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Administrative Notice

July 1, 2013

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles of Risk-based Monitoring

The Guidance on Ministerial Ordinance on Good Clinical Practices (PFSB/ELD Notification No. 1228-7 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 28, 2012. Hereinafter referred to as the Guidance on GCP.) indicates that not all clinical trial data has to be verified against the source data for trial monitoring. Introduction of this kind of risk-based monitoring is expected to increase efficiency of trial operations as well as to ensure safety of the subjects and the integrity of clinical trials.

The Research on the Operation of Investigator-initiated Clinical Trials, one of the research projects receiving the FY 2012 Health and Labour Sciences Research Grants of Research on Regulatory Science of Pharmaceuticals and Medical Devices, has recently compiled a report on their discussions held regarding measures and principles of trial monitoring operations to increase efficiency via application of a risk-based SDV approach.

Based on this research report, the basic principles of risk-based monitoring have been compiled in the attachment of this administrative notice. We ask you to inform relevant manufacturers and medical institutions placed under your department to utilize this as their reference for their operations.

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Attachment

Basic Principles of Risk-based Monitoring

1. Background

In conducting clinical trials, it has been pointed out that monitoring requires a large workload and many expenses and that further increased efficiency is necessary to activate clinical trials. The Five-Year Plan for Activation of Clinical Research and Clinical Trial, 2012 (March 30, 2012, Ministry of Education, Culture, Sports, Science and Technology/ Ministry of Health, Labour and Welfare) has also set short-term targets to increase efficiency of clinical trial procedures by “increasing efficiency in monitoring operations (including direct inspections) with the consideration of the concept of sampling SDV (source document verification).”

The introduction of appropriate and efficient monitoring methods is expected to not only increase efficiency of corporate-initiated clinical trials but to help conduct smooth investigator-initiated clinical trials where there are many limitations on human and economic resources.

2. Risk-based monitoring

Because clinical trials have recently become diversified and because quick and centralized management of clinical trial data has become possible with the wide use of EDC (electronic data capture), the effects on the quality of the clinical trials have begun to be evaluated more in order to investigate monitoring methods based on those risks from the perspective of both the importance of data when referred to the objective of the clinical trial and of ensuring the safety of the subjects.

In August 2011, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have each issued a draft guidance regarding either risk-based monitoring or quality management. Both of these draft guidances have recommended applying appropriate methods of risk-based monitoring to increase efficiency of the

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monitoring operation, while at the same time indicated the importance of quality management of clinical research.

The Ministerial Ordinance on Good Clinical Practices (hereinafter referred to as GCP) allows monitoring to be conducted by methods other than onsite SDV as long as the safety of the subjects and scientific integrity are ensured. Centralized monitoring is defined in the guidance on Article 21 Paragraph 2 and Article 26-7 Paragraph 3 of the GCP (PFSB/ELD Notification No.1228-7 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 28, 2012).

3. Risk-based SDV approach

It is possible to apply the risk-based SDV approach when conducting SDV for monitoring. The risk-based SDV approach is a method of conducting SDV on data (not only the data items but also data on subjects physicians, medical institutions, and time of visits) that were extracted according to a certain pre-established procedure, with consideration of the effects on the quality of the clinical trial from the perspective of both the importance of data when referred to the objective of the clinical trial and of ensuring safety of the subjects. The guidance pertaining to Article 21 Paragraph 1 and Article 26-7 Paragraph 1 of the GCP clearly states that “if clinical research core hospitals are able to appropriately manage clinical trials (including data quality assurance) in medical institutions and other facilities, not all clinical trial data have to be verified against the source data in trial monitoring.”

4. Basic principles for applying risk-based monitoring and SDV approaches

Based on the above situations, the following are the current basic principles for applying risk-based monitoring and SDV approaches when conducting clinical trials.

- With monitoring methods becoming diversified, medical institutions must make efforts to promptly submit data assuming that monitoring may not be conducted based on SDV.
- When applying risk-based monitoring and SDV approaches, the investigator, subinvestigator, clinical research coordinator, and other relevant people must have a

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thorough understanding of the objectives and procedures of these methods in order to ensure the quality of the clinical trial. With this as a basis, relevant people are required to be aware of the fact that accurate case report forms must be completed as their own responsibilities at medical institutions and to carry out their duties with this in mind.

- Medical institutions are required to put emphasis in managing the clinical trial process and to take appropriate measures to have case report forms be completed accurately. For example, for appropriate management of trial-related data that were collected at medical institutions, measures are to be taken in order to have the items (data) from usual clinical records and the items especially for clinical trials to be clearly distinguished, and to establish rules and systems to appropriately keep records of both of those data.
- It is important for sponsors (or the sponsor-investigators) to make the study design (ex. protocols and case report forms) clear and concise by focusing on collecting data that are necessary for achieving the objective of the clinical trial.
- When determining specific approaches for risk-based monitoring and SDV, the trial objective, study design, endpoint, study population, and the experience of the investigator and medical institutions and their clinical study system should be considered.