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Workshop on Good Clinical Practices in Clinical Trials and Post-Marketing Surveillance

A Report
New Delhi, India, 13-17 March 2007

World Health Organization
Regional Office for South-East Asia
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1. Introduction

The South-East Asia Region (SEAR) is emerging as a major producer and supplier of vaccines to the global and regional markets. India, Indonesia and to some extent Thailand, the three South-East Asia vaccine producing countries, are expected to increasingly take over the supply of traditional EPI vaccines and new combination vaccines to meet the regional and global vaccine demands. At the same time, these countries are investing in the research and development of new vaccines. Vaccine production requires a strong regulatory system to monitor safety, quality and efficacy, and clinical trials during the different phases of vaccine development are important and critical activities.

Furthermore, vaccine manufacturers in industrialized countries (IC) are increasingly looking at developing countries to conduct clinical trials, to produce or finalize vaccines (filling, packaging) and to distribute vaccines worldwide. Different approaches are taken such as joint ventures, installation of facilities by such manufacturers in developing countries, for example, joint ventures have already been established in India, Thailand, Indonesia and in Myanmar.

In this context, national regulatory authorities (NRA) in developing countries are faced with the challenge of fully regulating vaccines to ensure their safety, quality and efficacy including the oversight of clinical trials that may be conducted. Developing countries are expected to establish accredited scientific and technical review committees as well as research ethics committees to ensure compliance with principles of Good Clinical Practice (GCP) consistent with international ethics norms and a monitoring system for Adverse Events Following Immunization (AEFI) in the post-licensing era of vaccine. While some Member countries in the Region have developed capacity, most either do not have such regulatory processes in place or even if they are in place, they are not often implemented adequately. Therefore, assisting Member countries in strengthening capacity in this area is a priority activity for IVD.

It was in this context that a GCP workshop was organized by the WHO Regional Office for South-East Asia in New Delhi from 13-17 March 2007. Where clinical trials are conducted, trial-specific GCP training is carried out by the agencies coordinating trials, but there has never been a GCP course aimed at National Regulatory Authority/National Control Laboratory (NRA/NCL) of Member countries. WHO's special programme on tropical diseases research (TDR) has been conducting GCP training and training to develop a pool of clinical trial monitors. In November 2005, TDR conducted a biregional training course on GCP attended by participants from some SEAR countries as well as from IVD unit in SEARO. It was felt that a similar workshop specifically targeted at NRA/NCL would be indeed very useful for Member countries in the Region.

The participants attending this workshop were officials from the NRA, NCL and key persons/officials involved with vaccine regulations as well as representatives of national medical research institutes currently involved in clinical trials.

In his address at the inaugural session, delivered by Dr Than Sein, acting Regional Director, Dr Samlee Pliangbangchang, Regional Director, WHO South-East Asia Region emphasized the importance of clinical trials and noted that "the conduct of a clinical trial requires that human safety be considered as the first and predominant concern." Explaining the importance of this workshop as part of WHO's efforts to strengthen national capacity the Regional Director said that "while we must promote clinical trials to develop new products, we need to ensure that they are carried out within established international standards and practices. Training workshops such as these are important to highlight not only the scientific steps and procedures but also the pitfalls and the issues that one needs to be aware of while designing or evaluating a clinical trial." Cautioning over too restrictive an attitude over development of new vaccines and vaccine delivery technology the Regional Director said "there is no single technology that is absolutely safe; the challenge before us, therefore, is to ensure that risks are minimized while attempting to maximize benefits."

2. Overview of the subjects discussed

Good clinical practice is defined as "a set of internationally recognized ethical and scientific quality requirements which must be observed for designing,

conducting, recording and reporting clinical trials that involve the participation of human subjects." Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible and accurate.

Prior to the 1990s most countries did not have standards for clinical practice defined except for the regulatory authorities of USA, Japan and Europe. Realizing that there was a need to harmonize standards and practices across the world, an International Conference on Harmonization (ICH) took place in April 1990 in Brussels. Since then, the ICH meets regularly to recommend ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

The course began with a brief history of the development milestones for the ICH and GCP standards. GCP is an internationally accepted ethical and scientific quality standard in the design, conduct, recording and reporting of trials that involve human subjects. Subsequently, the participants were taken through the various steps in the design and conduct of a clinical trial of vaccines with real-life experiences and examples from actual trials. The following areas were covered during the workshop:

- Phases of clinical development
- Principles of GCP (historical perspectives and current GCP requirements)
- Ethical considerations in medical research
- Responsibility of Institutional Review Board/Independent Ethics Committee (IRB/IEC)
- Responsibility of sponsor
- Responsibility of monitor
- Responsibility of investigator

- Safety issues in clinical trials –concepts and definitions
- Data safety and monitoring board (DSMB)
- Critical role in meeting trial objectives
- Development of statistical analysis plans
- Data management plan and structure
- Clinical trial registry
- GCP and quality improvement
- Preparing and ensuring proper application of GCP principles
- Case study-HIV vaccine trials
- Clinical laboratory
- Trial audit and inspections
- Regulatory requirements-international and Asian studies
- Ethical considerations in HIV/AIDS vaccine clinical trials
- Standard operating procedures (SOP) and writing SOPs
- Principles of post-marketing surveillance
- Current situation of post-marketing surveillance in the Region and future plan.

Apart from didactic lectures on the various topics, there were group discussions, question and answer sessions and an open forum to share experiences, clarify doubts and obtain specific information where appropriate. The workshop also included hands-on practice in the development of standard operating procedures on a topic chosen by each group.

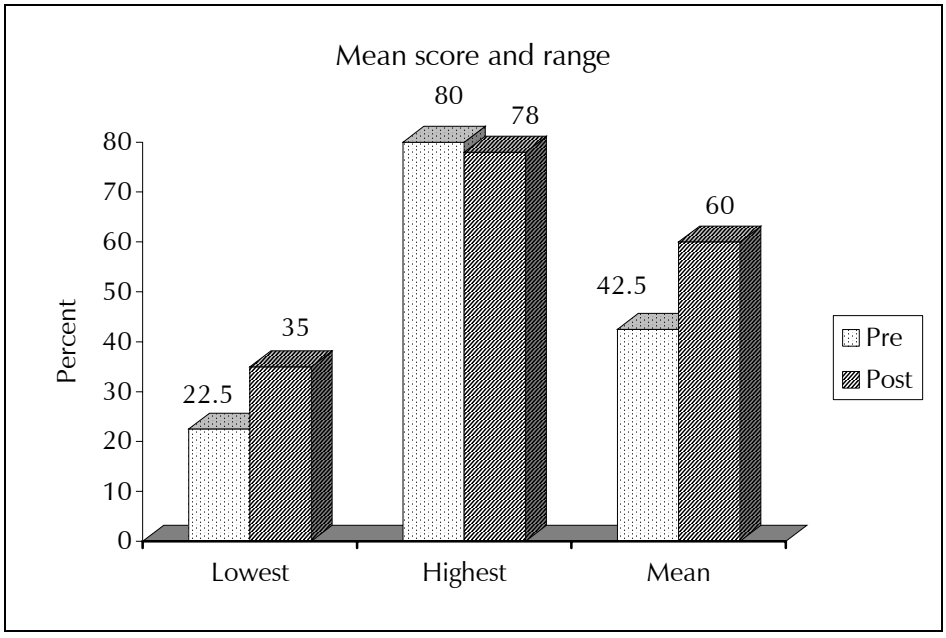
One key element that has been highlighted for this workshop was the issue of adverse events following immunization (AEFI). This is becoming increasingly important for countries that do not produce vaccines but use them. In recent years there have been changes, for example, in European Agency for the Evaluation of Medicinal Products (EMEA) that will allow a medical product to be produced in a European country meant for use outside Europe; the only condition required to allow export is a scientific opinion. While there is nothing wrong with this, the onus of post- marketing surveillance for long-term adverse events is shifted to the country importing the product and is no longer the responsibility of the NRA of the country of manufacture.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) which is a non-profit, non-governmental Organization (NGO) representing national industry associations and companies from both developed and developing countries provided technical assistance to the workshop. Member companies of the IFPMA are research-based pharmaceutical, biotech and vaccine companies. IFPMA identified a facilitator from Sanofi Pasteur based in India who provided excellent insights into how the pharmaceutical industries approach the issue of post-market surveillance.

3. Assessment of the course

Dr. Juntra Karbwang-laothavorn, the key facilitator for this workshop, devised a 40, multiple- choice test paper that was administered to the participants both before the course as well as after the course. The questionnaire aimed to pick out key information related to clinical trials, good clinical practices including issues of ethics. It was clear that the course helped to improve the knowledge base of the participants.

Figure 1. ***Score of the pre-and-post-course assessment results of the GCP Course***



4. Collaborative approach to organizing this workshop

This course was made possible due to the strong collaboration efforts between WHO, the International AIDS Vaccine Initiative (IAVI), WHO/TDR/HQ, and specialized entities such as the Indian Council of Medical Research (ICMR), and the IFPMA. This course is an example of WHO's ability to bring together a host of partners to provide much-needed support to strengthen the capacity of Member countries. (For a detailed list of people involved, please see Annex 2)

5. Feedback from the course

At the end of the course, apart from the evaluation questionnaire, there was an opportunity to obtain feedback from the participants as follows:

- The participants appreciated the course and felt that there was much they learnt despite many being senior national regulators with several years of experience.
- They also highlighted the vast scope of the GCP and the need to trim the course down to manageable components
- The participants pointed out that sometimes there was repetition and sometimes it was hard to follow the link from one subject area to the next
- Participants requested WHO to focus, in future courses, on quality assurance with emphasis on site visits and practical aspects of GCP
- The participants also requested WHO to organize courses that focus primarily on GCP inspection and NRA review of clinical trial protocols
- WHO was requested to provide Training of Trainers (ToT) for GCP and clinical trials
- WHO was requested to support country-level training of GCP so that more people could be involved and benefit from such training.

6. Future steps

Based on the feedback from the course, IVD/SEARO will pursue the following strategies in future:

- IVD, in collaboration with other partners, will organize regional training for GCP periodically, although it may not be on an annual basis.
- If countries decide to organize country-level training, IVD will provide whatever support it can to facilitate the course
- IVD will explore with partners the possibility of organizing a specific GCP course on GCP inspection and NRA review of clinical trial protocols.

Annex 1

Agenda

13 March 2007

08:30 – 09:00	Registration	
09:00 – 09:40	Opening session	
	• Welcome speech and opening address	Regional Director, WHO/SEARO
	• Workshop objectives and expected outcome	*Dr Pem N.*
	• Introduction of participants/facilitators	
09:40 – 10:30	Assessment of GCP Knowledge	
10:30 – 11:00	Tea/Coffee break	
11:00 – 12:00	Overview on Process of Product Development	
	• Phases of clinical development	*Dr Juntra K*
	• Principles of GCP (historical perspectives & current GCP requirements)	*Dr Juntra K*
12:00 – 13:00	Discussions	
13:00 – 14:00	Lunch	
14:00 – 14:30	• Ethical Considerations in medical research	*Dr Vasantha M*
14:30 – 15:00	• Responsibility of IRB/IEC	*Dr Vasantha M*
15:00 – 15:30	• Discussions IRB/IEC issues	
15:30 – 16:00	Tea/Coffee	
16:00 – 17:00	Movie on GCP	

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09:00 – 09:30	Responsibility of sponsor Responsibility of monitor	*Dr Juntra K* *Dr Juntra K*
09:30 – 11:00	Responsibility of investigator	*Dr Juntra K*
11:00 – 11:30	Tea/Coffee	
11:30 – 13:00	• Safety issues in clinical trials – concepts and definitions	*Dr Juntra K*
	• Data Safety and Monitoring Board (DSMB)	*Dr Juntra K*
13:00 – 14:00	Lunch	

14:00 – 15:30	Data management and statistics	
	• Critical role in meeting trial objectives	*Dr Jeyaseelan*
	• Developing statistical analysis plans	*Dr Jeyaseelan*
15:30 – 16:00	Tea/Coffee	
16:00 – 17:00	Data management plan and structure	*Dr Jeyaseelan*
15 March 2007		
09:00 – 10:00	• Clinical Trial Registry	*Dr K Weerasuriya*
	• Discussion	
10:00 – 10:30	Tea/Coffee break	
10:30 – 11:30	Quality assurance and quality control	
11:30 – 13:00	• GCP and Quality improvement	*Dr Juntra K*
	• Preparing and ensuring proper application of GCP principles, Case Study – HIV vaccine/Malaria	*Dr Jean-Louis*
13:00 – 14:00	Lunch	
14:00 -15:30	• Clinical laboratory	*Dr Vijayasekaran*
	• More issues on trial monitoring	
15:30 – 16:00	Tea/Coffee	
16:00 – 17:00	Trial audit and inspection-	*Dr Vijayasekaran*
16 March 2007		
09:00 – 10:30	Regulatory issues in clinical trials	
	• Regulatory requirements – International and Asian status	*Dr Vasantha*
	• Discussion on regulatory issues in clinical trials	*Dr K Weerasuriya*
10:30 – 11:00	Tea/Coffee break	
11:00 – 13:00	• Ethical considerations in HIV/AIDS vaccine clinical trials	*Dr Jean-Louis*
	• Standard Operating Procedures	*Dr Vijayasekaran*
13:00 – 14:00	Lunch	
14:00 -17:00	Case study (SOP writing workshop): Moderator	*Dr Juntra K*
	Case study: informed consent form development - HIV/AIDS	*Dr Jean-Louis*
15:30 – 16:00	Tea/Coffee	

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09:00 – 09:45	Principles of post marketing surveillance	*Dr Shailesh Mehta*
09:45 – 10:15	Current situation of post marketing surveillance in the Region and Future plans	*Mr Stephane G.*
10:15 – 10:45	Tea/Coffee break	
10:45 – 11:30	Discussion on Safety and Post Marketing Surveillance	Moderator: *Jean-Louis*
11:30 – 13:00	AOB – Open Forum Discussion	Moderator: *Dr K. Weerasuriya*
13:00 – 14:00	Lunch	
14:00 – 14:30	GCP course feedback (workshop evaluation)	
14:30 – 15:00	Closing	
15:00	Disperse	

Annex 2

List of participants

Country participants

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