KFDA Inspection Program for Quality and Compliance Efforts

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1. Introduction
2. Regulatory basis for clinical trials in Korea
3. KFDA’s inspection (Clinical trials)
4. 2011 inspection plan
5. Strengthen the competitiveness of clinical trials
INTRODUCTION
KOREA FOOD AND DRUG ADMINISTRATION

Promoting the public health by ensuring the safety and efficacy of foods, pharmaceuticals, medical devices and cosmetics, and supporting the development of the food and pharmaceutical industries.

The government agency committed to protecting consumers and promoting the public health.

Strengthening clinical trial management

**Mission**
Protect and improve national civil health through enhancement of management system and strengthening clinical trial policies

**Vision**
Construct highly globalized level of clinical trial infrastructure and regulation-advanced country
Clinical Trials under control of KFDA

Accreditation

Reports

Inspection

Adverse events

Approval

KFDA

Drugs
- Phase 0
- Phase 1 to 3
- Phase 4
- IIT
- Emergency use

Biologics/Herbal Medicines
- Phase 0
- Phase 1 to 3
- Phase 4
- IIT
- Emergency use

Medical Devices
- Clinical trials

Health functional food/Functional cosmetics
- Test for humans

Drug Information Association www.diahome.org
IND Approval in Korea

KFDA database

Drug Information Association

www.diahome.org
2. Regulatory Basis of Clinical Trials in Korea

REGULATORY BASIS FOR CLINICAL TRIALS IN KOREA
Continuous effort for legalization to support harmonization of clinical related regulations to international standards since KFDA formed in 1998
1987  Establishment of KGCP (recommendation)
1995  Requirement for compliance of KGCP
1999  Adoption of the Bridging Concept (E5)
2000  Harmonized with ICH guideline E6
       Establishment of Pharmaceutical Act Article 26-4
       (‘07. 4. 11 changed to Article 34)
       - protect the rights and safety of subjects
       - clarify the responsibility of investigator
       - reinforce the function of IRB

2002  Introduction of IND
       - Separation between developmental clinical stage and commercial product
         approval, IND and NDA
       - Participation in multinational study at any stages

2006  KFDA Clinical management team establishment
2007  Management of joint IRB for multi-site clinical trial
2010  Shortened review period for phase 1 clinical trials (healthy volunteer)
Overview of Clinical Trials

Principal Investigator
- Writes Study Report
- Selects Study Subjects

Investigator

Sponsor
- Protocol
- Preclinical Studies
- Compensation
- Study Monitoring
- Data Audit

Director of Investigational Site
- IRB
- Establishment of SOPs
- Create Administrative Office
- Select Administrator
- Protect Patients’ Rights
- Maintain Clinical Trial records

Auditor

Written Informed Consent

Patient

Protocol Submission

Adverse-Event Reports

Director of Investigational Site

Protocol Submission

IRB

Inspection

KFDA
- Protocol approval
- Inspection
- Institution accreditation

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Overview of Investigator initiated Clinical Trials

- Principal Investigator
  - Writes Study Report
  - Selects Study Subjects
  - Compensation
  - Study Monitoring
  - Data Audit

- Investigator
  - Patient
  - Provider
  - KFDA
  - Director of Investigational Site
    - IRB
    - Establishment of SOPs
    - Create Administrative Office
    - Select Administrator
    - Protect Patients’ Rights
    - Maintain Clinical Trial records

- Auditor
  - Written Informed Consent

- Drug / Medical device
  - Adverse-Event Reports

- Protocol Submission
  - Adverse-Event Reports

- KFDA - Protocol approval
  - Inspection
• Aim is to assure the quality of clinical trials according to the requirements and to qualify clinical institutes since 1997 (drugs) & 2006 (medical devices)

• What are necessary to be accredited?
  – Appropriate facilities and equipments
  – Pool of personnel to support the clinical study
  – Pertinent IRB structure and activities
  – Educational program (KGCP)
  – Infrastructure for the clinical trial management
KFDA’S INSPECTIONS (CLINICAL TRIALS)
• **KFDA inspects sponsors and accredited institutions:**
  - To protect the rights, safety, and welfare of subjects involved in clinical trials in Korea
  - To verify the integrity and reliability of clinical trial data submitted to KFDA in support of research/NDA
  - To ensure full compliance with the protocol and the regulations, guidelines and standard operating procedures of clinical trials

• **Scope of inspection**
  - Sites: Clinical Investigator, IRB etc
  - Sponsors: Contract Research Organization (if applicable), Monitors etc
• **Inspection type**
  - Scheduled (Regular) inspection
  - Unscheduled (Directed) inspection – for-cause

• **Inspection strategy**
  - Inspection of on-going and completed clinical trials
  - Selection of trials based on the risk assessment process and IIT
    - Development phase
    - Product type (NCE, Recombinant product, Cell therapy, gene therapy, others)
    - Complexity of the trial design
    - Subject enrollment
    - Therapeutic indication or area
    - Study population (pediatric, other vulnerable, general)
    - Serious unexpected adverse drug reaction at the clinical trial site
<Regular Inspection>

- **Target**
  - All Sponsors
  - All accredited clinical institutes ('07: number of 70) ('08: number of 43) ('09: number of 35)

- **Inspectors**
  - More than two inspectors in one team

- **Contents**
  - Fulfillment of overall institutional management in clinical trials

- **Period**
  - One institute, One team, No more than 5 days (personnel and time can be appropriately changed when required)
<Directed Inspection>

Enforcement regulation of PAL Art 32 / MDL Art 13 and KGCP compliance inspections

- **Annual report**
  - First subject registry
  - Annual report related to progression of clinical trial
  - Termination report

- **Safety report**
  - SAE reports Individual SUSAR e.g. Death etc.

- **Completion report**
  - Reliability of final report submitted to the KFDA in support of NDA

- **Etc**
  - Civil complaint
  - Confirmation of process related to take-back and discard of IMP
**Inspection Process**

### Prior to an Inspection

- **2 weeks ~ 10 days**
  - **Preparation**
    - ✓ arrange an inspection (if site personnel plan to participate in the inspection)
    - ✓ send an official notice
    - ✓ obtain a list of IRB-approved protocol

### During an Inspection

- **1 ~ 5 days**
  - **Progress**
    - ✓ inspect facilities
    - ✓ review background materials (e.g., study protocol, informed consent documents, CRF)
    - ✓ interview
  - **Close**
    - ✓ communicate inspectional issues and observations with site staff
    - ✓ documents full narrative reporting of any deviations found during inspection

### After an Inspection

- **2 weeks**
  - **Debriefing**
  - **Follow-up**
    - ✓ summarize and report of findings
    - ✓ classify the findings into categories
    - ✓ notify a post-inspectional correspondence (Warning Letter or Notice etc)
• **Preparation**
  – The ‘Annual inspection plan’ is developed and finalized by KFDA

  – The inspection dates are arranged and confirmed with the inspectee

  – A ‘Notice of inspection’ is sent to the inspectee of the site to be inspected within 10 days prior to the proposed date(s) of site inspection

  – The inspectee should submit a ‘List of approved protocol by IRB’ to KFDA within 5 days of receipt of the Notice of inspection
    - To select the studies and request relating documents for inspection

  – Check-list for inspection on investigators, IRBs and sponsors have been published to guide the related stakeholders for preparation of KGCP inspection
• During Inspection
  – Opening Meeting with key site staff
  
  – Facility Tour
    - Visit drug storage & laboratory & archiving room etc
  
  – Document Review
    - Study files for essential documents, informed consent documents
    - Data in source documents and CRF
    - Drug accountability
    - Monitoring visit reports
    - Documents related to Laboratory
  
  – Interview with study staff and site personnel
  
  – Check the roles and responsibilities of study staff
• During Inspection
  – Closing meeting after inspection
    - Thank site staff for their cooperation and time for this inspection
    - Explain what was reviewed during the inspection
    - Explain positive aspects of study conduct at the site
    - Discuss identified issues and findings during inspection
    - Explain corrective actions on significant findings and
    - Make an agreement with study staff
    - Final report and conclude the inspection
• **Follow-up**
  
  – A ‘Inspection report’ of the finding is issued to inspectee within 2 weeks after inspection
  
  – The inspectee should submit the ‘Corrective Action and Preventive Action Plan’ to KFDA within 30 days of receipt of the site inspection report
  
  – Once the ‘Corrective Action and Preventive Action Plan’ is deemed to be adequate, a site inspection will be closed. Appropriate action will be taken if non-compliance is detected
• Violation (Critical)
  – A significant issue that poses unacceptable risks
    - Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data
    - Immediate realization of importance of the problem and pertinent action is required to solve such issue
    - Take an administrative measure according to the Pharmaceutical affairs Law if necessary

• Correction (Major)
  – An issue that poses or has the potential to pose high risks
    - Conditions, practices or processes that might adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data
    - Realization of the problem and pertinent action is required to solve such issue
    - Corrective actions (Supplement materials) are requested to be submitted to KFDA
    - Additional inspection is not necessary once the requested documents are fully submitted (e.g., pictures and/or source documents)
Classification of inspection findings

• Caution (Minor)
  – An issue that poses or has the potential to pose moderate risks
    - Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data
    - Realization of the problem is required to be done
    - Point out letter is issued to inspectee to instruct how to improve quality and/or reduce the potential of deviation to occur in the future

• Recommendations
  – The observations that might raise suggestions on how to improve quality and/or reduce the potential of deviation to occur in the future
    - Proceed without further action
• **An informational letter**
  - Consists of deviations and the relating statutes and regulations. Voluntary corrective action is necessary. Occasionally, such letter requests response from the IRB

• **A warning letter**
  - Consists of serious deviations and the relating statutes and regulations. A warning letter generally requests prompt corrective actions and also a formal written responses to KFDA
4. 2011 Inspections

2011 INSPECTION PLAN
* Establish **standard criteria** for inspection results open to public
* Improve **reliability** of inspection quality
  – Establish inspection SOP for clinical trial inspection
* Construct a **voluntary safety management system**
  – Open the information of inspection (date and plan) to public for institutions to prepare all the documents to be inspected
  – Establish Inspection Q&A
  – Itinerant education
  – Establish voluntary inspection SOP for institutions
* **Strengthen the subject protection** by providing accurate information to the subjects
  – Inspect ICF and information to trial subjects
  – Inspect IRB approval for subject advertisement before conducting clinical trials
  – Inspect labeling of investigational drugs
2011 Inspection Plan - Targets

• **Targets**
  
  – Regular(scheduled) inspections
    • Accredited clinical trial institutions
  
  – Directed(unscheduled) inspections
    • Sponsors, accredited clinical trial Institutions
  
  – Voluntary inspection
    • Initiated and performed by accredited clinical trial institutions
Regular(scheduled) Inspection

- Triennial/each institution
- 62 accredited clinical trial institutions
  - 58 institutions accredited for drugs
  - 27 institutions accredited for medical devices
  - 23 institutions accredited for both drugs and medical devices

Inclusion criteria
- 22 institutions – have not been inspected so far
- 3 institutions – have not been inspected due to no history of conducting clinical trials

Exclusion criteria
- 55 institutions inspected in ’09, ’10
- 16 institutions inspected in ‘09, ’10 related to the final report submitted for NDA
- Institutions conducting no clinical trials since last inspection
• Directed(unscheduled) Inspection
  • Unexpected safety report
    – SUSAR report (e.g. death case etc.)
    – Issues related to safety concerns

• Complaints

• Sponsors submit NDA along with final report of clinical trials
  – Request from NDA review division
  – Targets both sponsors and institutions
STRENGTHEN THE COMPETITIVENESS OF CLINICAL TRIALS
5 main ‘Issues and tasks’ of ‘2020 Clinical Future Creation Planning Group’

- Strengthen the regulatory competitiveness
- Establish strategic plans for medical devices clinical trials development
- Strengthen the capability of clinical trials
- Enhance the communication system of clinical trials
- Strengthen the safety protection system of clinical trials
New KFDA Office in Osong Healthcare Administration Town

We are in Osong Health Administration Town
THANK YOU FOR YOUR ATTENTION