

## GUEST EDITOR'S NOTE: CLINICAL TRIALS AND GCP IN EAST ASIA

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THE CURRENT TREND of harmonizing regulatory requirements for the registration of pharmaceuticals is a great stride toward globalizing efforts to manufacture safe, effective, and quality drugs and making these drugs available to all regardless of ethnic background, sex, or creed. This goal, while still seen by many as a utopia, is slowly reaching realization. The finest example of this harmonization effort, the International Conference on Harmonization (ICH) of Requirements for the Registration of Pharmaceuticals for Human Use, received an astounding accord not only from the three participating regions, that is, Europe, Japan, and the United States, but also from countries in other parts of the globe. Yet despite the positive attitude toward this movement, there are obviously a number of differences that must be resolved to instill a general acceptance of the ICH recommendations by non-ICH countries. The process of reaching an accord is taking a slow but steady pace.

The DIA Workshop "Clinical Trials and GCP in East Asia," held on July 7, 1996 in Tokyo, Japan, is one similar effort initiated by non-ICH countries in East Asia: China, Republic of Korea, Singapore, and Taiwan. Japan, as an ICH member, provided the cata-

lyst for this effort. These countries grouped together to thresh out areas of differences in Good Clinical Practice (GCP) to enable each of them to adapt the recommendations of the ICH and join the globalization movement. Additionally, scarce resources and a competitive global market have compelled them to join efforts to ensure that their clinical trials meet global standards and likewise to protect them from substandard clinical trials conducted outside their countries.

The increasing number of multinational pharmaceutical companies operating in China, Korea, Japan, Singapore, and Taiwan has somewhat affected the way drug regulatory authorities in these countries handle new drug applications. These authorities are becoming more aware of the need to internationalize their standards and requirements, particularly those affecting clinical trials, in order to keep pace with global competition in trade and technology, while protecting the well-being of their citizenry. This led to the drafting or revisions of GCP guidelines in these countries.

The new drug approval processes in these countries are not much different from each other and from those in the ICH member countries. As presented by the speakers, the differences in their regulatory requirements or standards are attributable mainly to the differences in their countries' local regulatory structures and the need to evaluate and monitor the clinical trial process, which is imperative in all cases. Technically, there are

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no major issues of disparity and all these countries are in agreement with the recommendations of the ICH. An issue emanated, however, on the acceptance of clinical trial data given the socio-cultural differences and ethical values of East Asian (or generally, Asian) countries and Western countries.

Ethical values and socio-cultural differences in the acceptability of foreign clinical data were extensively discussed during the workshop's panel discussion. There was a strong conviction on the part of some participants that these factors, consciously or unconsciously, invariably influence the acceptance of foreign clinical data. There was an extensive debate on the ethical value of clinical data generated from trials conducted in less developed countries for the benefit of more developed countries. The vast diversity in economies and differences in the level of technology of countries in Asia have also raised a question of acceptability of data even between Asian neighbors. These differences provided considerable impact on other issues such as informed consent, monetary compensation to investigators and trial subjects, the issue of insurance and compensation in case of clinical trial-related accidents (adverse events, adverse drug reactions), and so forth. The issue of socio-cultural differences has delineated new arguments with regard to the content of the informed consent form, for example, the level of comprehension of the trial subject or his/her representative or the sagacity of the decision made.

In the course of the discussion, however, there was an apparent consensus among the panelists that these ethical factors and socio-cultural differences should be integrated in the conduct of clinical trials and should not be delineated in such a way as to impede the smooth exchange of information.

There was also an extensive discussion on the characteristic features of GCP guidelines in each East Asian country particularly with regard to the qualifications of monitors/investigators, audits/inspections, requirements for institutional review boards (IRB), and so forth. Some panelists, however, were not

very concrete in their positions since the GCP guidelines in their countries are still in the drafting process and/or under revision. There was a strong consensus to have a follow-up meeting to further discuss these regulatory issues and to tackle future problems which the East Asian countries as well as neighboring countries in Asia might face, particularly if data obtained from trials conducted in less developed Asian country are presented for acceptance by the more developed Asian countries.

A brief discussion of these issues is presented in the following paragraphs. Ethical values turned out to be the most debated issue during the panel discussion. The panelists lengthily debated on the controversy of doing clinical experiments using minorities or underprivileged or people in less developed countries for the benefit of people in the developed countries. There was also the question of whether data obtained from clinical trials conducted in less developed countries can be accepted in more developed countries given the existing differences in the level of technology even between Asian neighbors.

The ethical value of clinical trials has greatly influenced the discussion on informed consent which focused on such questions as the validity of the informed consent, the content of the information to be given the trial subject, and the level of comprehension of the trial subject or his/her representative.

As Dr. Carl Becker (Japan) described it, decisions made in an Asian society are often a product of third party influence. This Asian attitude brings about the question of validity of informed consent, that is, whether the informed consent given by a trial subject is really voluntary or a product of third-party influence. More often than not, Asian people have the tendency to solicit reactions from others or think of what the other person has to say before making their own decisions. It is true therefore that: "decisions made by Asian people are not completely free from third party influence and so to use the criterion of freedom from third party influence

in assessing the voluntariness of an informed consent is somewhat inappropriate in the Asian culture."

This Asian attitude also brought into question the content of the informed consent document or how much information should be given the trial subject. Dr. Becker mentioned a survey conducted in Japan which shows that: "the more the doctor informs his patient, the more the patient tends to let his doctor decide for him." This attitude does not apply to Japan only but also to other Asian countries, and, as he further mentioned, this attitude defeats the purpose of informed consent, in that: "the document in itself is an informed consent but the content goes the other way." There is also the question of mental competence on the part of the trial subject or how much the patient understands the document presented to him. This issue is important particularly in structuring an informed consent document to be used in a multicenter clinical study. There is always the possibility that a single term may be interpreted differently in each country (particularly with the use of different writing systems, eg, Han [Chinese], Kanji, Hangul, etc.) and the use of technical terms may pose problems in patients who are not familiar with the term or, even when explained, have difficulties in comprehension.

A misnomer of the term "in-house IRB," that is, an IRB operating within the company sponsoring the study, posed a slight confusion during the discussion of this subject. Dr. Robert Teoh (Singapore) expressed disagreement with the existence of such "in-house IRBs in pharmaceutical firms" saying that: "it defeats the whole purpose of the neutrality and independence of an IRB." But the ensuing discussions clarified this issue and identified IRBs as a special committee or body responsible for the review of protocols and other clinical trial data and documents. Dr. Sang Guo-Wei (China) mentioned that in China, they prefer to call this body an ethics committee and that this committee may belong to the hospital or institution conducting the trial. The panelists were all in agreement

that the IRB or ethics committee (EC) should be independent from the study.

While the term "in-house IRB" might be a misnomer, it may be used to refer to such a group or committee which can be convened or called upon very quickly when necessary to give oversight or provide relevant opinions. This group or committee is particularly helpful when serious adverse drug reactions occur during a study and recommendations on whether to terminate or continue the study should be readily obtainable. Dr. Tominaga (Japan) stressed the need for these kinds of committees to clarify responsibility for assessing the continuation or termination of a clinical trial. Multidisciplinary membership appears to be the general criteria for IRB/EC composition and there is the common practice of recruiting nonmedical persons as members to ensure unbiased recommendations and independent status.

The utilization of contract research organizations (CROs) in the conduct of clinical trials has long been practiced in the West. Most of the GCP guidelines in East Asia, however, are still vague on this point (particularly with regard to the activities and conduct of the CROs) and the panel discussion was limited to the general existence of CROs. Albeit the absence of exact guidelines on such a practice, it suggests that these types of facilities/entities are already widely utilized in East Asia especially in the conduct of multicenter clinical studies.

As for the educational qualifications of monitors and investigators, these are somewhat varied, presumably because of differences in local regulatory structures in each East Asian country. Pharmacy and nursing education are the most common educational backgrounds. In China, however, they favor recruiting medical practitioners as monitors/investigators.

The audit/inspection of clinical trial documents is usually the responsibility of the sponsor and is reflected as an integral part of the GCP guidelines in East Asia. Currently, preliminary audit of trial documents by regulatory authorities is only a prerogative func-

tion and the current GCP guidelines in East Asia have no definite provision on this. It was acknowledged, however, that this government function is very vital in ensuring the integrity of clinical trials and regulatory authorities are now amending their GCPs to clearly state this function.

The question raised regarding the reimbursement of trial-related diagnostic or laboratory tests may well be taken as a concern about financial gains by trial subjects or investigators. This is a controversial issue in the sense that it can invariably influence the conduct and eventual result of clinical trials. Previous discussions on this topic have been directed to the issue of how independent an investigator or how cooperative a trial subject might be given the financial gains that he would reap from the results of the study.

There is also a question on product liability, in particular, if a clause on limitation of liability should be included in the informed consent. The "duty of care" is inherent upon all those responsible for the conduct of the trial. It should also be acknowledged, however, that there is always a potential risk involved not only to the participating trial subjects but also to the manufacturer. Trial-related injuries often develop into costly lawsuits even when a trial subject has voluntarily participated in the trial. On the other hand, the limitation of liability can hamper the recruitment of potential trial subjects which could hinder the development of much needed new drugs for the treatment of diseases, particularly those with no current treatments.

The fast growing economies of countries in Asia makes this region conducive to pharmaceutical development. Realizing this, the governments in these countries have launched programs to better educate and train their medical practitioners and related personnel in the conduct of clinical studies to keep pace with the demand of multinational pharmaceutical companies establishing businesses in this region. A number of workshops and seminars in GCP are now being conducted by both governments and private organizations.

Information dissemination through print media, however, is still limited to medical or scientific journals and the use of the media is still not very popular.

The recent health-related scandals in Japan have prompted calls for the government to better provide the public with this kind of information and the media has clamored for this. But it now raises the question of whether the information released through the media is accurate or reliable given the notorious attitude of media personnel in exaggerating news stories for the sake of publicity or sensationalism. Yet, the immense power of the media in information dissemination cannot be taken for granted.

Nowadays, people can put communication at the tip of their fingers. Technological innovations such as computers, satellites, fiber optic cables, the Internet, and so forth have practically shrunk the world. Through these high-tech innovations, people from opposite sides of the globe are now able to swiftly and easily communicate with each other. Yet, despite the fascinating effects of modern technology, socio-cultural differences and ethical values are still very much affecting the way people think. While people may want to believe that these differences are not barriers in the advancement of modern science, including the development of new drugs, they sometimes cannot avoid confronting these issues in real-life situations. Ironically, racism oftentimes clouds this issue and it is sometimes difficult to make an objective assessment or conclusion.

Dr. Sang's statement: "there will not be an ethical problem because first we have to think about potential benefits not only to the manufacturing country but also the countries in the world who will use it" guarantees an equal treatment of all clinical trial cases. When thinking of mutual benefits, however, it is worth considering the respect for the ethical values and socio-cultural differences inherent in each individual.

The development of the concept of viewing health care (drug development) not only from the viewpoint of the caregiver (govern-

ment and pharmaceutical manufacturer) but also from the viewpoint of the receiver (patient) is needed. This is a very ideal approach in medical care and if ICH principles are to work effectively in non-ICH countries, GCP

guidelines must be structured based on this concept.

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