences between GCP in the US and Japan that make it difficult to analyze and utilize clinical trial data from one GCP system in support of marketing approval in the other. Language and cultural barriers may add to the complexity. By understanding the nature of these differences, it may be possible to more accurately determine whether data from an alternate GCP provide similar assurances of valid scientific information and patient protection.

GCP, as described in standards and regulations, governs the quality of clinical trials for medical products, including medical devices, but the differences between GCP requirements have not been well studied. Further study of these differences is needed to enhance the meaning of compliance with one set of GCP requirements versus another.

One of the specific aims of the Harmonization-by-Doing program's Working Group 4 (WG4) is to share information on important similarities and differences in laws, regulations and regulatory practices related to the clinical evaluation and marketing approval of medical devices in the US and Japan. Importantly, WG4 includes constituents from government, academia and industry in both countries. Recognition of inefficient practices and unnecessary efforts provides an opportunity to define best practices that will improve the quality and reduce the cost of clinical studies and regulatory approvals in both countries, thereby lowering the costs of product development and of the devices themselves.

Therefore, a WG4 subcommittee conducted a study comparing international GCPs important to Japan and the US. The objective was to determine if the differences identified were substantive with respect to four fundamental criteria pertinent to well-controlled clinical studies intended to support medical device marketing approval. We further sought to develop approaches to address these differences, thereby making it scientifically reasonable and justified to rely upon an alternate GCP.

Methods for Comparison

Several current sources of GCP regulations, standards and guidelines were identified as the most important influences on Japanese and US clinical trials. The GCPs chosen for this analysis were: The International Conference on Harmonisation's (ICH) *Guideline for Good Clinical Practice E6(R1)*, ISO14155:2003, Japanese

Table 1. Currently Issued GCPs Compared in This Study

ICH GCP	International Conference on Harmonisation (ICH) *Good Clinical Practice E6 (R1)*
ISO GCP	ISO14155:2003. Clinical Investigation of Medical Devices for Human Subjects, Parts 1 and 2[1]
JGCP (Medical Devices)	• The *Pharmaceuticals Affairs Law* (*PAL*) (Law No.145, 1960), Revised July 2002), PAL Enforcement Ordinance (Cabinet Order No.11, 1961), Revised December 2003, and PAL Enforcement Regulations (Ordinance of the Ministry of Health and Welfare No.1, 1961, Revised July 2004) • Ordinance of the Ministry of Health, Labour and Welfare No. 36, 23 March 2005 (JGCP) • Japanese Ministry of Health and Welfare, Yakushokukihatsu No.0720005, 20 July 2005 Operation of Good Clinical Practice for Medical Devices (JGCP Manual) • Office memo of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, Essential Documents for Criteria Concerning Clinical Tests for Medical Devices, 20 July 2005 And related notifications and administrative documents
US GCP (Medical Devices)	• 21 CFR 11 Electronic Records; Electronic Signatures • 21 CFR 50 Protection of Human Subjects • 21 CFR 54 Financial Disclosure by Clinical Investigators • 21 CFR 56 Institutional Review Boards • 21 CFR 812 Investigational Device Exemptions • 21 CFR 820 Good Manufacturing Practices • Compliance Program Guidance Manual 7348.809 Institutional Review Boards (CPGM 7348.809) • Compliance Program Guidance Manual 7348.810 Sponsor Inspections (CPGM 7348.810) • Compliance Program Guidance Manual 7348.811 Investigator Inspections (CPGM 7348.811)[2] • 42 USC section 1320a-7b. The Anti-kickback Statute • FDA. *Guidance for Industry: Guideline for the Monitoring of Clinical Investigations*, January 1988 with minor editorial and formatting changes November 1998. • FDA. *Guidance to Industry: Financial Disclosure by Clinical Investigators*, 20 March 2001. • FDA. *Guidance for Industry: Guidance for Institutional Review Boards and Clinical Investigators* And other related guidances and documents

1. The ISO 14155:2003 standard was under a major revision at the time of this study. It was included in the analysis; however, differences were not expounded upon in the results section.
2. Note: CPGM 7348.811 was recently updated in December 2008 to include a new section on international inspections that reflects recent updates to FDA's regulation under 21 CFR 312.120 for acceptance of non-US, non-IND studies. A parallel revision to pertinent sections of 812 is underway.

regulations (JGCP (Iryoukiki no Rinsyosiken no Jisshi no Kijun nikansuru Shorei) (2005)) and US Food and Drug Administration (FDA) regulations current as of 2007 (see **Table 1**).

To achieve the study's objectives, methods for comparison were developed and implemented. Fundamental criteria for a well-controlled trial were established from the preambles of the GCPs for use in guiding and focusing the comparison:

- research subjects' rights, safety and welfare
- scientific integrity of the trial methods
- data quality and integrity
- reliability as a basis for regulatory decision making

To identify similarities and differences across the GCPs chosen for the study, the text of each was studied line by line. Recognizing that the organization of topics, grammar, sentence structure and wording choices differed, the corresponding texts from each GCP addressing a particular topic were collated in an exhaustive comparison table.

After aligning the relevant text of each GCP by topic in the comparison table, their requirements were compared. Similarities and differences were identified and discussed by topic. The practical implementation of each GCP based upon cultural norms was considered. Potential differences were debated by clinical trial experts from the US and Japan in numerous face-to-face meetings. Similarities, differences and the results of the expert deliberation were documented.

Each difference among GCPs was rated as to its importance with respect to the fundamental criteria. Specifically, the impact of each difference on the fundamental criteria was categorized as substantive, nonsubstantive or administrative according to the following definitions:

- "Substantive" differences were likely to have a tangible impact and would be cause for nonacceptance of clinical trial data for regulatory decision making; these differences would require changes to the GCP(s) for convergence.

Table 2. Nonsubstantive Differences

Area of Difference	Documentation Should Demonstrate
Specifying medical experts to advise sponsor on the clinical trial[1]	A medically qualified person is available to advise the sponsor regarding the trial, with involvement in developing the protocol and in the direct line of data review regarding patient outcomes.
Indemnification or compensation for trial-related injuries[2]	There are provisions for patients to be compensated for any trial-related injuries.
Disclosure of potential or actual financial conflicts of interest[3]	Conflicts of interest are identified and disclosed and do not bias or otherwise adversely affect the trial.
Required content of informed consent documents[4]	The informed consent process is adequate according to each investigative site's requirements.
Scope of nontherapeutic provisions of informed consent documents[5]	The informed consent document is appropriate for the trial patient population.
Medical credentials of investigator[7]	The investigators are trained, experienced, and legally qualified or authorized to make medical decisions pertaining to subjects in the trial.
Investigator responsibility for ensuring patient follow-up[8]	The subjects understand instructions on device use and instructions are followed according to the protocol.
Informing other physicians of patient's participation in trial[9]	The investigator attempts to inform the subject's relevant primary physician as the subject permits.
Specifics of IRB documentation requirements	The IRB approval is documented by sponsor according to applicable requirements.
Definition of reportable adverse events and timing of reporting[10]	Adverse events are reported in a reasonably timely manner to appropriate parties.
Labeling investigational product with device trade name, indications and instruction for use in package insert[11]	The product identification and proper instructions for use in the clinical trial are available to the principal investigator and the investigational devices are properly used.
Requirement for auditing[12]	A quality system at the sponsor and investigator sites ensures data quality and integrity and the protection of human research subjects in the trial.

1. JGCP, Article 4, Paragraph 2(1); FDA *Guidance for Industry: Guideline for the Monitoring of Clinical Investigations*, January 1988 with minor editorial and formatting changes November 1998
2. JGCP, Article 14, Paragraph 1; 21 CFR 50.25 Elements of informed consent
3. 21 CFR 54.4 FDA; *Guidance for Industry: Financial Disclosure by Clinical Investigators*, 20 March 2001
4. JGCP Article 71 Paragraph 1; 21 CFR 52.25, 812.40 and 812.100
5. JGCP Article 70 Paragraph 4, JGCP Article 7 Paragraph 2; US 21 CFR 50.53 and 50.24
6. JGCP Article 4, Paragraph 2, Article 16, Paragraph 2; 21 CFR 812.25; FDA *Guidance for Industry: Guideline for the Monitoring of Clinical Investigations*, January 1988 with minor editorial and formatting changes November 1998
7. JGCP Article 2, subparagraph 3 and 11; 21 CFR 812.3 (i)
8. JGCP Article 65, Paragraph 1; 21 CFR 812.100
9. JGCP Article 65, Paragraph 2
10. 21 CFR 812.3(s), 812.150(a)(1) and (b)(1); PAL Enforcement Regulation Article 273, modified by Article 275
11. JGCP Article 24, Paragraphs 2 and 7
12. JGCP Article 31; 21 CFR 812.140 and 812.46

- "Nonsubstantive" differences had some potential for impact on the fundamental criteria but, due to common local practices, were not likely to have a tangible impact (i.e., these differences could be addressed through requests for additional information).
- "Administrative" differences were related solely to documentation or administrative issues and unlikely to have an impact with respect to the fundamental criteria.

For each difference identified pertinent to the four criteria, we debated the underlying focus of each GCP and formulated a statement to describe what the trial documentation should demonstrate to adequately address the underlying issue. We assumed the availability of the documentation required for compliance with the GCP under which the trial was performed. Thus, the statement describes supplementary documentation that may be required to address the difference.

Results

This study found that the organization and depth of coverage of topics, style and word usage varied among the GCPs. However, analysis revealed no substantive differences with respect to the four fundamental criteria. Moreover, there were no contradictory requirements, that is, no requirement of one GCP would necessarily cause noncompliance with one or more of the other GCPs studied.

Table 3. Administrative Differences

Area of Difference	Documentation Should Demonstrate
Signatory personnel in contracts[1]	The trial has written agreements that adequately define delegation of trial activities; responsibilities are fulfilled.
Budget details[2]	Written agreements outline responsibilities and budget arrangements between sponsor and investigator.
Involvement of head of hospital as document signatory[3]	The trial-related documents are appropriately handled, e.g., trials disapproved by the IRB are not approved by the institution.
Investigator brochure	The relevant information is provided to the investigators and IRB.
IRB appeal process[4]	The IRB reviews relevant information and has authority for the final decision.
Notification to patient if informed consent document is changed[5]	The trial subjects receive updated safety information pertinent to their participation and are given an opportunity to consider their continued participation.
Title, protocol number, and date on protocol[6]	The version of the protocol in effect at any point in the trial is clear.
Method of identifying investigator to regulatory authority[7]	The institutions and investigators participating at any point of the trial are detailed in the final report of the clinical trial.
Method of reporting emergency deviations[8]	Local regulations are followed and deviations are reported in final report of the clinical trial.
Need for case report forms in multicenter trials[9]	The primary and supplemental data (if applicable) are collected in a systematic manner.
Timing of device delivery[10]	The time of device delivery has no effect on trial, conformity with IRB/ethics committee or regulatory requirements.
Method of device delivery[11]	The method of device delivery has no effect on the trial.
Details of suspension or termination of trial[12]	The appropriate notification (format, content, and timing) is provided.
Duration of record retention	There is no impact on the clinical trial and records are kept for the period required by each country to ensure traceability of safety and performance of the product.
Differences in the titles and contents of essential documents	The validity of the trial and data integrity can be assessed.

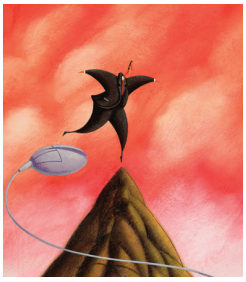
1. JGCP, Article 13, Paragraph 1(1-3); CPGM 7348.810 Part III (B)(1)(c)
2. JGCP, Article 13, Paragraph 1(13); 42 USC section 1320a-7b. *Anti-kickback Statute*
3. JGCP Article 55, Paragraph 2(2)
4. 21 CFR 56.109 (e)
5. JGCP Article 74, paragraphs 2 and 3; 21 CFR 50.25 (b)(5)
6. JGCP Article 7
7. 21 CFR 812.150 (b)(4) and 812.10
8. JGCP Article 66, Paragraph 1; 21 CFR 812.150(a) (4) and 812.35(a)
9. JGCP Article 26, Paragraph 2(1)
10. JGCP Article 11 and Article 25; 21 CFR 812.1
11. JGCP Article 25, Paragraph 2
12. 21 CFR 812.150(b)(2 and 3); JGCP Article 32, Paragraph 2

Our analysis revealed 13 nonsubstantive differences (see **Table 2**) that could potentially be resolved by additional supporting information in the trial records. Trial documentation needed to adequately address each difference is listed in the second column of **Table 2**. For instance, ICH E6 and Japanese regulations define an investigator as a qualified physician or dentist, while ISO and US regulations allow a qualified or licensed practitioner other than a physician or dentist (e.g., a wound care specialist) to be an investigator. Given the licensure and qualification that would be required under each of the GCPs, this difference was considered nonsubstantive. Available trial documentation should be adequate to demonstrate that the investigator is trained, experienced and legally qualified to make medical decisions pertaining to subjects in the trial.

The analysis also revealed several administrative differences between GCPs (see **Table 3**). Trial documentation to adequately address each administrative difference is provided in column 2 of **Table 3**. For example, the location of investigator contact information differed between GCPs. Under Japanese regulations the investigators need to be listed in the protocol, while US regulations do not require this list as a protocol element if it is submitted periodically to FDA. This difference does not affect trial quality and is simply

administrative; the final study report would contain the list of investigators regardless.

Promoting GCP Convergence



GCPs provide a platform for quality in clinical trials. The results of this study may be worth considering when judging the acceptability of trials conducted under one of these GCPs. The lack of contradictory requirements means it may be possible to conduct a trial that meets the requirements of all GCPs studied. Given that this study found no substantial differences among GCPs, trials under any one of them may have acceptable quality. Of course, these findings assume that the trial design is appropriate, that personnel conducting the trial are properly trained and exhibit professional conduct, and that the study is compliant with one of the cited GCPs. In addition to conformity with GCPs, it is necessary to consider the differences in medical practice and population, when determining the acceptability of clinical trial data.

One approach to avoiding concerns about nonsubstantive differences may be to provide adequate trial documentation to address them. A second approach is to in time better harmonize the GCPs by using consistent definitions and ensuring that each GCP addresses the same topics in the same depth.

In fact, modifications to GCPs and research infrastructure have been recognized as important by several medical device trial constituencies. For example, the Ministry of Health, Labour and Welfare (MHLW) has published a five-year plan to boost clinical trial infrastructure and facilitate clinical trials in Japan.[4] Moreover, the US has an opportunity to guide sponsors who perform multinational clinical trials by making US regulations and guidance more consistent in organization and nomenclature with globally recognized standards. The ISO 14155 standard, which had less detail than the other three GCPs on some topics, is currently under revision. So, there is room to further improve and harmonize this standard.

Drug trials may differ from medical device trials; this study focused only on medical device trials. In the same vein, there are regulatory options in the US that are not explicitly provided for in Japanese regulations, e.g. exempt studies such as nonsignificant risk; thus the results and conclusions drawn from this analysis may not apply to these trials.

Language has been a significant barrier to the conduct of a global clinical trial, increasing the cost, duration and complexity of trials as well as delaying approvals. In this study, available translations thought to be reasonably accurate were used.

Summary

This study compared four GCPs important to the conduct of clinical trials in the US and Japan, identified their differences and rated the importance of these differences. No substantive differences, as defined by this article, were found; therefore, it may be possible to accept data from trials conducted in compliance with any of these GCPs, at least in the case of medical device clinical trials in Japan and the US. Non-substantive and administrative differences remain. Hence, the results also support further convergence and harmonization of GCP regulations.

Acknowledgements
The authors would like to thank GCP experts: Yoshihiro Noda, Satoshi Takahashi, Yuuichi Kouzaki, Izumi Fukuzawa, David LePay, Joanne Less, Jessica Greenwood, Sandra Maddock, Kazuhiro Sase, Susan Dunsmore and Christina Allen for their contributions to this project. The authors would like to express appreciation for the hard work from WG4 committee chairs, Carole Carey, Shinichi Takae, Hiroshi Yaginuma and Kentaro Azuma.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guideline. (Note: While the ICH E6 guideline is specifically applicable to drug and biological products, it has been applied as a GCP reference standard for some device studies, and has therefore been included in our analysis).
2. ISO14155:2003. Clinical Investigation of Medical Devices for Human Subjects, Parts 1 and 2
3. HBD Working Group 4 (Regulatory Convergence and Communication http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/InternationalInformation/ucm054026.htm
4. Ministry of Health, Labour and Welfare. New 5 Years' Plan for the clinical trial activation in Japan. April 26, 2007. Available at www.mhlw.go.jp/shingi/2007bunya/iryou/shinkou/dl/03/s0330-5.html.pdf. Most recently accessed 16 December 2009.

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This article represents the analysis and personal views of the authors and does not represent official FDA correspondence or guidance or official MHLW correspondence or guidance. The Harmonization-By-Doing program is focused on collaborative efforts and demonstration projects that promote harmonization of clinical trial practices and medical device regulatory approval processes between the US and Japan.