KFDA Inspection Program for Quality and Compliance Efforts

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INTRODUCTION

식품의약품안전청 www.kfda.go.kr

KFDA MISSION

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.

KFDA

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

Strengthening clinical trial management

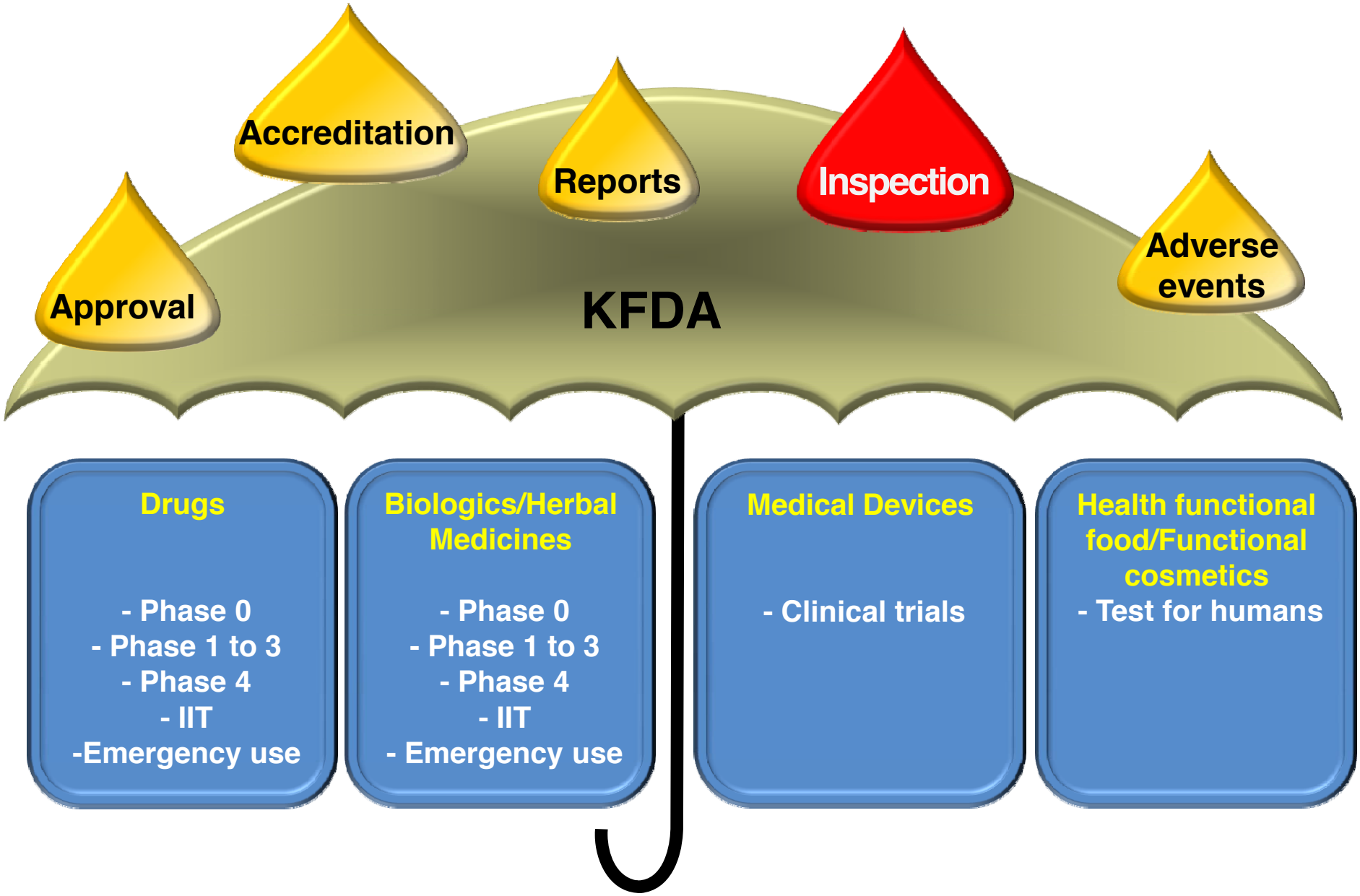
Mission	**Protect and improve national civil health through enhancement of management system and strengthening clinical trial policies**
Vision	**Construct highly globalized level of clinical trial infrastructure and regulation-advanced country**

KFDA Organization (Apr. 2009)

National Institute of Food and Drug Safety Evaluation

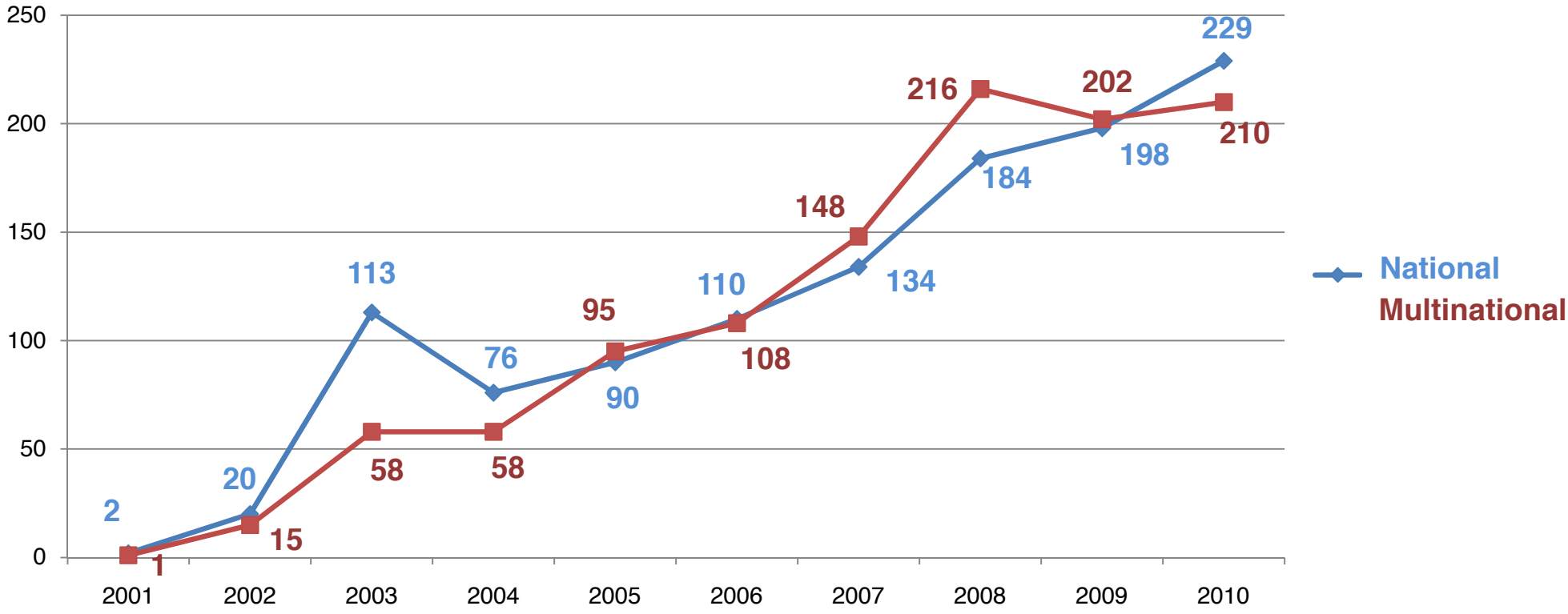
6 Regional KFDA Offices

Clinical Trials under control of KFDA



IND Approval in Korea

KFDA database



REGULATORY BASIS FOR CLINICAL TRIALS IN KOREA

Regulatory hierarchy of clinical trial

Pharmaceutical Affairs Law (Art 34)

Enforcement Regulation of Pharmaceutical Affairs Law (Art 31, 32, 33, 34)

- **Guidance for GCP**
- **Guidance for INDs**
- **Guidance for Accredited Clinical Institutes**

Medical Device Law (Art 10)

Enforcement Regulation of Medical Device Law (Art 12 & 13)

- **Guidance for GCP**
- **Guidance for INDs**
- **Guidance for Accredited Clinical Institutes**

- **Continuous effort for legalization to support harmonization of clinical related regulations to international standards since KFDA formed in 1998**

Milestone of KGCP

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

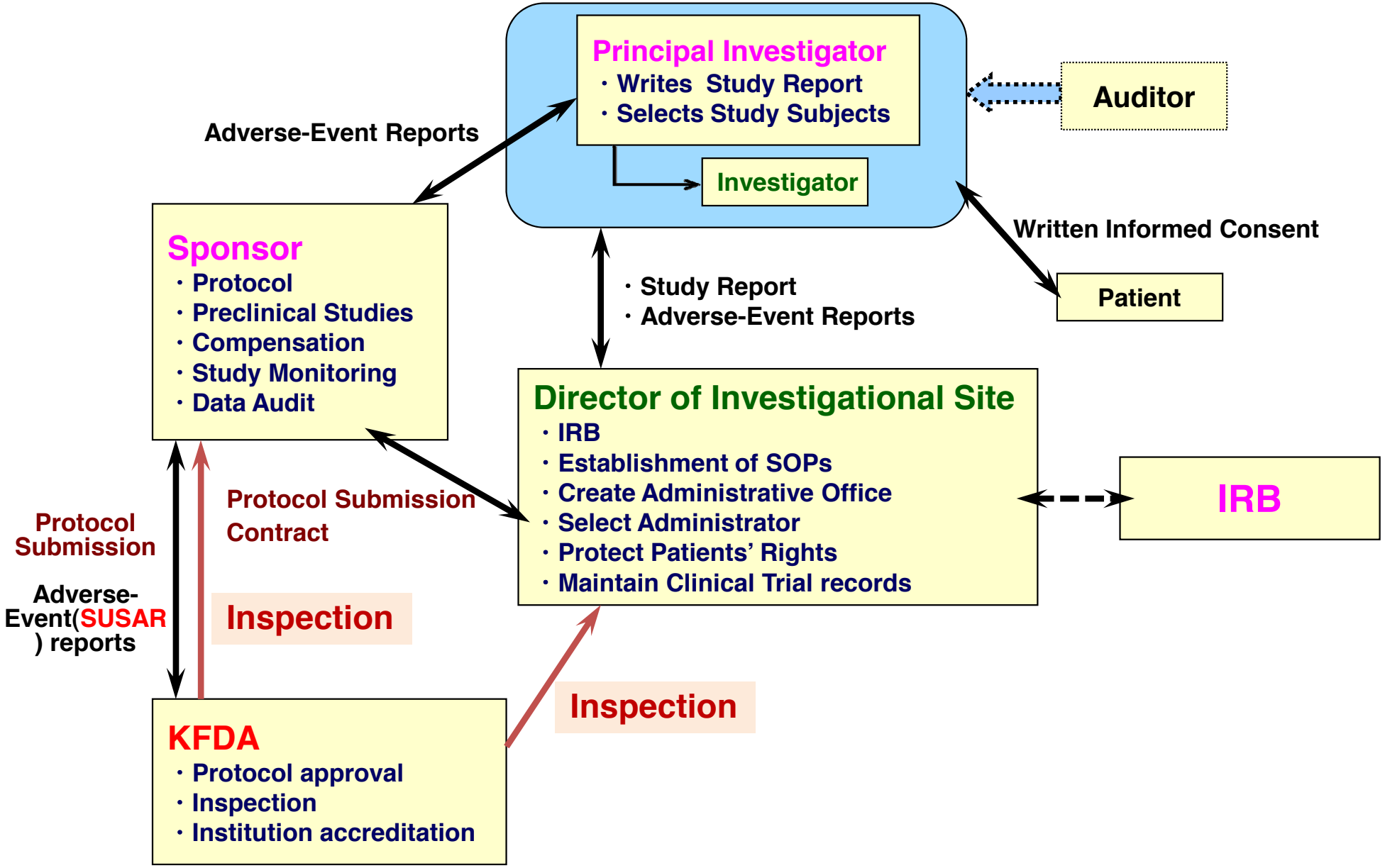
- **Separation between developmental clinical stage and commercial product approval, IND and NDA**
- **Participation in multinational study at any stages**

2006 KFDA Clinical management team establishment

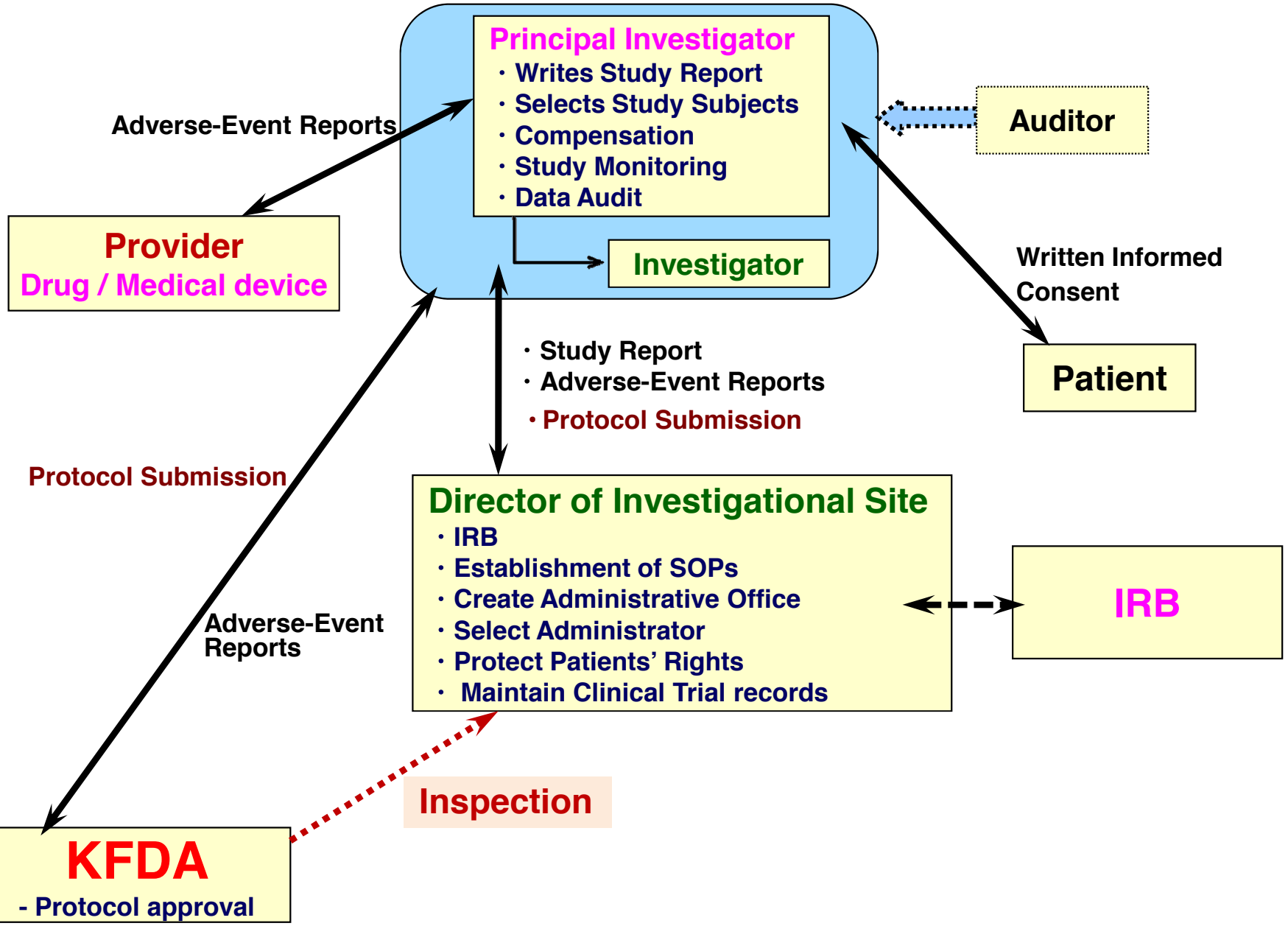
2007 Management of joint IRB for multi-site clinical trial

2010 Shortened review period for phase 1 clinical trials (healthy volunteer)

Overview of Clinical Trials



Overview of Investigator initiated Clinical Trials



Guideline on Accredited Clinical Institutes

effective since 1997 (drug) & 2006 (medical device)

- 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)

Objectives of Inspection

- 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

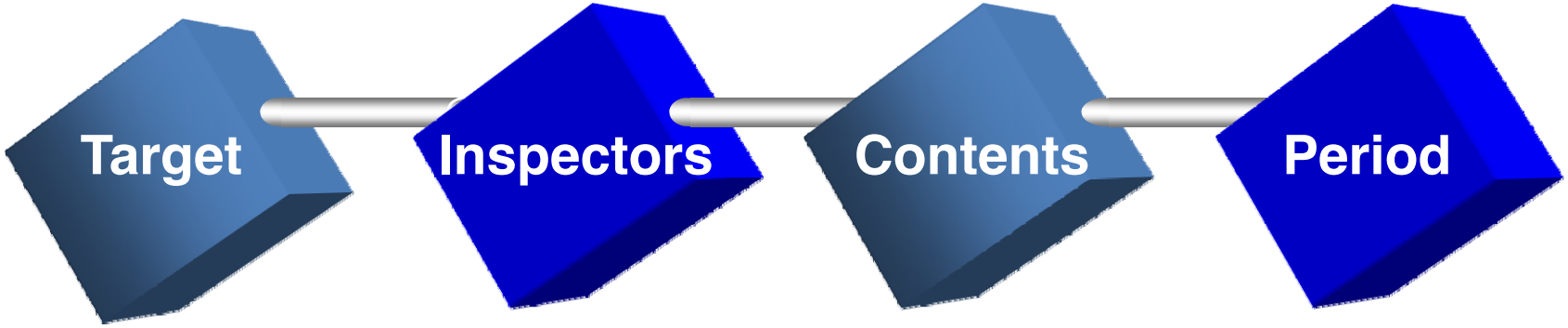
KFDA Inspection

- 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

Inspection Type

<Regular Inspection>



Target	Inspectors	Contents	Period
• All Sponsors • All accredited clinical institutes ('07: number of 70) ('08: number of 43) ('09: number of 35)	• More than two inspectors in one team	• Fulfillment of overall institutional management in clinical trials	• 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	Safety report	Completion report	Etc
- First subject registry - Annual report related to progression of clinical trial - Termination report	- SAE reports Individual SUSAR e.g. Death etc.	- Reliability of final report submitted to the KFDA in support of NDA	- 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

- ✓ **summarize and report of findings**

Follow-up

- ✓ **classify the findings into categories**
- ✓ **notify a post-inspectional correspondence (Warning Letter or Notice etc)**

Inspection Process - Preparation

- 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

Inspection Process – During 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

Inspection Process – Follow-up

- 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

Classification of inspection findings

- 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

Classification of inspection findings - Actions

- 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

2011 INSPECTION PLAN

2011 Inspection Plan - Objectives

- 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

2011 Inspection Plan – Regular Inspection

- 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

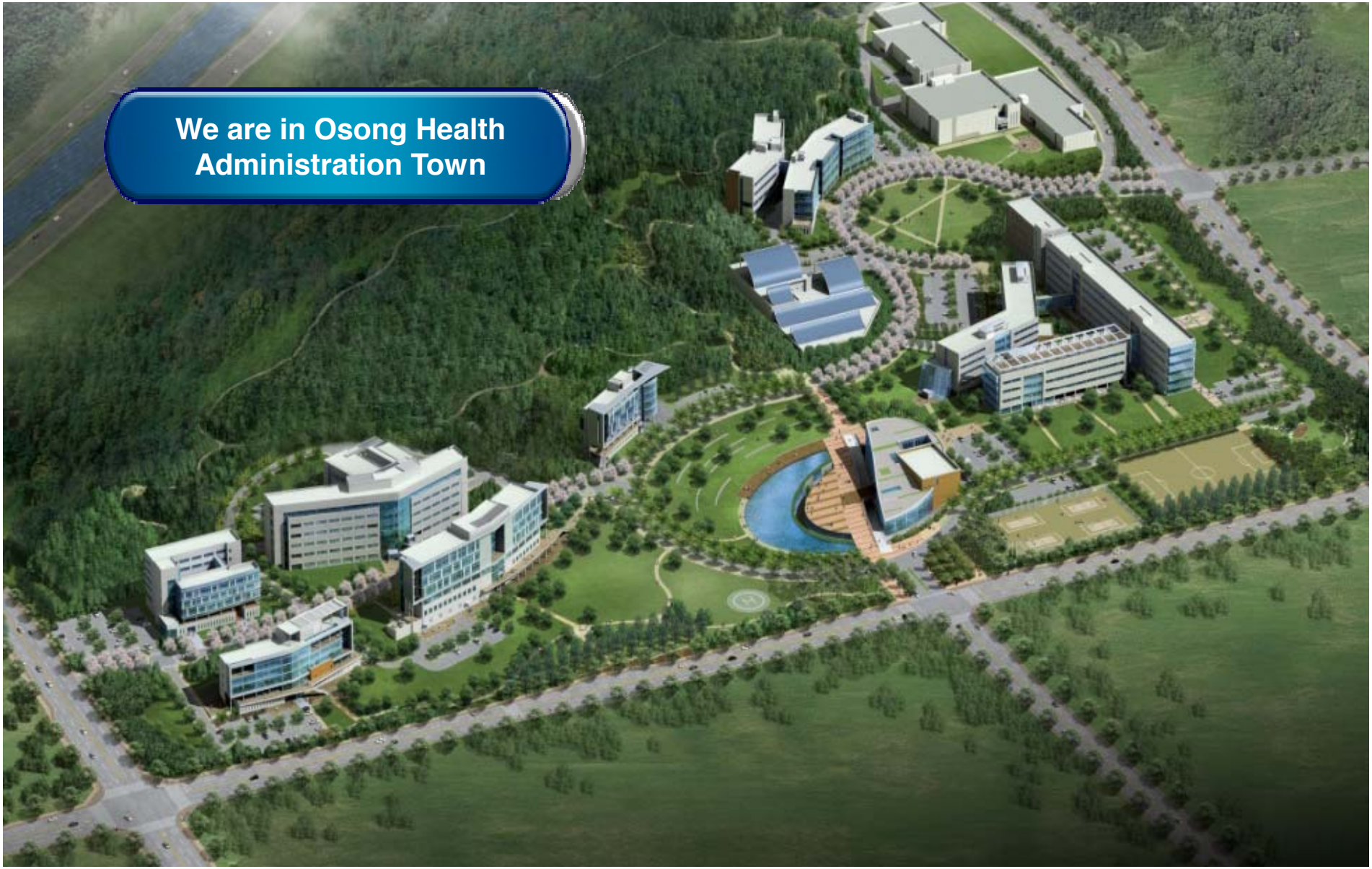
2011 Inspection Plan – Directed Inspection

- 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’

New KFDA Office in Osong Healthcare Administration Town



THANK YOU FOR YOUR ATTENTION