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What is This?
General Principles for the Education and Training of GCP Inspectors: The Outcome of Discussions by International Regulatory Experts in the Discussion Group on ICH E6 guideline

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Abstract
In response to the globalization of drug development, regulatory inspection of Good Clinical Practice (GCP) has recently been conducted not only by International Conference on Harmonisation (ICH) regions but also non-ICH regions. To promote the international implementation of GCP, consistent understanding and interpretation of its concept among regions are important. This article summarizes the background and past activities of the E6 Discussion Group, established under the Regulators Forum.

Supplementary material for this article is available on the journal’s website at http://tir.sagepub.com/supplemental.

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Introduction

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—E6 Guideline on Good Clinical Practice (ICH-GCP) was reached in step 4 of the ICH process in 1998, followed by official implementation in all ICH member regions (EU, Japan, US). In the past decade, ICH-GCP has also been implemented in non-ICH regions, such as Australia, Chinese Taipei, Singapore, Korea, and Russia, as well as in the member countries of the following organizations: the Association of Southeast Asian Nations (ASEAN), the Cooperation Council for the Arab States of the Gulf (GCC), the Pan American Network for Drug Regulatory Harmonization (PANDRH), and the Southern African Development Community (SADC). Simultaneously, drug development has been globalized, and clinical trials based on ICH-GCP have been conducted in many regions of the world, both domestic and multiregional. Regulatory agencies currently face challenges of reviewing data collected outside their jurisdiction for drug approval. More foreign clinical data will be included in the future new drug applications submitted to each regulatory agency, as drug development is becoming more globalized. To facilitate the use of clinical data including a foreign population for regulatory submission in multiple regions, a prerequisite is that the clinical trial be ethically conducted and data reliability be properly confirmed in all regions participating in it.

In recent years, as a response to the globalization of drug development, an increasing number of drug regulatory agencies in non-ICH regions have reinforced their activities to conduct inspections in their own capacities based on ICH-GCP. However, if the practical implementation of ICH-GCP guideline varies from region to region, data from a clinical trial conducted in one region may not be accepted in other regions. Therefore, regulatory inspections in terms of ICH-GCP should be conducted with consistent understanding and interpretation of its concept, while specific inspection procedure or regulatory decision may be different.

Establishment of the E6 Discussion Group

In 2008, the Regulators Forum (currently called the International Pharmaceutical Regulators Forum) was established to create a regulator-only environment for open discussion of important issues regarding the implementation of ICH guidelines. Based on the discussion at the first forum, the Ministry of Health, Labour, and Welfare and the Pharmaceuticals and Medical Devices Agency of Japan conducted a survey regarding implementation status of ICH-GCP to the non-ICH regulatory agencies. The results of the survey were discussed at the 3rd Regulators Forum, held in Yokohama in 2009; these results indicated that many non-ICH regulatory agencies had already implemented ICH-GCP and that practical harmonization of ICH-GCP was recognized as a high priority for promoting appropriate drug development at the global level. The forum agreed to form the E6 Discussion Group to discuss this topic further among regulatory experts. The missions of the group are to identify critical factors for a proper implementation of ICH-GCP in terms of harmonization and to propose practical ways of improving ICH-GCP implementation.

E6 Discussion Group Activities Since Its Establishment

The Pharmaceuticals and Medical Devices Agency served as chair of the E6 Discussion Group and invited the members of the forum for their interests in this topic. Originally, the regulatory agencies of Australia (Therapeutic Goods Administration), Korea (Korean Food Drug Administration; currently, the Ministry of Food and Drug Safety), and Singapore (Health Science Authority) joined the group. The first web-based meeting was held in September 2009. The group discussed practical approaches and tasks for the proper implementation of ICH-GCP in each country and agreed to share knowledge and experiences and discuss issues related to ICH-GCP implementation by e-mails or teleconference. The outcome of each group meeting was reported to the forum in a timely manner. From the second web-based meeting, held in April 2010, the group started to share experiences of ICH-GCP implementation, such as the GCP inspection process and its results. The number of regulatory agencies in the E6 Discussion Group gradually increased from 4 at its inception to 8 at the third meeting in September 2010 (new members were from Russia, Saudi Arabia, and Thailand and Philippines) and 10 at the fourth meeting in January 2011 (new members from Indonesia and Chinese Taipei). Before the fifth meeting, a representative from Costa Rica (from PANDRH) and members from the SADC
Table 1. Contents of “General Principles for Training/Education of GCP Inspectors” (E6 Discussion Group, May 2013).

Introduction

Purpose

General Steps for Training GCP Inspectors

1. Step 1: Understanding of fundamental information
   1.1. Process of drug development
   1.2. Drug regulation and review/approval process in local regulatory body
   1.3. GCP and related regulations/guidelines
   1.4. Process and procedures at clinical trial sites

2. Step 2: Domestic inspection
   2.1. Before inspection
      2.1.1. Coordination with organization to be inspected
      2.1.2. Preparation for inspection
   2.2. During inspection
      2.2.1. Review of source documents and concerns
      2.2.2. Practice of communication skills
      2.2.3. Clarification of findings and communication with the inspected organization
   2.3. After inspection
      2.3.1. Report of inspection findings
      2.3.2. Conclusion of inspection (regulatory decision making) and notification of inspection result

3. Step 3: Inspection in other jurisdictions
   3.1. A GCP inspector should understand difference(s) between his/her own standard (domestic standard) and the international standard (ICH-GCP).
   3.2. A GCP inspector should understand difference(s) between the international standard (ICH-GCP) and the local standard according to the jurisdiction applied to the inspected organization, including culture/customs, regulatory framework and related regulations.
   3.3. A GCP inspector should have good communication skills including linguistic and/or communication abilities through interpreters.

4. Step 4: Cooperation with foreign agencies and contribution to regulatory science
   4.1. Cooperation with foreign agencies
   4.2. Contribution to regulatory science


joined. At the fifth meeting, in April 2011, the group discussed future topics and agreed to develop a document focusing on effective and appropriate trainings for GCP inspection, noting that training of inspectors is one of the key approaches for proper implementation of ICH-GCP. At the seventh meeting, regulatory agencies from the EU (European Medicines Agency) and Malaysia (from ASEAN) joined the group.

Development of the “General Principles for the Training/Education of GCP Inspectors”

In its sixth meeting, the group began discussions for the development of a statement on general principles for training and education of GCP inspectors. The purpose of this document was to suggest general steps necessary for training/educating GCP inspectors but not the procedures of GCP inspection. The document provides a basis for a national regulatory agency to implement GCP inspection training/education program and to facilitate further international harmonization in implementing ICH-GCP. While various types of inspections are conducted (sites, sponsors, contract research organizations [CROs], etc), the group agreed to focus on those at clinical trial sites that are currently conducted most often in non-ICH regions. However, part of the document could also be applied to GCP inspections targeted to sponsors, CROs, and so on. It would be useful not only for a regulatory agency that has recently started GCP inspection but also for one that has had many experiences of GCP inspection, because current program and quality of training in such agency may be improved and better harmonized. Based on the intensive discussion in the group, the document was finalized on May 23, 2013 (see the online supplementary material). It is not officially endorsed by respective agencies or by the forum.

The document starts with an “Introduction and Purpose” section, followed by the section “General Steps for Training GCP Inspectors,” which consists of 4 steps (Table 1).

Step 1: Understanding of Fundamental Information
In this step, a GCP inspector should learn fundamental knowledge relevant to GCP inspection, such as process of drug development, review/approval process of drugs and clinical trials/investigational drugs in the local regulatory body, GCP-related regulation, and process and procedures at clinical trial sites. This step is achieved through internal and external training opportunities in the forms of lectures, mock up inspection, and so on. A well-planned and well-organized training program is a key to success in this step. Thus, Appendixes 1 and 2 in the online supplementary material are included to present a model of a recommended training program for basic and advanced training, respectively. An inspector who has recently joined a regulatory authority but has sufficient knowledge from his or her previous career may skip part of this step.

Step 2: Domestic Inspection
In this step, the knowledge and skills obtained in step 1 are applied to actual domestic inspections. An inspector initially learns practical skills from experienced inspectors in a way of observational/OJT (on-the-job training) inspections and then becomes able to be independent, although experienced inspectors have always important roles in training and educating the new inspector. As described in section 2.1 of the document, the GCP inspector should well prepare for inspection by reviewing presubmitted documents and
facilitating internal discussions in the agency, as well as by acquiring knowledge about the target disease. The GCP inspector cannot be an expert in all therapeutic area, but knowing about the target disease to the extent possible will increase the quality of the inspection from the scientific viewpoint. During or after inspection, the GCP inspector should also organize the findings from the inspection by having effective communication with the inspectees and propose possible regulatory action(s) according to the internal procedure of the agency, as described in sections 2.2 and 2.3 of the document.

Step 3: Inspection in Other Jurisdictions
In this step, a GCP inspector starts overseas inspection (inspections in other jurisdictions). Thus, additional or different skills from those in domestic inspection are necessary. For example, a GCP inspector should understand differences among the standards in his or her own jurisdiction, the international standard (ICH-GCP), and the local standards applied to the inspected organization.

Step 4: Cooperation With Foreign Agencies and Contribution to Regulatory Science
An experienced inspector should have a more advanced role related to GCP inspection, such as collaborative activities with foreign agencies, including information/experience sharing, observing inspection conducted by a foreign agency, and sharing inspection results/reports. More practical points to consider in the observational inspection are provided in Appendix 3. This step also describes how an experienced inspector can contribute to advancing regulatory science. The ultimate goal of a GCP inspector would be to evolve as a regulatory scientist. On the basis of accumulated knowledge and experiences from the inspection work, the inspector may improve current regulation, establish an international guideline, or present/publish consideration in a scientific meeting/journal, which will result in advancing regulatory science and promoting international harmonization.

Conclusion and Future Activity
The members of the E6 Discussion Group hope that this document (General Principles for Training/Education of GCP Inspectors) will be a reference to many regulatory agencies. Future activity of the group is under discussion, but we will work together in promoting proper implementation of ICH-GCP at the global level. We conclude that the general principles could contribute to establishing better training/educational programs for GCP inspectors.

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Author Note
The views expressed in this manuscript are the personal views of the authors and do not necessarily reflect the official views of the respective regulatory agencies.

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