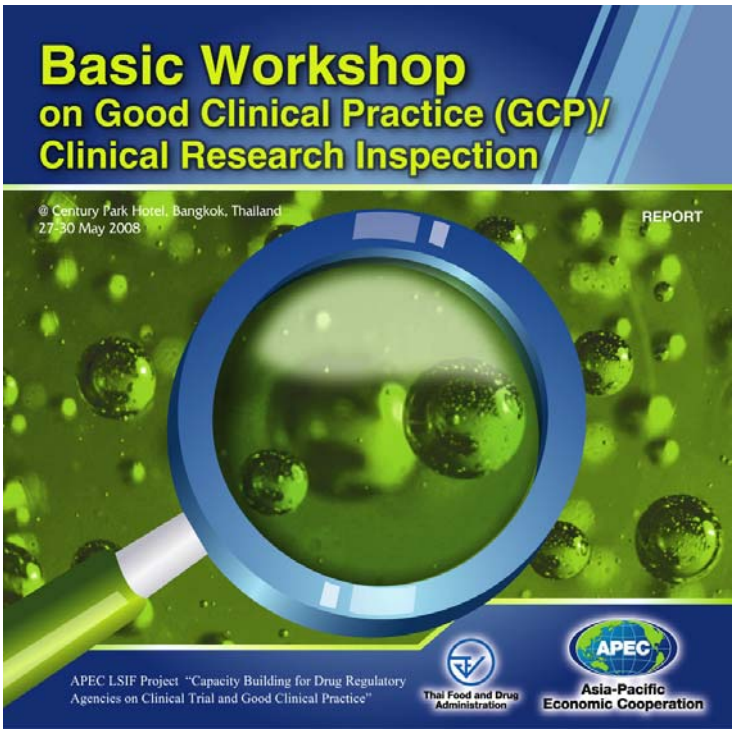


Basic Workshop on Good Clinical Practice (GCP) / Clinical Research Inspection

27-30 May 2008

Electronically reproduced in August 2008
CTI 24/2007T

Prepared By
Thai Food and Drug Administration
Ministry of Public Health
Tiwanont Road Nonthaburi Thailand
Tel : (66)25907061 Fax : (66)25918390
Email : drug@fda.moph.go.th Website : www.fda.moph.go.th

Produced for
Asia-Pacific Economic Cooperation Secretariat
35 Heng Mui Keng Terrace Singapore 119616
Tel: (65) 68 919 600 Fax: (65) 68 919 690
Email: info@apec.org Website: www.apec.org

Publication Number : **APEC#208-CT-04.3**

Table of Contents

Introduction to FDA's Bioresearch Monitoring Program

Inspector Qualifications

g. Inspector's Preparation for a Clinical Investigator Inspection

The Protocol and the Science

h. Inspector's Preparation for a Clinical Investigator Inspection

Review of Inspection SOPs (FDA Compliance Programs)

The Record Inventory

i. The Opening Interview

j. Auditing Clinical Data

k. Review of Day 2

l. Common GCP Deficiencies Encountered at Clinical Investigator Sites

m. Misconduct in Research (Fraud)

Recognizing Research Misconduct

Tips to Prevent Misconduct

n. Documenting an Inspection

Exhibits

Reports

o. Assessing Sponsor and Ethics Committee Compliance from the Clinical Investigator Inspection

Sponsor/Ethics Committee Roles and Responsibilities to the CI

Documentation at the clinical trial site

p. The Close-Out Discussion

Review of GCP deficiencies/violations with the investigator

Educating the investigator/site staff on GCP

q. Summary of Clinical Investigator Inspecting

r. Inspecting Sponsors and Contract Research Organizations

s. Inspection of Ethics Committees

t. Enforcement Strategies to Address Identified Serious Deficiencies

FDA Enforcement Options

Due Process

Part III. Round Table Discussion:

Identifying Specialized Topics and Defining Objectives and Approaches for the Advanced GCP Inspection Workshop

Part IV. Participants

List of Participants

Part V. Questionnaire Survey Results

Questionnaire Survey Results

Part I.
BACKGROUND

Project Background

In response to APEC's ultimate goal of effective facilitation and liberalization of trade and investment among APEC economies, the key issue of harmonization of standards and regulations has become one of the prime interests because the harmonized standards and regulations would greatly prevent and reduce trade barriers. Regularly, the harmonization of standards and regulations of products is implemented for 'ready to sale' or developed products. Unlike other products, "health care products" or "therapeutic products" needs special attention since the initial stage of research and development. It is because these products directly affect people' health and welfare, and surely to survive in market each therapeutic product must prove itself as effective and safe by evidences shown since the beginning of the research and development process and continuous surveillance throughout its lifecycle. It means that if the product has shown life threatening adverse effects, it would be withdrawn from the market regardless of how much the company invested in research, development or even marketing of the product. Therefore, the promotion and harmonization of international standards and regulations applying to each stage of product's lifecycle are also critical tools to reduce risks and to ensure the sustainability of healthcare products. Particularly, research and development process has become the most significant step to accelerate availability of safe and effective innovative therapeutic products as people request for them to prevent or solve health problems that increase due to changes of environment and people' lifestyles

One of the processes in research and development stage of a therapeutic product, Clinical trial, is a critical research study on human volunteers that is usually used to provide scientific evidence to support the effective and safe use of new pharmaceutical products. More importantly, APEC LSIF's strategic plan indicates that the area of clinical trials would help in quick and effective creation of life sciences innovation. The harmonization of regulatory practices in this area, i.e. Good Clinical Practice (GCP), which is an international standard that every clinical trial needs to comply with in order to ensure the human subjects' rights, safety and the credibility of trial's data, is one of the specified best practices to reach our goals. To ensure that trials are conducted in compliance with GCP and appropriate scientific approach, Drug Regulatory Authorities (DRA) need to review and evaluate drug development in clinical trials and to inspect the conduct of trials at their sites.

Even though ICH Good Clinical Practice (ICH GCP) is the widely implemented standard across the world, all economies accept that the differences in standards exist and many economies need improvement. Thailand by Thai Food and Drug Administration(TFDA), Ministry of Public

Health, has foreseen this and later proposed the APEC Project CTI24/2007T or “Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice” for the year 2007-2008.

The main activities are two training series. The first series include 5 day practical workshop on reviewing of drug development in clinical trials, and the second series consist of 4 a practical workshop on GCP inspection.

Since the world’s leading economies are also members of APEC, the international standards implemented economies, e.g. USA, Canada, and Japan, are all willing to help other economies. No educational institution in the world could offer specific courses like what TFDA proposed in the project. The training workshops will also provide useful opportunities for information and experience sharing between concerned officers from different National Drug Regulatory Agencies in the APEC region.

The project‘s objectives are to strengthen DRA’s capacity as a part of APEC LSIF’s readiness and preparation strategies to handle new therapeutic life science innovations through the best practice area of clinical trials by evaluation of clinical drug development in aspects of quality and safety of investigational pharmaceutical products, inspection of Clinical Trials in compliance with ICH Good Clinical Practice (GCP), and forum for APEC members to discuss and share experiences in controls of clinical trials towards the harmonization of regulatory practices.

The first workshop is “the Preliminary Workshop : Review of Drug Development in Clinical Trials” held in Bangkok on 17-21 Mar 2008 (please see the report from APEC publication number ‘APEC#208-CT-041’) The latest workshop (2nd) is “the Basic Workshop on Good Clinical Practice (GCP)/ Clinical Research Inspection” held in Bangkok on 27-30 May 2008. Both of the workshops will be followed by the advanced workshops under the APEC project ‘CTI 36/2008T’ in later of 2008 and 2009.

Workshop Information

The Basic Workshop on Good Clinical Practice(GCP)/ Clinical Research Inspection is the second workshop conducted under the APEC Project CTI24/2007T. Thai Food and Drug Administration hosted the workshop in Bangkok on 27-30 May 2008. 2 trainers, 24 trainees and 2 observers are from 11 different APEC economies and countries i.e. Brunei, Chile, Indonesia, Malaysia, Philippines, Saudi Arabia, Singapore, Chinese Taipei, Thailand, United States and Viet Nam. The trainers are from United States Food and Drug Administration (US FDA). The trainees are all drug regulatory agencies' officials.

The workshop provided training presentations, exercises and discussion opportunities according to clinical trial inspection and regulations. The main topics were Roles and Responsibilities under GCP, Elements of Data Quality and Integrity, Introduction to GCP Inspection Techniques and Documentation, Inspecting at a Clinical Investigator Site Including On-site Exercise, Compliance and Enforcement Tools, and Introduction to the Inspection of Sponsors/Contract Research Organizations and Independent Ethics Committees. The participants of this workshop also had opportunities to suggest interested topics to cover in the advanced workshop, which was tentatively scheduled in March 2009.

Opening and Welcome Remarks
By
Dr Chatri Banchuin
The Secretary General of
Thai Food and Drug Administration
The Century Park Hotel, Bangkok
27-30 May 2008

Dr David Lepay

Dr Jean Toth-Allen

Distinguished participants,

Ladies and Gentlemen:

It gives me a great pleasure to welcome all of you and chair the Opening Ceremony this morning for the "Basic Workshop on Good Clinical Practice (GCP)/Clinical Research Inspection" jointly organized by Asia Pacific Economic Co-operation(or APEC) and Food and Drug Administration, Thailand.

I would like to recall APEC supported project titled "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice". The project activities are composed of 2 workshops. The first workshop on 17-21 March 2008 had already trained 20 regulators from 8 difference economies to review drug development in clinical trials by 5 trainers from leading economies. It had been an effective kick-off training that provided both technical experience and network opportunity for regulators.

The second workshop starting from today until 30 May will aim for GCP Inspection that only performed by regulators. This workshop is supported by numbers of parties; those are APEC, ICH Global Cooperation Group, ASEAN Working Group in Technical Cooperation, United States Food and Drug Administration, and Thai Food and Drug Administration. All of the parties accept that there is still difference in regulatory practices over APEC member economies, even though it is the same ICH GCP standard. Therefore, USFDA as a representative of the leading organizations has actively assisted and designed this workshop as a basic course providing both technical knowledge and practical techniques of GCP Inspection.

Today's workshop is attended by 2 speakers from USFDA, 24 officers from Drug Regulatory Authorities, and 2 observers of 11 different economies and country including Brunei, Chile, Indonesia, Malaysia, Philippines, Saudi Arabia, Singapore, Chinese Taipei, Vietnam and Thailand. Therefore, this workshop will provide us not only essential knowledge but also a great opportunity to share experiences both technical and regulatory issues

I would like to take this opportunity to express my sincere thanks to the organizers and in particular our honorable speakers. Both of them, Dr Lepay and Dr Toth-Allen have been working with us since the beginning of the planning stage and they are still here to day for all of us, even though they are both very busy with their responsibilities at the US FDA. We truly appreciate your dedication. Again, this training program could not have been made possible without APEC, ICH, ASEAN and US FDA, who foresee the importance of Clinical Research Inspection. We all expect to take the results of this program to develop our regulatory system to ensure the protection of patient safety and promote best quality clinical trials.

Furthermore, I would like to inform you good news. APEC Budget and Management Committee have just approved to support phase 2 of this capacity building project. That means we could carry on the advanced training courses for 'Review of Drug Development in Clinical Trials' tentatively in November 2008 and 'GCP Inspection' in March 2009.

Finally, this is an opportune time for me to declare the official opening of the "Basic Workshop on Good Clinical Practice (GCP)/Clinical Research Inspection" and I wish all 4 fruitful days of interesting and beneficial program and also that you have a pleasant stay in Bangkok. I warmly welcome you all again.

List of Speakers

No.	Name and Contact Information
1	**David A. Lepay, MD, PhD** FDA/Office of the Commissioner/Office of Science and Health Coordination/Good Clinical Practice Program address: 4510 Executive Dr., ste 225, San Diego, CA 92121 USA phone: +1 858-550-3850 ext 103 fax: +1 858-550-3860 Email : david.lepay@fda.hhs.gov
2	**Jean Toth-Allen, PhD** FDA/Office of the Commissioner/Office of Science and Health Coordination/Good Clinical Practice Program address:5600 Fishers Lane, HF-34, Rockville, MD 20857 USA phone:301-827-1585 fax: 301-827-1169 Email : jean.toth-allen@fda.hhs.gov

Speakers' Biographical Sketches

1. David A. Lepay, M.D., Ph.D.

David A. Lepay, M.D., Ph.D., is FDA Senior Advisor for Clinical Science, Science/Health Coordination and International Programs, and also served as Director of Good Clinical Practice Programs within FDA's Office of the Commissioner from 2000-2006. In his position, Dr. Lepay advises on GCP policy and initiatives at FDA, on the coordination of FDA's Bioresearch Monitoring program of GCP inspections for human clinical trials, and on international GCP and human subject protection activities, and contributes broadly to GCP education and outreach. Dr. Lepay joined FDA in 1992, and has held previous positions as Director of the Division of Scientific Investigations (1996-2000) and as Senior Medical Review Officer (1992-1996) in FDA's Center for Drug Evaluation and Research.

Dr. Lepay earned his B.S. degree from Yale College, his M.D. degree from Cornell University Medical College, his Ph.D. in Cellular Immunology from the Rockefeller University, and completed residency training at Brigham and Women's Hospital and Harvard Medical School. He serves on a number of government working groups and panels and is a frequent speaker on GCP, both domestically and internationally.

2. Jean Toth-Allen, Ph.D.

Jean Toth-Allen, Ph.D., a biophysicist, is presently a member of the Good Clinical Practice Program (GCPP) in the Office of Science and Health Coordination (OSHC) in the Office of the FDA Commissioner. Previous to joining GCPP, she was a reviewer in the Division of Bioresearch Monitoring (DBM) in the Center for Devices and Radiological Health (CDRH), with responsibilities for the assignment, conduct, review, and evaluation of bioresearch monitoring (BIMO) inspections supporting medical device applications. She worked in DBM from January 1997 until joining GCPP, initially on detail, in November of 2005 and was designated a CDRH Master Reviewer in October 2003.

Before joining FDA in 1994 as a member of the training branch in the Division of Mammography Quality and Radiation Programs, she taught at George Mason University, Fairfax, VA, where she held a joint appointment in both the biology and physics departments. She received both her M.S. and Ph.D. in Biophysics from Michigan State University.

Part II.
Presentations

Disclaimers

The information within all presentations in this report is based on the presenters' expertise and experience, and represents the views of the presenters for the purposes of a training workshop

WORKSHOP ON GCP INSPECTION
BANGKOK, THAILAND
27-30 MAY 2008

Country Report

DEPARTMENT OF PHARMACEUTICAL SERVICES
MINISTRY OF HEALTH, COMMONWEALTH DRIVE,
BANDAR SERI BEGAWAN BB3910, BRUNEI DARUSSALAM
Tel No.: +673 2381640 Ext: 7718 **Fax No.: +673 2381001**
Website: www.moh.gov.bn
Email: pharm@brunet.bn

By:
Jamilah Metussin
Pharmacist
Drug Registration Unit
Dept. of Pharmaceutical Services

OVERVIEW

- Background
- Current GCP Laws and Practices
- Committees
- Goals for GCP Inspection Training

BACKGROUND

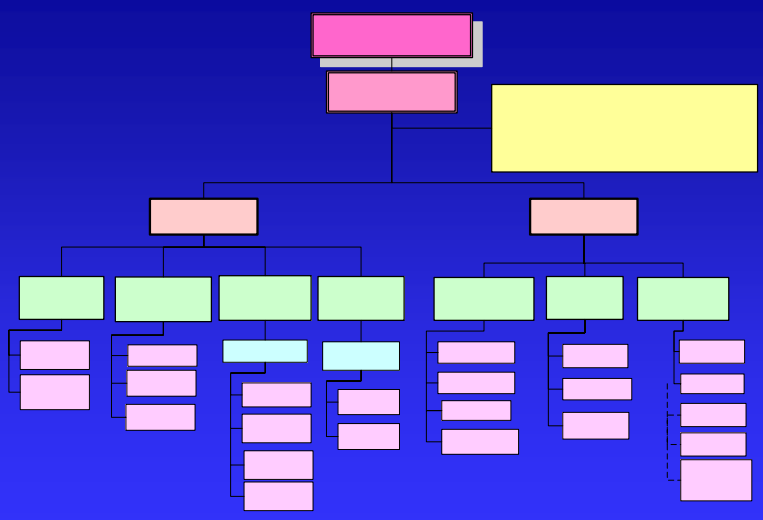
DEPARTMENT OF PHARMACEUTICAL SERVICES (DPS)
MINISTRY OF HEALTH

RESPONSIBLE FOR

Implementation of Drug Policies and other related policies pertaining to the Department of Pharmaceutical Services

- Headed by Director of Pharmaceutical Services
- Comprises of 2 divisions:
  - Pharmaceutical Care and
  - Pharmacy Regulatory

ORGANISATION CHART



CURRENT GCP LAWS & PRACTICES

- Pharmacy Regulatory Division
  - The regulatory arm that is mainly involved and / or responsible for executing the regulation of clinical trials.

LEGISLATION

- Pharmacy Regulatory Division
  - Regulates the conduct of Clinical Trials in Brunei Darussalam through the Medicines Order 2007 under part IV Section 23 of the order
  - Gazetted - early 2008
- Medicines Order – 'any person(s) who wish to conduct a clinical trial must possess the relevant *Clinical Trial Import Licence* and *prior written approval from the Authority (BDMCA)'*

GUIDELINE

- Ministry of Health Brunei Darussalam official launch of Guideline for Good Clinical Practice (early May 2008)
- Back to back with second National Workshop on GCP
- Guideline was formulated in accordance with WHO and ICH

FUTURE LEGISLATION

- Brunei Darussalam
  - Currently in process of drafting the relevant rules under the provisions of the Medicines Order in collaboration with the Attorney Generals Chambers
  - Regulate the conduct of clinical trials and GCP Inspection.

CURRENT STATUS ON CLINICAL TRIAL

- No clinical trial has yet been conducted in Brunei so far
- Medical Research and Ethics Committee have the intention of conducting assessment and inspection activities related to clinical trials to be executed by a mix of resources

COMMITTEES

- Assurance of ethical research in BD is a joint responsibility between:
  - Sponsors
  - Medical & Health Research & Ethics Committee (IEB/IRC)
  - Brunei Darussalam Medical Research Committee, and
  - Regulatory authority - Brunei Darussalam Medicines Control Authority (BDMCA)
    - executes the regulations on GCP through the Medicines Order 2007
    - ensuring the safe use of regulated products that are themselves safe and efficacious
    - ensuring the implementation of trial related guidelines and legislations.

GOALS FOR GCP INSPECTION TRAINING

- Two National Workshops on Good Clinical Practice had been conducted since March 2007
  - organized by the Ministry of Health Medical Department
  - attended by selective participants comprising Physicians and Pharmacists.
- Some of the challenges considered by the Committee are:
  - Assessment on the conduct of clinical trials
  - Compliance to the methodology as well as ethics
- Hence, as GCP is new to Brunei, it is hoped that the GCP inspection worksop shall provide further insight and knowledge into the conduct of GCP inspection and its activities particularly from a regulatory perspective.

THANK YOU

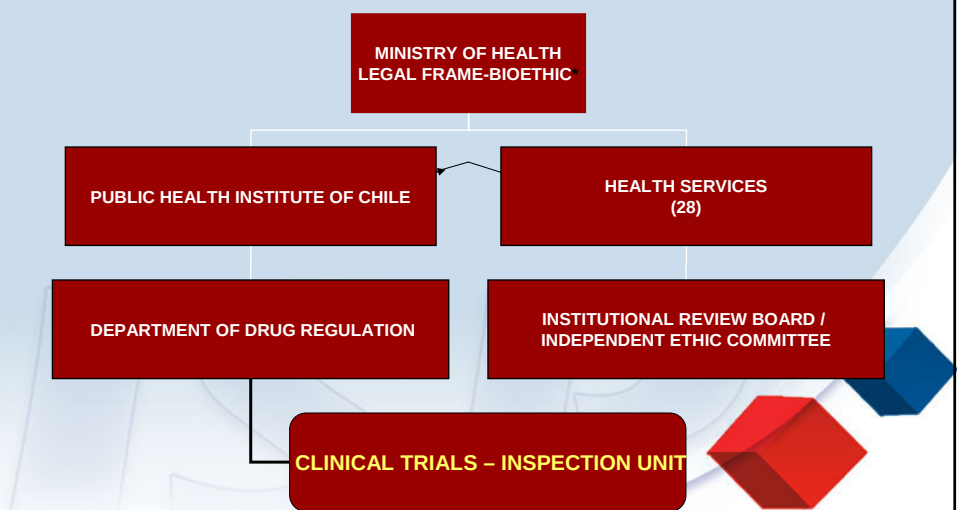
INSTITUTO DE SALUD PÚBLICA DE CHILE

INSPECTION

Miguel Gonzalez G . (PS)
CLINICAL TRIALS - INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

Regulatory Organization in Chile



* Approved by Congress

INSTITUTO DE SALUD PÚBLICA DE CHILE

Red Pública, Servicios de Salud

CHILEAN PUBLIC HEALTH NETWORK: HEALTH SERVICES SYSTEM

CLINICAL TRIALS -INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

ORGANIZATIONAL CHART DEPARTMENT OF DRUG REGULATION

MISSION

“ Improvement of Public Health, Guaranteeing Quality of Goods and Services through the Strengthening of Reference, Inspection and Regulation.”

Laws/Regulation in Chile

- Law N° 20.120 Scientific investigation (2006)
- DS. N°1876 regulatory requeriments of pharmaceutical product.(1995 – 2005)
- N° 57 normative of clinical trial.(2001)
- D.S Nº 494 .Autorized ethics committees that review biomedical research. (1999)
- D.S Nº 1.935 Hospital Director’s (administrative authority) authorization the clinical trial. (1993)

INSTITUTO DE SALUD PÚBLICA DE CHILE

Law/Regulation in Chile

- This regulation is to provide a regulatory framework within which clinical trials should be monitored for the ISP in order to comply with international standars.
- This regulation represent the minimun national requerement when conducting a clinical trial in Chile.
- ISP : Evaluation and Authorization of Clinical Trials that use Drugs not Registered in the Country.

INSTITUTO DE SALUD PÚBLICA DE CHILE

Regulatory Organization in Chile

Clinical Trials – Inspection Unit, Chilean Public Health Institute (ISP)

Objective:

To review authorize and inspection Clinical Trials in order to allow entry into the country of non registered products.

CLINICAL TRIALS -INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

Autority regulatory: ISP

INSPECTION

The act by regulatory authority of conducting an oficcial rewiew of documents, facilities, records, and other resorces that are deemed by the authority to be related to the clinical trial y that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishment deemed appropiate by the regulatory autority.

(ICH Guideline)

INSTITUTO DE SALUD PÚBLICA DE CHILE

Objectives of Inspection

- Verify that:
  - The rights and well-being of human subjects are protected.
  - The reported trial data are accurate, complete, and verifiable from surce documents.

INSTITUTO DE SALUD PÚBLICA DE CHILE

Criteria used for Evaluation and Authorization

- Ethically acceptable :
  - Informed Voluntary Consent
  - Random Selection of the participants
  - Equal benefit opportunity potencial
  - Favorable Risk / Benefit Ratio in order to minimize risks and maximize benefits
  - Independent Evaluation
  - Value of the Investigation: improvement of health, welfare or knowledge of the community .

INSTITUTO DE SALUD PÚBLICA DE CHILE

Criteria used for Evaluation and Authorization

- Ethically acceptable (Cont.) :
  - Respectful of the participants will
  - Change of opinion
  - Information privacy and confidentiality
  - Knowledge of new information
  - Protection from adverse events
  - To be of Scientific Value
  - Appropriate methodology and design to obtain statistically significant results

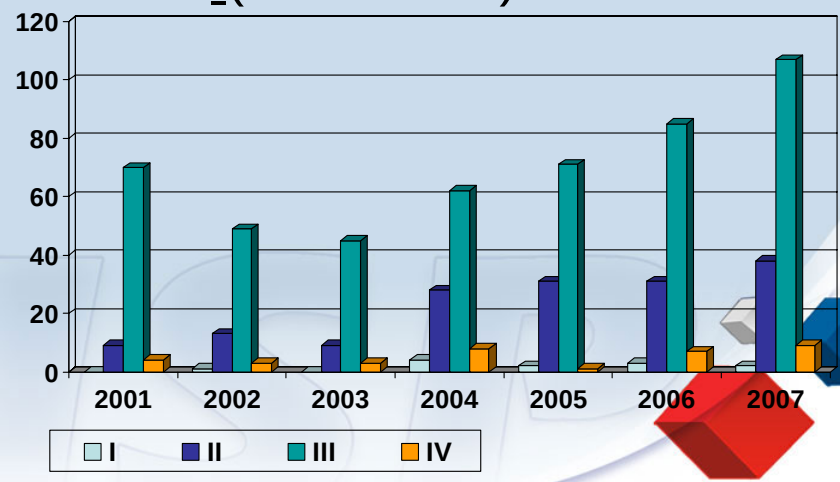
INSTITUTO DE SALUD PÚBLICA DE CHILE

Regulatory Documentation Required for Authorization at ISP

- Investigational Protocol
- Informed Consent
- Authorization of the corresponding Ethics Committee
- Principal Investigator's C.V.
- Participant Insurance
- Principal Investigator's Brochure

INSTITUTO DE SALUD PÚBLICA DE CHILE

Clinical Trials Research Phase (2001-2007)

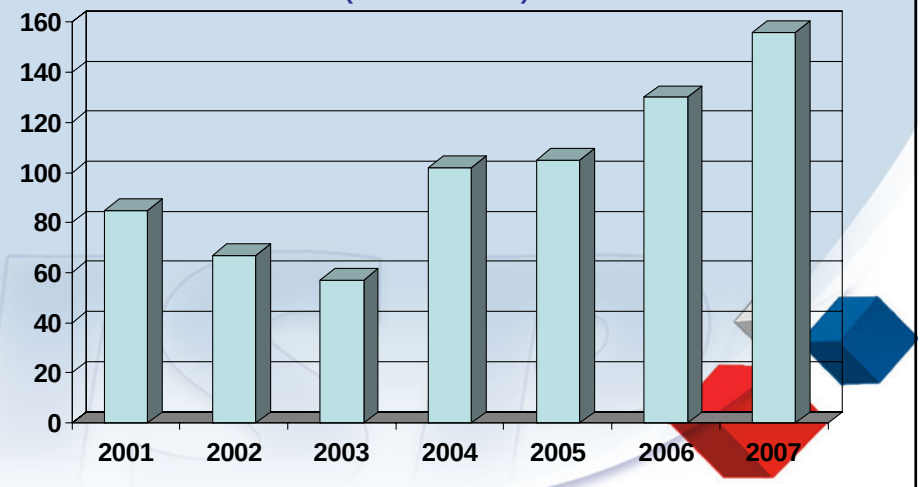


CLINICAL TRIALS -INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

N° of Clinical Trials CHILE

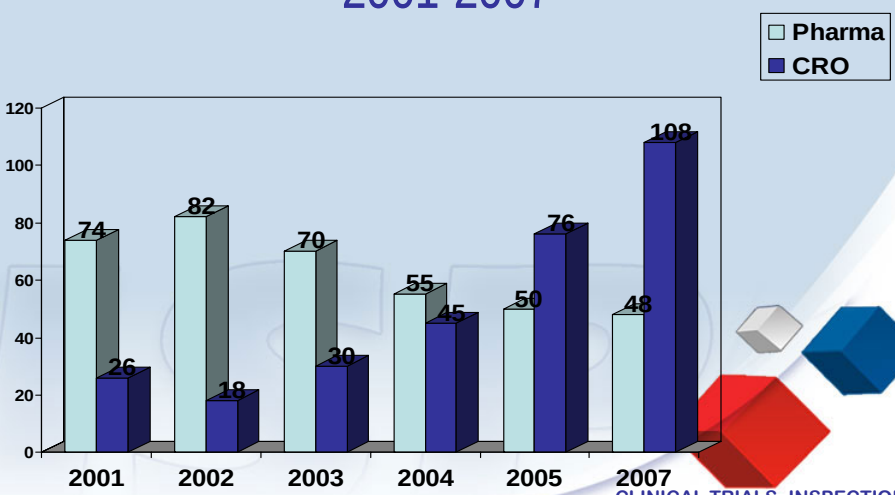
(2001-2007)



CLINICAL TRIALS -INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

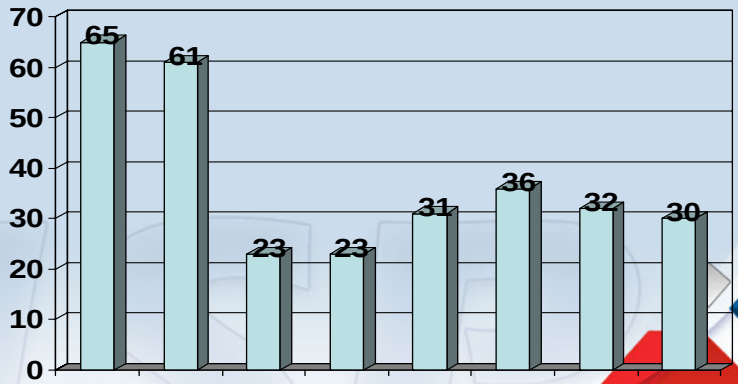
Chilean Trial DistributionPharma/CRO 2001-2007



CLINICAL TRIALS -INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

Average Approval Time of Clinical Trials
2000-2007 (working days)



INSTITUTO DE SALUD PÚBLICA DE CHILE

Thank you

Muchas Gracias !!!

CLINICAL TRIALS -INSPECTION

CLINICAL TRIAL : Indonesia Current Situation

Good Clinical Practice Workshop

National Agency of Drug and Food Control,
Republic of Indonesia
Bangkok, 27-30 May 2008

System Established for Clinical Trial

- Clinical Trial Authorization
- GCP Inspection

↓

To support quality system for pre market evaluation

Indonesian Guideline for Good Clinical Practice

- Issued in 2001
- Consist of :

  - GCP guideline → adopted from ICH-GCP E6

  - Regulation on CT (Head of NADFC Decree regarding Clinical Trial Procedures).

Clinical Trial Authorization

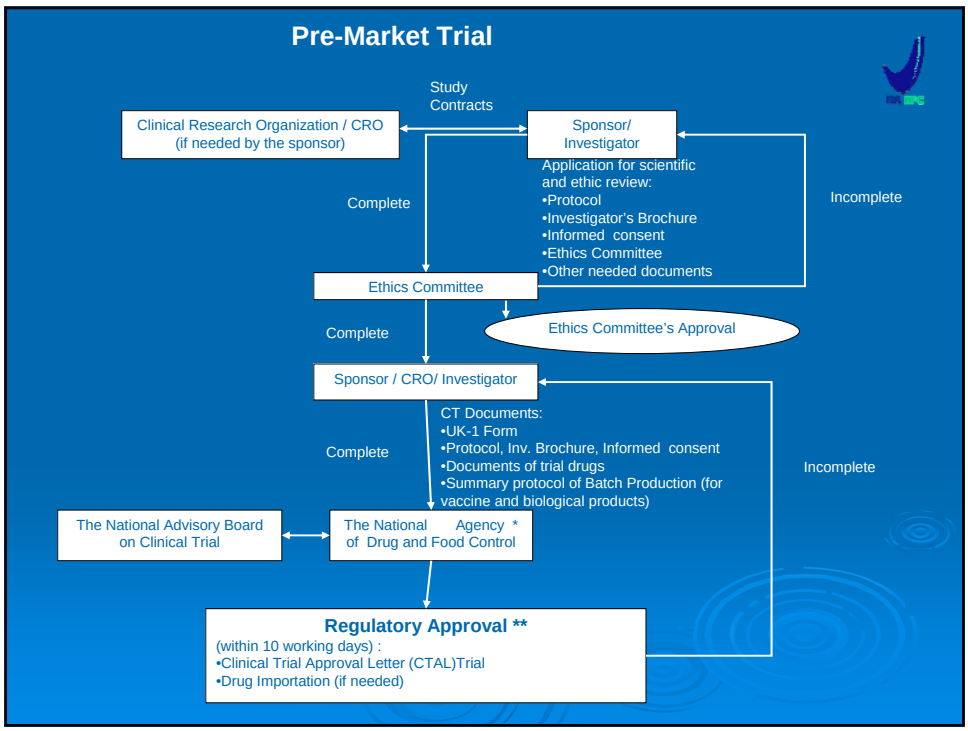
Legal basis : Head of NADFC Decree regarding CT procedure (2001).

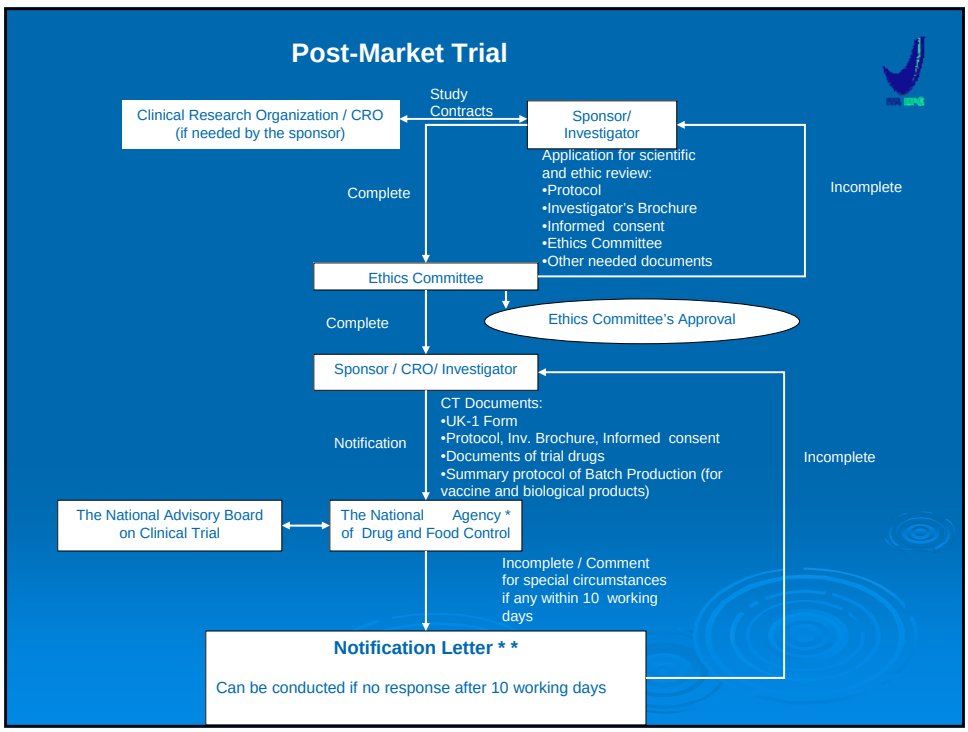
To give approval or notification :

- To a trial to be conducted.
- To the trial drugs to be imported

How to get approval or notification

- Submission of clinical trial documents
- Submission of clinical trial drug documents
- Evaluation of the submitted trial and trial drug documents.


Pre-Market Trial
Study Contracts
Clinical Research Organization / CRO (if needed by the sponsor)
Sponsor/ Investigator
Application for scientific and ethic review:
•Protocol
•Investigator's Brochure
•Informed consent
•Ethics Committee
•Other needed documents
Incomplete
Complete
Ethics Committee
Complete
Ethics Committee's Approval
Sponsor / CRO/ Investigator
CT Documents:
•UK-1 Form
•Protocol, Inv. Brochure, Informed consent
•Documents of trial drugs
•Summary protocol of Batch Production (for vaccine and biological products)
Complete
Incomplete
The National Advisory Board on Clinical Trial
The National Agency * of Drug and Food Control
Regulatory Approval **
(within 10 working days) :
•Clinical Trial Approval Letter (CTAL)Trial
•Drug Importation (if needed)


Post-Market Trial
Study Contracts
Clinical Research Organization / CRO (if needed by the sponsor)
Sponsor/ Investigator
Application for scientific and ethic review:
•Protocol
•Investigator's Brochure
•Informed consent
•Ethics Committee
•Other needed documents
Incomplete
Complete
Ethics Committee
Complete
Ethics Committee's Approval
Sponsor / CRO/ Investigator
CT Documents:
•UK-1 Form
•Protocol, Inv. Brochure, Informed consent
•Documents of trial drugs
•Summary protocol of Batch Production (for vaccine and biological products)
Notification
Incomplete
The National Advisory Board on Clinical Trial
The National Agency * of Drug and Food Control
Incomplete / Comment for special circumstances if any within 10 working days
Notification Letter * *
Can be conducted if no response after 10 working days

GCP Inspection

Legal basis : Head of NADFC Decree regarding GCP Inspection (2004).

Mechanism :

- **Pre Inspection**
  - **Contact with sponsor and investigator to arrange inspection schedule**
  - **Letter to the sponsor and investigator about the date of inspection**
- **GCP Inspection on site**
  - **Introduction and Interview**
  - **Inspection on site (facilities and documentation):**
    - ✓ **Supported with checklist & report form for Inspection consistency**
    - ✓ **Data and document verification**
    - ✓ **Clarification (if any)**
  - **End of Inspection :**
    - ✓ **Clarification**
    - ✓ **Investigator and GCP inspector sign the finding form**

- **Post Inspection**
  - **Report to the office**
  - **Letter to the sponsor/CRO and Investigator, that covers also result of inspection (based on (finding form).**
  - **In some cases, response from sponsor/Investigator is required (corrective actions which are taken).**

GCP Inspection Classification

- Critical : direct subject safety implications or regulatory offence or directly casts doubt on validity of data
- Major : non-compliance with regulations that could have impact on the subject or validity of data
- Minor (others) : minor non-compliance. Lots of minor non-compliance may add up to a major non-compliance

Categories for Regulatory Actions

- ***NAI (No Action Indicated)***

  No objectionable conditions or practices were found during the inspection. A letter will be sent states that generally NADFC observed no significant deviation .

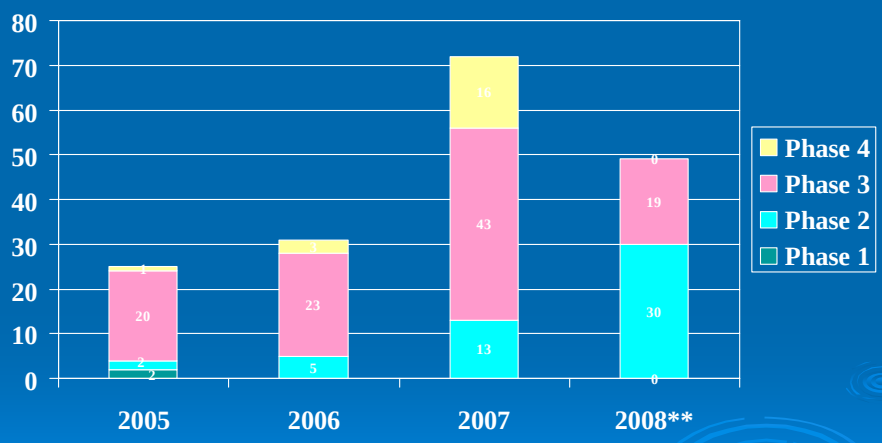
- ***VAI (Voluntary Action Indicated)***

  Objectionable conditions or practices were found, but do not need any administrative or regulatory action. A letter will be sent identifies deviations from statutes and regulations for which voluntary corrective action is needed. Occasionally such letter request response from the clinical investigator and sponsor/CRO.

- ***OAI (Official Action Indicated)***

  Regulatory and/or administrative actions will be recommended . A warning letter will be sent identifies serious deviations from applicable statutes and regulations. A warning letter request a prompt action by the clinical investigator and sponsor/CRO

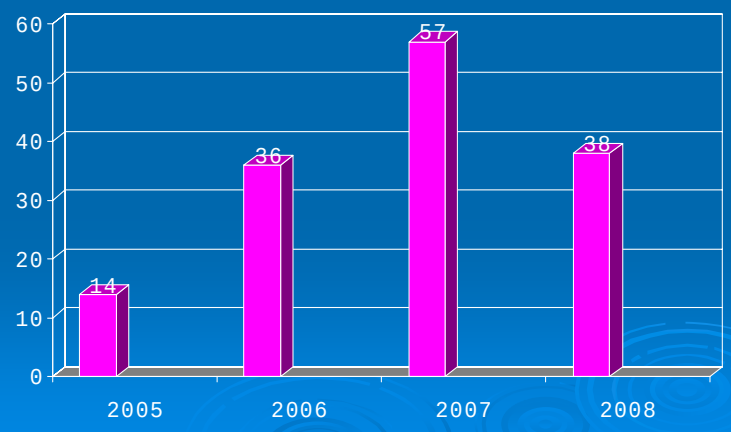
CT APPLICATION IN INDONESIA *



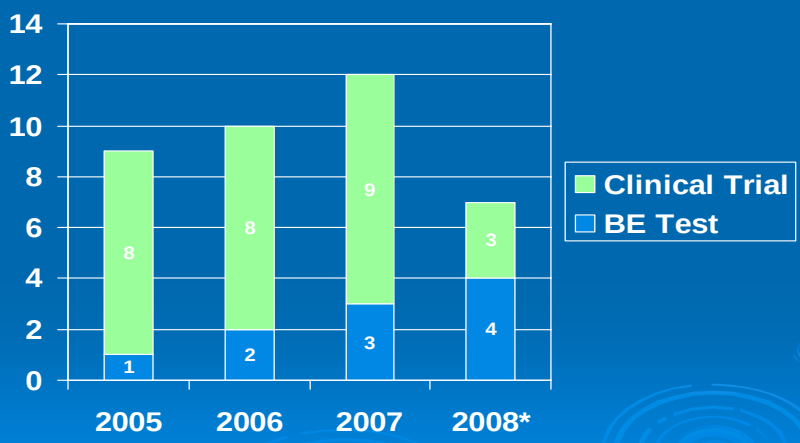
* Not including Bioequivalence Studies

** Until April 2008

BE STUDY APPLICATION IN INDONESIA



GCP INSPECTION



*Until April 2008

Future Challenges

- How to strengthen the clinical trial system
- Indonesia can be involved in more pivotal global study

Indonesia NADFC : Global Participation

- Join the WHO NRA Assessment team for CT authorization
- WHO-Developing Countries Vaccine Regulators Network (DCVRN) meeting annually.
- WHO-DCVRN GCP Inspection Workshop to develop GCP Inspection Checklist for DCVRN training module, 2006
- WHO Agreement of Performance Work to develop GCP Inspection Checklist Manual (as a team), 2007

- Trainer in the GTN WHO GCP Inspection Training Course (as a team) in Zimbabwe , 2007
- Trainer in the GTN WHO GCP Inspection Training Course (as a team) in Philippines, February, 2008.

THANK YOU

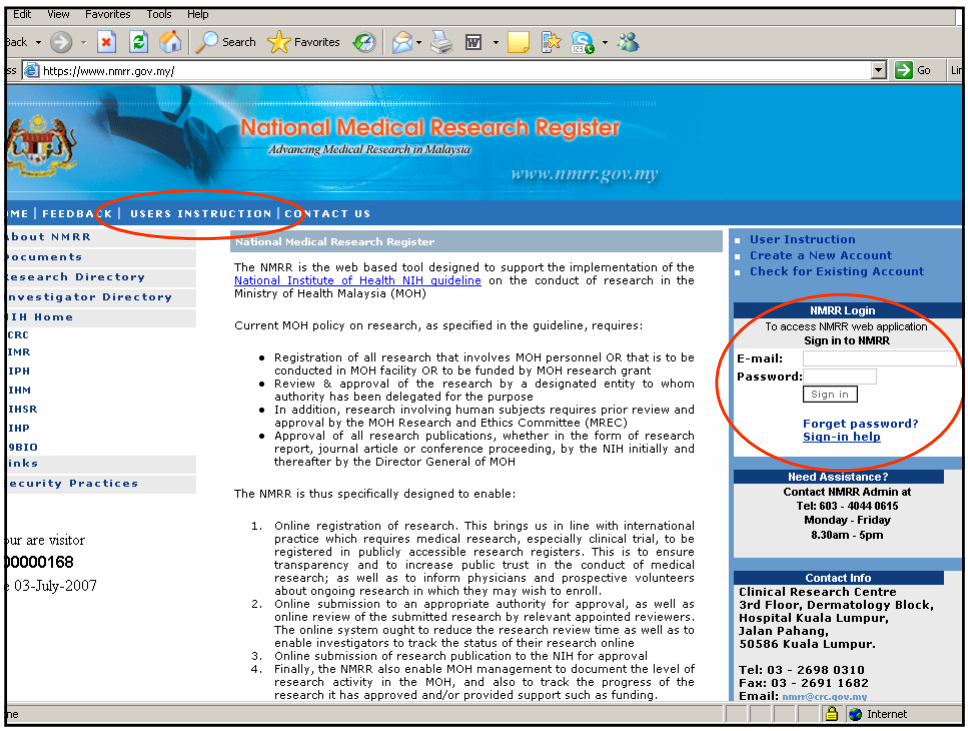
for your attention

CLINICAL TRIAL IN MALAYSIA

Clinical Trial and Compliance Section
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

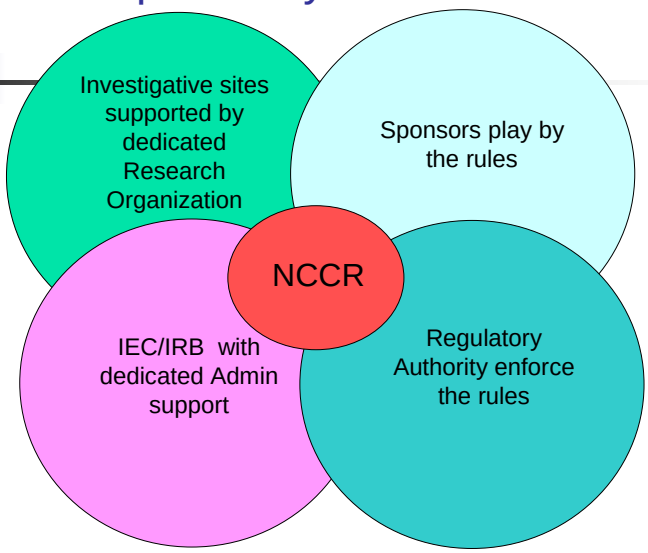
OUTLINE

- Introduction
- Regulation and Ethical Oversight of Clinical Trial in Malaysia
- Guidelines and Legal Requirements
- Compliance



Regulation and Ethical Oversight of Clinical Trial in Malaysia

Ensuring Ethical Research: A joint responsibility



1. National Committee for Clinical Research(NCCR)

- Forum for dialogue among all parties: Regulatory authority, IECs, Sponsors, Investigators from MOH/Universities/ Private hospitals
- Promulgate & implement various guidelines:

- GCP, Bioequivalence (BE) studies, GLP, Guidelines for Application For CTIL/ CTX etc

- Training on GCP
- Site-inspection for clinical trials
- Review processes for approval of clinical trials

2. Investigative sites & Research organization

This is where the action is; where investigators enroll patients into the trial

Ethical trial conduct & compliance requires:

- Adequate resources to conduct the trial
- Training, eg GCP certification
- Independent monitoring of trial conduct

3. Sponsors

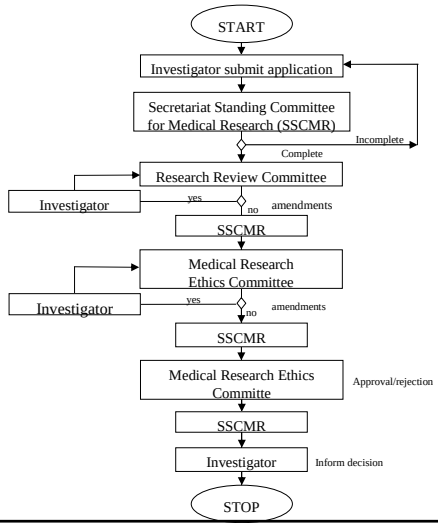
- Sponsor pay for the research, and own the IPR
- Mostly industry sponsors (mostly drug trials) or government grant agency (eg NIH of the MOH, MOSTE)
- Recruitment of well qualified investigators
- Avoid undue influence of investigators and patients
- Independent monitoring /audit by sponsors: common practice for industry

4. IEC/ IRB

"An independent body constituted of medical professionals and non-medical members whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects." ICH GCP 1.27

- In Malaysia, for MOH/private sites, this is the Medical Research & Ethics Committee of the MOH (MREC); universities have their own IECs.

Application for Conduct of Clinical Trial in MOH, Malaysia



5. Regulatory Authority

- Drug Control Authority (DCA)

  An authority established for the purpose of regulating the Control of Drugs and Cosmetics Regulations, 1984
- DCA has a broad public protection mission to ensure the safe use of regulated products that are themselves safe and efficacious
- Ensure Implementation of trial related guidelines and legislation

Guidelines and Legal Requirements

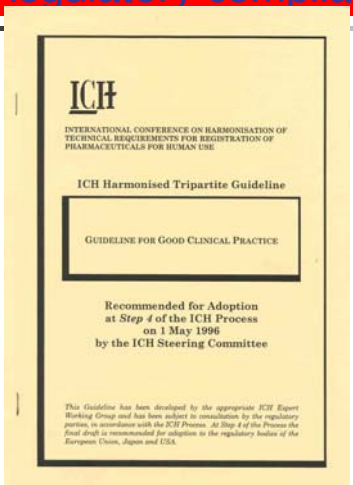
Guidelines:

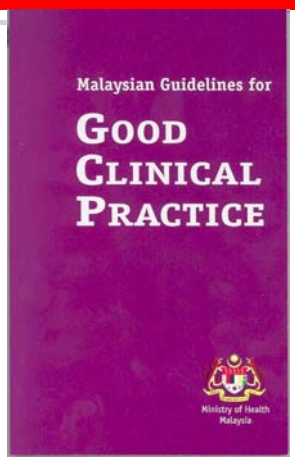
- Malaysian Guidelines for GCP (Updated 2004)
- Guidelines for Application of CTIL and CTX in Malaysia
- NIH Guideline for Research conduct in MOH

Laws

- Control of Drugs and Cosmetics Regulation 1984
- The Poison Regulation (Psychotropic Substances) 1989
- Sale of Drugs Act 1952

Regulatory compliance





Malaysia GCP Guidelines “5.20.3

The DCA will enforce the rules and punitive action will be decided by the DCA

4.Malaysian GCP
4.1 Investigator's Qualifications and Agreements

4.1.1The investigator (s) should be qualified by education, **approved training in Good Clinical Practice certification** and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement (s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/ or other relevant documentation requested by the sponsor, the IRB/IEC and/or the regulatory authority (ies)

Control of Drugs and Cosmetics Regulations 1984 (Revised 2006)

Regulation 29. Directions

(1) The Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he thinks necessary for the better carrying out of the provisions of these Regulations and in particular relate to-

(a) clinical trials or

(2) Any person to contravenes any **directives or guidelines** issued by the Authority under subregulation (1) commits an offence.

Control of Drugs and Cosmetics Regulations 1984

Regulation 12(1)(c): Clinical Trial Import Licence (CTIL)

A Clinical trial import licence in Form 4 in the Schedule,

- *authorising the licensee to import any product for purposes of clinical trials,*
- *notwithstanding that the product is not a registered product*

Control of Drugs and Cosmetics Regulations 1984

Regulation (15) Exemptions

Regulation 15(5) : Clinical Trial Exemption (CTX)

"Any person who wishes to manufacture any products solely for the purpose of producing samples for registration/clinical trials under these Regulations may on application be exempted by the Authority from the provisions of regulation 7(1)."

Contravention of Regulation 7(1) of the Control of Drugs and Cosmetic Regulations 1984

- The penalty comes under parent acts Section 12, Sale of Drug Acts 1952 (Revised 1989)

CTIL and CTX Application

CTIL Application

- For unregistered products.
- Product when used or assembled (formulated or packaged) in away different from the approved form.
- Form BPFK 442.4
- Fees : RM 500 for each product
- Licence A for Poisons (where applicable)
- DCA approval based on:-
  - approval from IRB/IEC
  - complete information on investigational products

CTX Application

- For unregistered products- manufactured locally.
- Form BPFK 443.1
- Fees : Free of charge
- Licence A for Poisons (where applicable)
- DCA approval based on:-
  - approval from IRB/IEC
  - complete information on investigational products

Factors affecting speed of approval

- How complete is the information submitted?
- How fast sponsor/ PI respond to queries ?
- Adherence to established procedures
- For CTIL and CTX - Ethical Approval given prior to release of CTIL/CTX

Compliance

Who does inspections?

- By the local Regulatory Authority
- External Regulatory Authorities

Don't just believe what we say

Malaysia's favorable experience with sponsor's audit and regulatory inspection

Sponsor pre-qualification or on-study audit

- Pfizer, Sanofi-Aventis, B Braun, Beaufour Ipsen, etc

Regulatory inspection

- EMEA
- FDA

Thank You
For Your Kind Attention

www.bpfk.gov.my

Country Report on Clinical Trial Regulation & GCP Compliance (PHILIPPINES)

Mr. Wenzel C. Asprec – Food-Drug Regulation Officer III
Ms. Cherry Rose R. Cruz – Food-Drug Regulation Officer II

Product Services Division
Bureau of Food and Drugs (BFAD)
Department of Health

27 to 30 May 2008
Century Park Hotel - Bangkok
THAILAND

Bureau of Food and Drugs

Filinvest Corporate City, Alabang, Muntinlupa City

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Bureau of Food and Drugs

- the national regulatory agency for:
  - Pharmaceuticals
  - Processed Food & Food Supplements
  - Traditional Medicine
  - Vaccines and Biologicals
  - Veterinary Products
  - Medical Devices & Gases
  - Diagnostic Reagents
  - Cosmetics
  - Household Hazardous Substances

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

VISION

The Bureau of Food and Drugs
as a world-class regulatory agency
and center of scientific excellence
composed of highly competent, efficient,
and confident staff with unfettered
enforcement capabilities.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

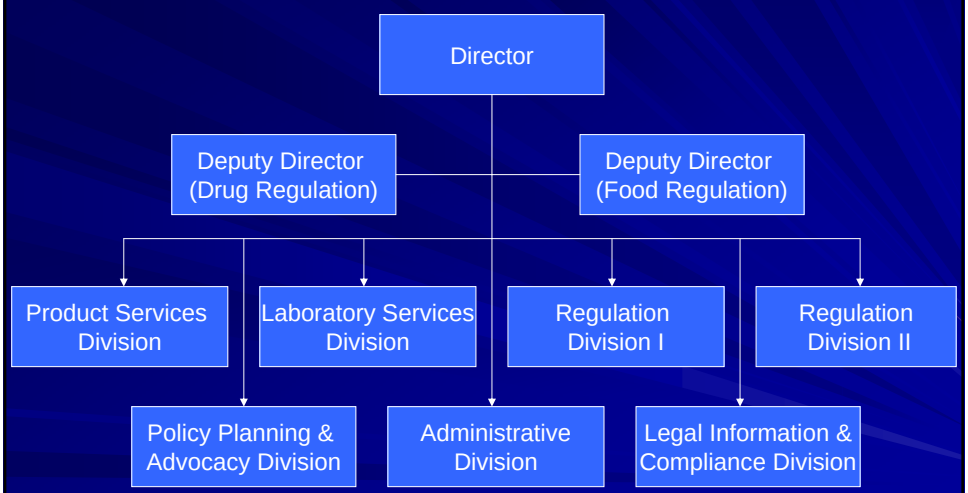
Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

MISSION

To ensure the safety, efficacy, purity and quality of processed foods, drugs, diagnostic reagents, medical devices, cosmetics and household hazardous substances through state-of-the-art technology, as well as the scientific soundness and truthfulness of product information for the protection of public health.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

ORGANIZATIONAL CHART



Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

FUNCTIONS

- Inspection and licensing of establishments
- Evaluation, testing and registration of products
- Approval of product label prior to marketing
- Monitoring of quality of products in the market
- Evaluation and monitoring of sales promotions and advertisements of regulated establishments and products
- Conduct of periodic seminars on inspection and licensing of establishments, and product registration

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Quality Control System

1) The **Regulation Divisions (I and II)** assure compliance of an establishment to GMP, GDP, and GSP.

2) The **Product Services Division** assures that a product meets the criteria for safety, efficacy and quality (GCP).

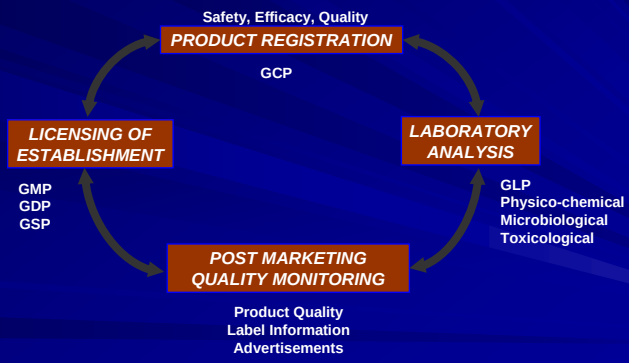
3) The **Laboratory Services Division** verifies compliance of a product with physico-chemical, microbiological and toxicological tests. Samples tested by LSD include products for registration, government deliveries, complaints and products randomly collected from the market.

4) The **Legal and Information and Compliance Division** and the Regulation Division I conduct Post-Marketing Monitoring through random sampling of products in the market, verification of labeling information and monitoring of sales promotions and advertisements.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

Quality Control Loop



Bureau of Food and Drugs – Department of Health (PHILIPPINES)

HISTORICAL BACKGROUND (1)

In 1963, in light of the tremendous growth of the food and pharmaceutical industries, the Philippine Congress found it imperative to enact a law that would ensure the safety and purity of food products, drugs, and cosmetics being made available to the consuming public. Thus Republic Act 3720, or the "Food, Drug and Cosmetic Act" was enacted.

To carry out the provisions of R.A. 3720, the Food and Drug Administration (FDA) was created, and its office and laboratories were constructed at the Department of Health (DOH) Compound in Manila.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

HISTORICAL BACKGROUND (2)

In December 1982, Executive Order 851 was passed which abolished the FDA and created the Bureau of Food and Drugs (BFAD).

Executive Order 119 s. 1987 reorganized BFAD and mandated the Bureau to be the policy formulating and sector monitoring arm of the Minister of Health pertaining to food products, drugs, traditional medicines, cosmetics and household products containing hazardous substances.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

HISTORICAL BACKGROUND (3)

In 1987, the Bureau moved to its present site south of Manila, in Muntinlupa City, and acquired new equipment including sophisticated analytical instruments and built a modern experimental animal laboratory courtesy of a grant from the Government of Japan through the Japan International Cooperation Agency (JICA).

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

LEGAL BASIS FOR REGULATION

1987 Philippine Constitution
Sec. 12, Article XIII
"The State shall establish and maintain an effective food and drug regulatory system…"

Laws/Regulations Concerning Clinical (Drug) Research

R.A. 3720 (1963)	-	Foods, Drugs, Devices and Cosmetics Act [as amended by E.O. 175 (1987)]
A.O. 67 s. 1987	-	Revised Rules and Regulations on Registration of Pharmaceutical Products
B.C. 5 s. 1997	-	Guidelines in Evaluating New Drug Applications
A.O. 2006-0021	-	Supplemental Guidelines to A.O. 67 s. 1987 and B.C. 5 s. 1997

National Guidelines for Biomedical/Behavioral Research*

* A Philippine Council for Health Research and Development - Department of Science and Technology (PCHRD-DOST) initiative

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

So what has been going on?

GCP Compliance Monitoring

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

GCP Compliance Monitoring (1)

- Currently, BFAD's team of inspectors for GCP compliance monitoring number only to 5.
- The inspection team ensures both GCP (as well as GLP) compliance of the Bioavailability/ Bioequivalence testing centers in the country.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

GCP Compliance Monitoring (2)

- There are four (4) local BA/BE testing centers, namely:

1) University of Santo Tomas - Center for Drug Research and Evaluation Studies*
2) University of the Philippines Manila – College of Medicine, Department of Pharmacology and Toxicology Bioavailability Unit**
3) De La Salle University Angelo King Medical Center Bioavailability Unit*
4) United Laboratories Bioavailability Unit*

* Privately-owned ** State-run

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

GCP Compliance (3)

- In the absence of an existing national guideline or Standard Operating Procedure (SOP), the inspection team uses the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Stumbling Blocks

Current Problems

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

Current Problems (1)

- Allocated resources for inspection had mainly been focused on Good Manufacturing Practice, Good Storage Practice, and Good Distribution Practice compliance.
- Inspectors ensuring Good Clinical Practice compliance are few (only 5) and mostly have basic know-how and training in this field.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Current Problems (2)

- In the current BFAD structure, ensuring GCP compliance are focused mainly on BA/BE testing centers, and does not cover multi-center clinical trial sites yet.
- After approval of the clinical trial protocol, the responsibility of ensuring that the clinical trial is conducted, recorded, and reported in accordance with the protocol, SOP and GCP is largely delegated to the sponsor.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

Current Problems (3)

- Currently, there is no official DOH or BFAD regulation (e.g. guideline, SOP) requiring GCP compliance in all clinical trial sites. Although widely-recognized, the ICH Harmonized Tripartite Guideline is considered "unofficial" without a written government issuance.
- There is selective reporting of trials, including Adverse Drug Reactions (ADRs) by sponsors, investigators and researchers.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

Current Problems (4)

- Concerted efforts involving several government agencies to come-up with a solid Philippine Health Research Framework have not yet really taken off.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

What Lies Ahead?

Future Plans

Future Plans (1)

- Drafting of an official national guideline in a form of a DOH Administrative Order or BFAD Circular adopting the ICH Harmonized Tripartite Guideline for Good Clinical Practice.
- Further strengthening of BFAD human resources through trainings, and expansion of the BFAD Inspection Team ensuring GCP compliance to cover multi-center clinical trial sites, in addition to the BA/BE testing centers.

Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

Future Plans (2)

- Implementation of the BFAD Integrated Information System (BIIS) to automate/computerize most of the Bureau's systems and processes, including licensing of establishments and product registration.*
- Creation of a Philippine National Clinical Trial Registry, in coordination with PCHRD-DOST, to ensure that all trials are registered, and thus a minimum set of results will be reported and publicly available.**

* In development stage ** In planning stage

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

At the end of this Workshop…

GOALS

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

GOALS (1)

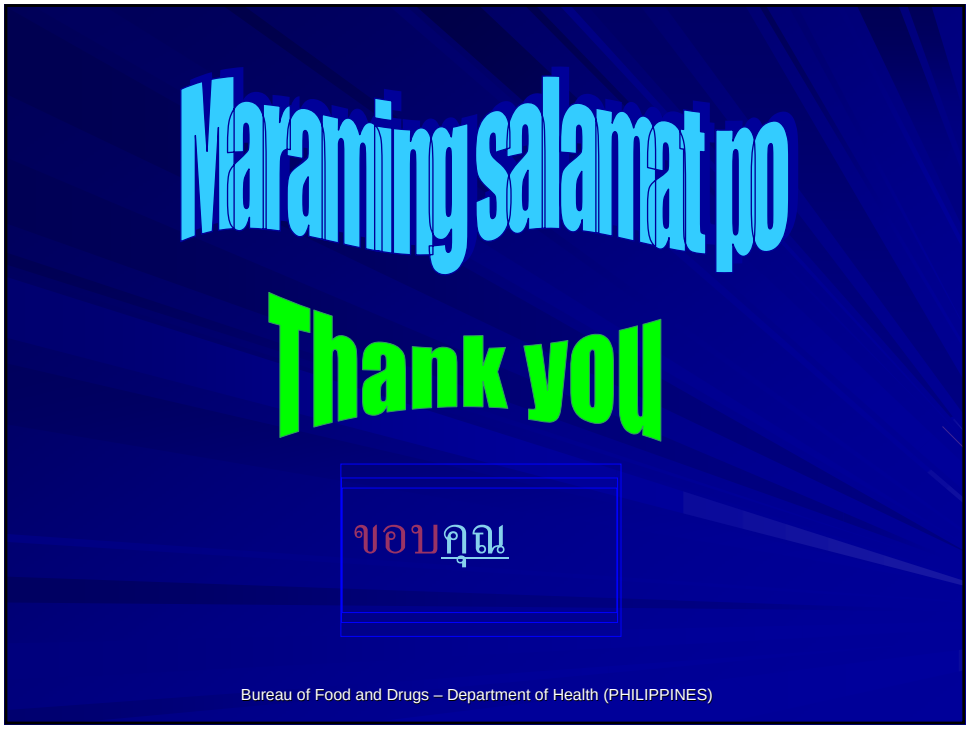
- Learn from other countries' experiences in GCP-compliance monitoring and clinical trial control, take note of the difficulties and challenges they have faced, and be able to assist in improving the current system (or the lack of it) back home.
- Fully understand the critical roles played by the sponsor, investigator, researcher, IRB/EC, and most importantly, the regulator in ensuring GCP compliance.

Bureau of Food and Drugs – Department of Health (PHILIPPINES)

GOALS (2)

- Acquire the necessary knowledge, techniques and skills to become a more effective clinical research inspector.
- ***Realize that upholding ethically-sound practices, above all, is topmost priority in every clinical trial.***

Bureau of Food and Drugs – Department of Health (PHILIPPINES)



Mr. Wenzel C. Asprec
Food-Drug Regulation Officer II
Bureau of Food and Drugs
Department of Health
Philippines

Clinical Trials in Singapore

Basic Workshop on GCP/Clinical Research Inspection
Bangkok, Thailand
27-30 May 2008

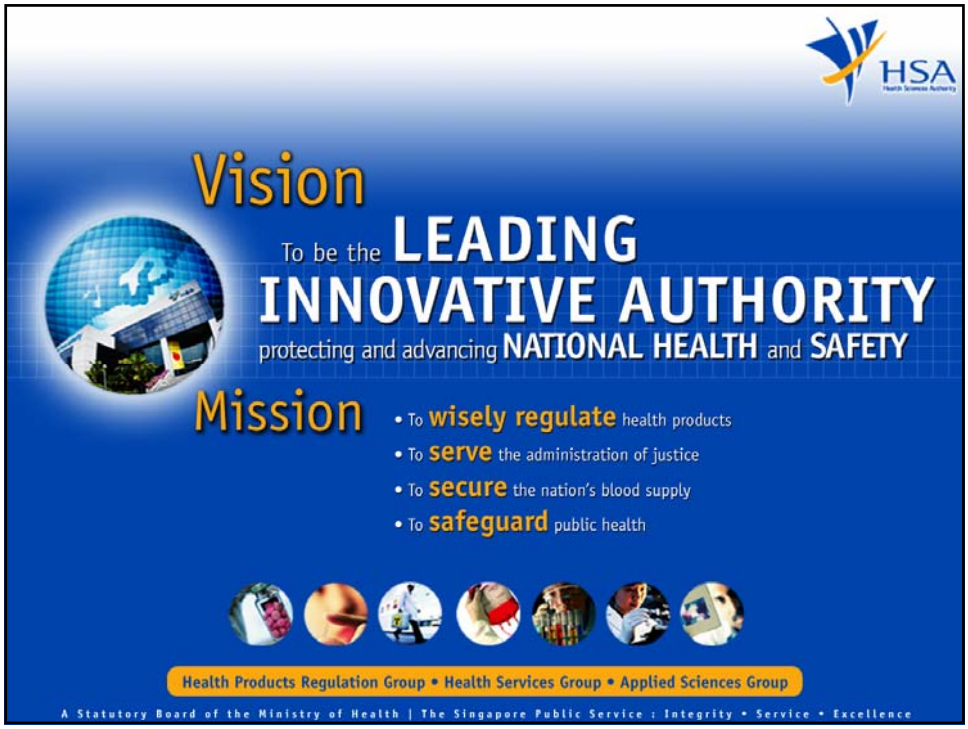
Foo Yang Tong
Head, Clinical Trials
Product Evaluation and Registration Division
Health Products Regulation Group
Health Sciences Authority
27 May 2008

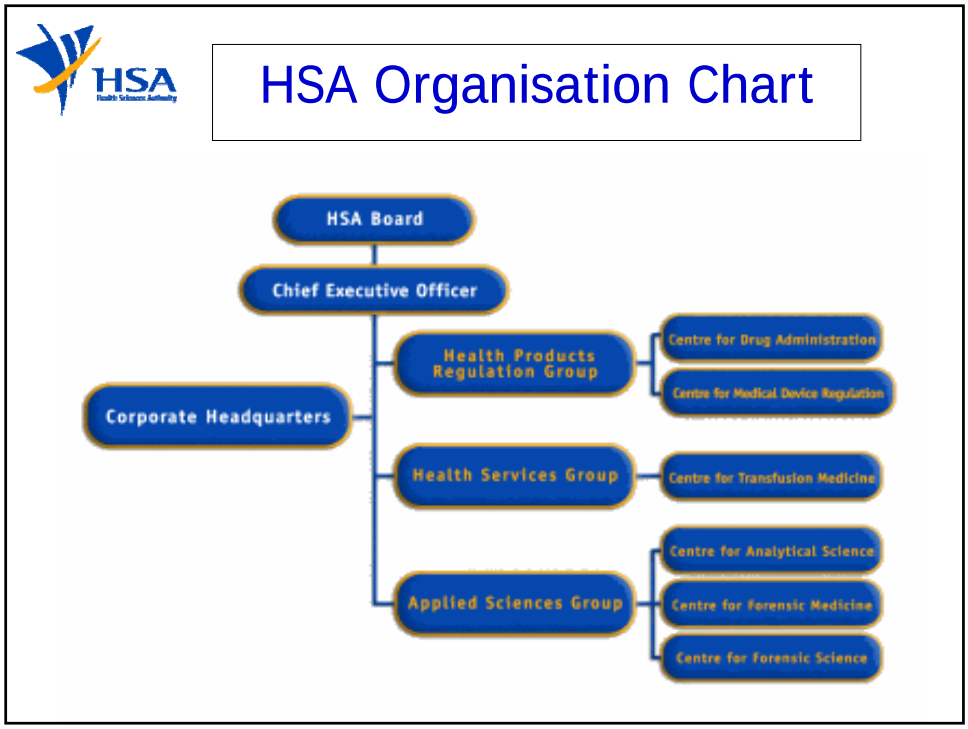
To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

Presentation Outline

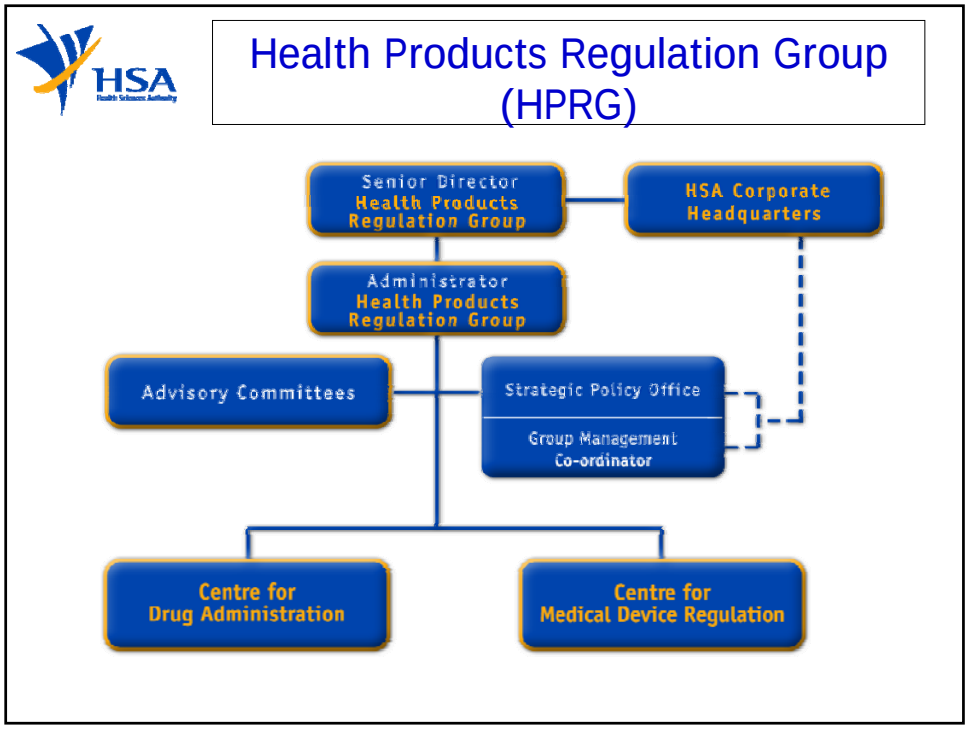
- Overview of the Health Sciences Authority
- Regulatory Framework for Clinical Drug Trials
- Clinical Trials Statistics & Trends in Singapore

To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY


HSA
Vision
To be the LEADING
INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY
Mission
• To wisely regulate health products
• To serve the administration of justice
• To secure the nation's blood supply
• To safeguard public health
Health Products Regulation Group • Health Services Group • Applied Sciences Group
A Statutory Board of the Ministry of Health | The Singapore Public Service : Integrity • Service • Excellence


HSA
HSA Organisation Chart
HSA Board
Chief Executive Officer
Corporate Headquarters
Health Products Regulation Group
Centre for Drug Administration
Centre for Medical Device Regulation
Health Services Group
Centre for Transfusion Medicine
Applied Sciences Group
Centre for Analytical Science
Centre for Forensic Medicine
Centre for Forensic Science


HSA
Health Products Regulation
Applied Sciences
Health Services
Drugs & Devices
• Product Risk Assessment
• Quality Systems Audit
• Clinical Trials Regulation
• Licensing
• Vigilance & Surveillance
• Enforcement
• Health Products
• Quality Analysis
• Blood Banking & Transfusion Services
• Hemovigilance
Options for new & greater synergies across Groups
ORITY
ATIONAL HEALTH and SAFETY
All Rights Reserved 2007 Health Sciences Authority | 5


HSA
Health Products Regulation Group (HPRG)
Senior Director Health Products Regulation Group
HSA Corporate Headquarters
Administrator Health Products Regulation Group
Advisory Committees
Strategic Policy Office
Group Management Co-ordinator
Centre for Drug Administration
Centre for Medical Device Regulation

Clinical Trial Oversight - Regulatory Basis

Legislation for oversight of clinical drug trials :

- Medicines Act (Chapter 176, Sec 18 and 74)
- Medicines (Clinical Trials) Regulations
- Singapore Guideline for Good Clinical Practice (SG-GCP, adapted from ICH E6 on GCP)

All clinical drug trials conducted locally have to comply with these standards

Regulation of Clinical Trials in Singapore

1978

Licensing of clinical trials, establishment of the CT Regulations & the Medical Clinical Research Committee (MCRC)

1998

Implementation of SG-GCP, revision of CT Regulations

Overview of Regulatory Framework

Singapore Guideline for Good Clinical Practice (SG-GCP)

- Implemented in Singapore in 1998
- Adapted from ICH E6
- International ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that involve the participation of human subjects

Overview of Regulatory Framework

Singapore Guideline for Good Clinical Practice (SG-GCP)

Compliance with GCP provides public assurance that the

- Rights, safety, well being & confidentiality of trial subjects are protected
- Clinical trial data are credible

Legal Requirements

The regulations cover the following areas:

- Need for regulatory approval – clinical trial certificates
- Duties of certificate holders (principal investigators)
- Informed consent (<21 years, unconscious or incapable of exercising rational judgment, emergency trials)
- Notification of serious adverse events
- Record keeping and test material labeling requirements
- Duty to comply with guidelines (including SG-GCP) and requirements of licensing authority
- Penalties for non-compliance

Legal Requirements

The regulations :

- Protect safety and interests of subjects in trials
- Prevent clinical trials that are unscientific, unethical or have unacceptable risks
- Clinical trial can only be conducted if it has a certificate issued by the Licensing Authority (HSA)
- Once approved, trial must be conducted under the supervision of the principal investigator at the premises specified in the certificate in accordance to guidelines, including Singapore Guideline for Good Clinical Practice

Current Framework for Clinical Trials

Supporting Documents for Regulatory Submission:

- Clinical Trial Protocol
- Investigator's Brochure
- Subject Information Sheet & Informed Consent Form
- GMP Certificate / Certificate of Analysis

General Guideline of application for Clinical Trial Certificate:

http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/guidelines/ctc_application.html

Current Framework for Clinical Trials

- Parallel Submission to both IRB & HSA
- Ethics and regulatory review and approval timelines ~ 4-6 weeks
- The Health Sciences Authority issues the regulatory approval, in the form of a Clinical Trial Certificate
- CTC validity: 2 years and specific for each study protocol, each PI and site involved in the study
- The Licensing Authority for clinical trials under the Medicines Act is CEO HSA

Current Framework for Clinical Trials

Post-Approval Requirements

www.hsa.gov.sg/html/business/ct.html (amend@prism)

For Approval:

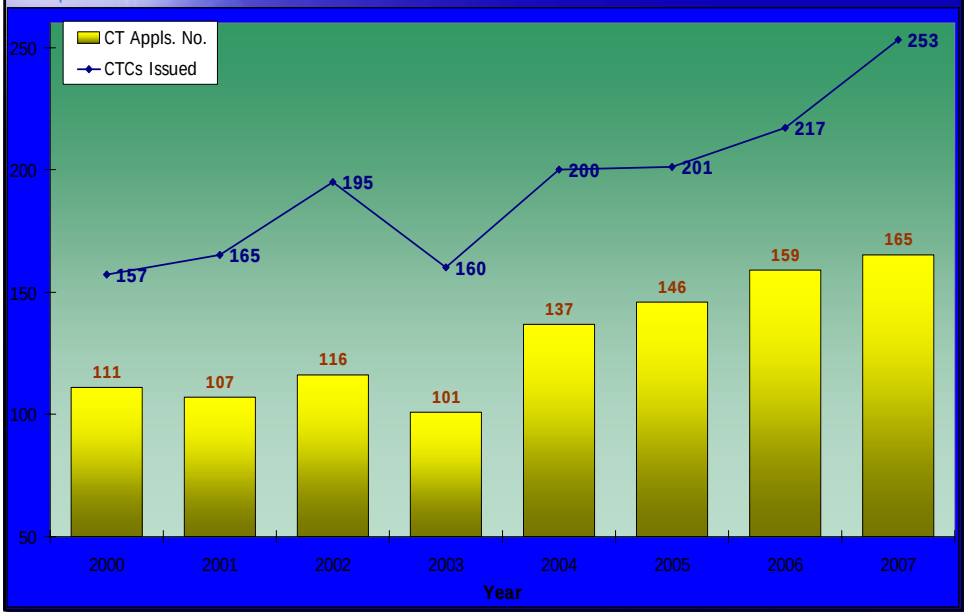
- Protocol and/ or informed consent form amendments
- Change in principle investigator
- Addition of trial site
- Extension of CTC (if required)

For Notification:

- Safety updates, DSMB reports, premature closure of trial
- Investigator's Brochure update
- Status report (6-monthly after CTC approved)
- Final report (when the clinical trial is completed)

To be the LEADING INNOVATIVE AUTHORITY protecting and advancing NATIONAL HEALTH and SAFETY

No of CT Applications & CTCs Issued

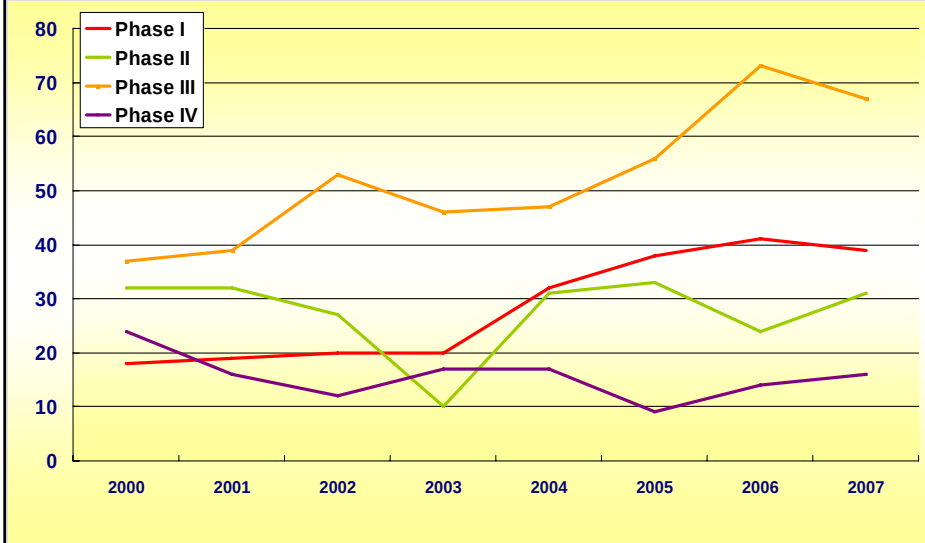


Number of Clinical Trial Certificates

Phase	2000	2001	2002	2003	2004	2005	2006	2007
I	21	19	20	24	31	44	48	47
II	44	50	52	19	49	50	35	45
III	63	68	97	91	88	90	116	135
IV	29	28	26	26	32	17	18	26
	157	165	195	160	200	201	217	253

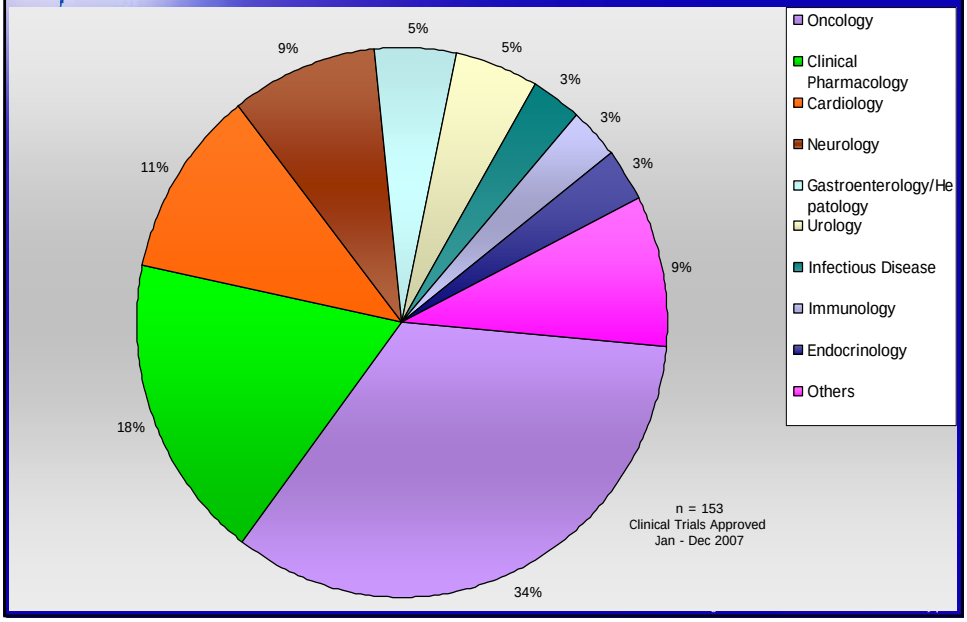
To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

No of Approved CT Applications



protecting and advancing NATIONAL HEALTH and SAFETY

Clinical Trials Therapeutic Areas (2007)



Clinical Trial Trends

- Multinational or global trials sponsored by pharmaceutical companies/CROs: 70-80%
- Multinational or global trials (Phase II-III) to support NDAs to major regulatory agencies: 50-60%
- Progress in Oncology research especially in molecular targeted therapies: 25-30%
  - Advancement in genomics
  - Supported by cancer research centres focusing in early drug development, cancer pharmacology, cancer genetics & cancer endemic in Asia, as well as collaborations with the US National Cancer Institute
- Bridging studies are not required for local drug registration because of market size and difficulty in identifying a homogenous population
- Growing phase I Clinical Pharmacology studies: 20-25%

To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

Contacts

Clinical Trials Branch
Product Evaluation & Registration Division
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way
#11-03 Helios
Singapore 138667

For any enquiries, please contact
Tel No. 65 6866 3446
Fax No. 65 6478 9034

To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

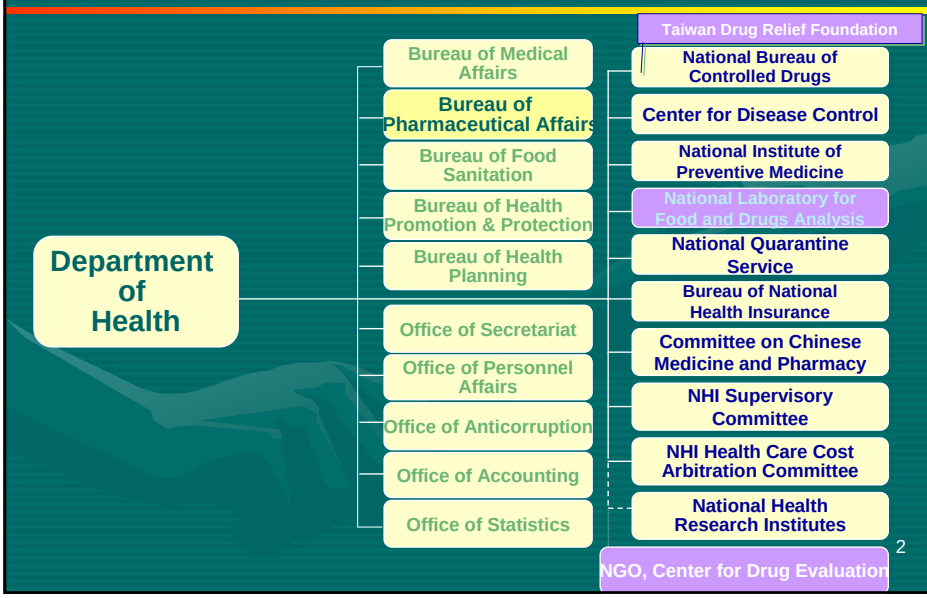
Thank you

To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

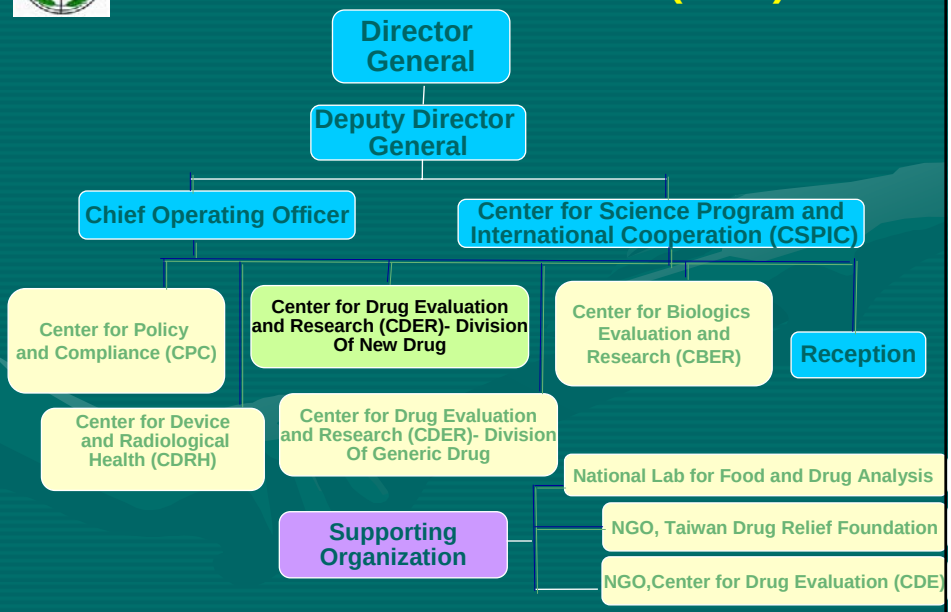
Status of GCP Laws/Regulations and Inspections in Chinese Taipei

Chao-Yi, Joyce, Wang
Bureau of Pharmaceutical Affairs,
Department of Health,
Chinese Taipei
May 27, 2008

Current Organization of the Department of Health (DOH)



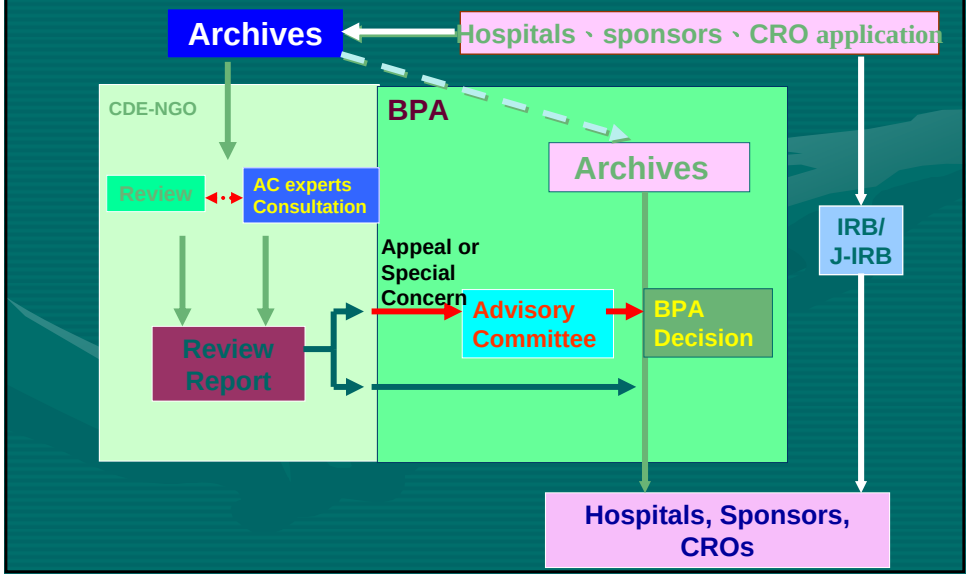
Organization Chart of the Bureau of Pharmaceutical Affairs (BPA)



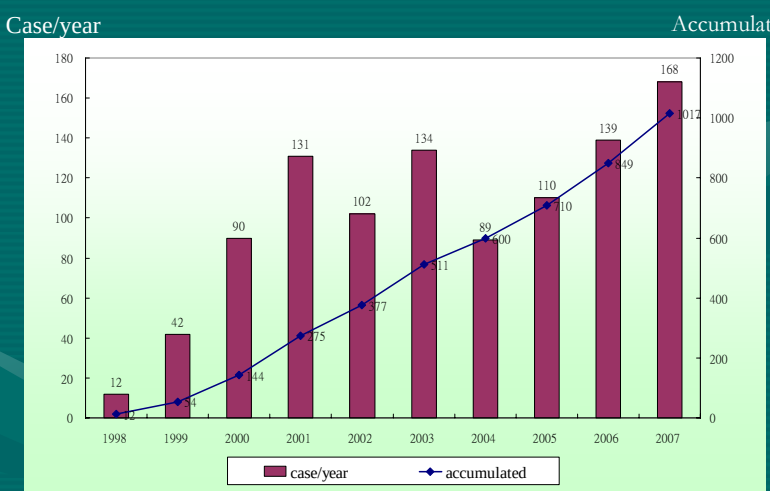
GCP Laws/Regulations in Chinese Taipei

- Medical Care Act and Enforcement rules
- Pharmaceutical Affairs Act and Enforcement Rules
- Regulations for Good Clinical Practice
- Pharmaceutical Manufacturer Inspection Measures

Review Process for IND in Chinese Taipei



IND Application(1998-2007)



Measures to Improve Clinical Trial Quality

- Conform to international regulations on protection of human subjects
- Improve IRB review quality
- Training programs for Health Professionals
- Establish clinical trial research centers
- Adverse Drug Reporting (ADR) System
- GCP Inspection

Conform to international regulations on protection of human subjects

- SIDCER Accreditation
  - Establish a forum for regional network
  - Promote protection for human subjects
- Status of SIDCER accreditation in Chinese Taipei
  - SIDCER conduct the first IRB accreditation in Chinese Taipei in 2005

Year	Asia Pacific Region accreditation	Chinese Taipei accreditation
2005	3	2
2006	7	4
2007	23	11

Establish clinical trial research centers

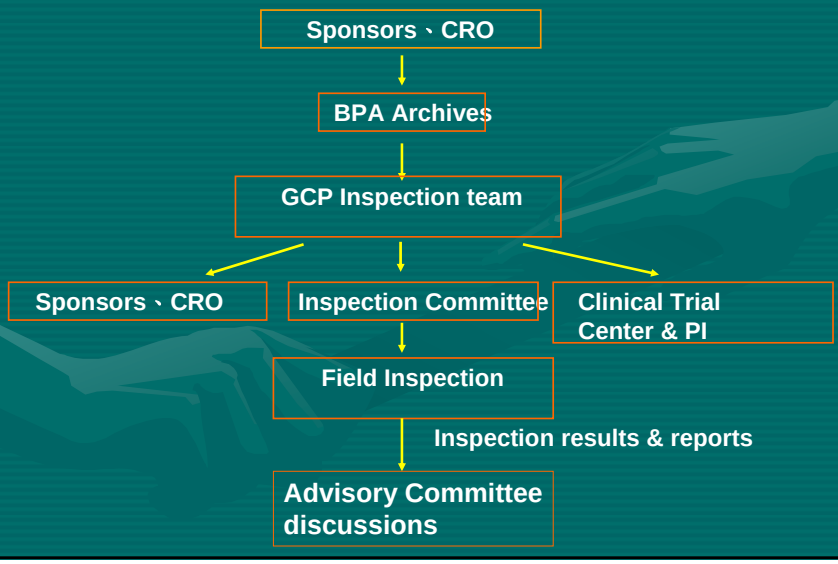
- 「New drug clinical trial research center and laboratory」--GCRC
- The Scientific and Technological Island Plan —Establish Center of Excellence for Clinical Trial and Research
- Clinical trial management institution (Site Management Organization, SMO）

Adverse Drug Reporting (ADR) system

Regulations for GCP-- Article 106

- Any Serious Adverse Event, (SAE) occurred in human subjects is required to be reported.
- In any SAE cases, Principal Investigator needs to inform sponsors.
- Sponsors is required to report to the DOH within 7 days of notification and provide written report within 15 days for any death or life threatening SAE reports.

Review process for Clinical Trial Report



Statistics for Clinical Trial Reports

Year	2002	2003	2004	2005	2006
Inspection cases	37	47	36	34	38
Disapproval Reports	4	4	5	2	2
Disapproval rate	11%	9%	14%	6%	5.2%

Clinical Trials Network in Chinese Taipei

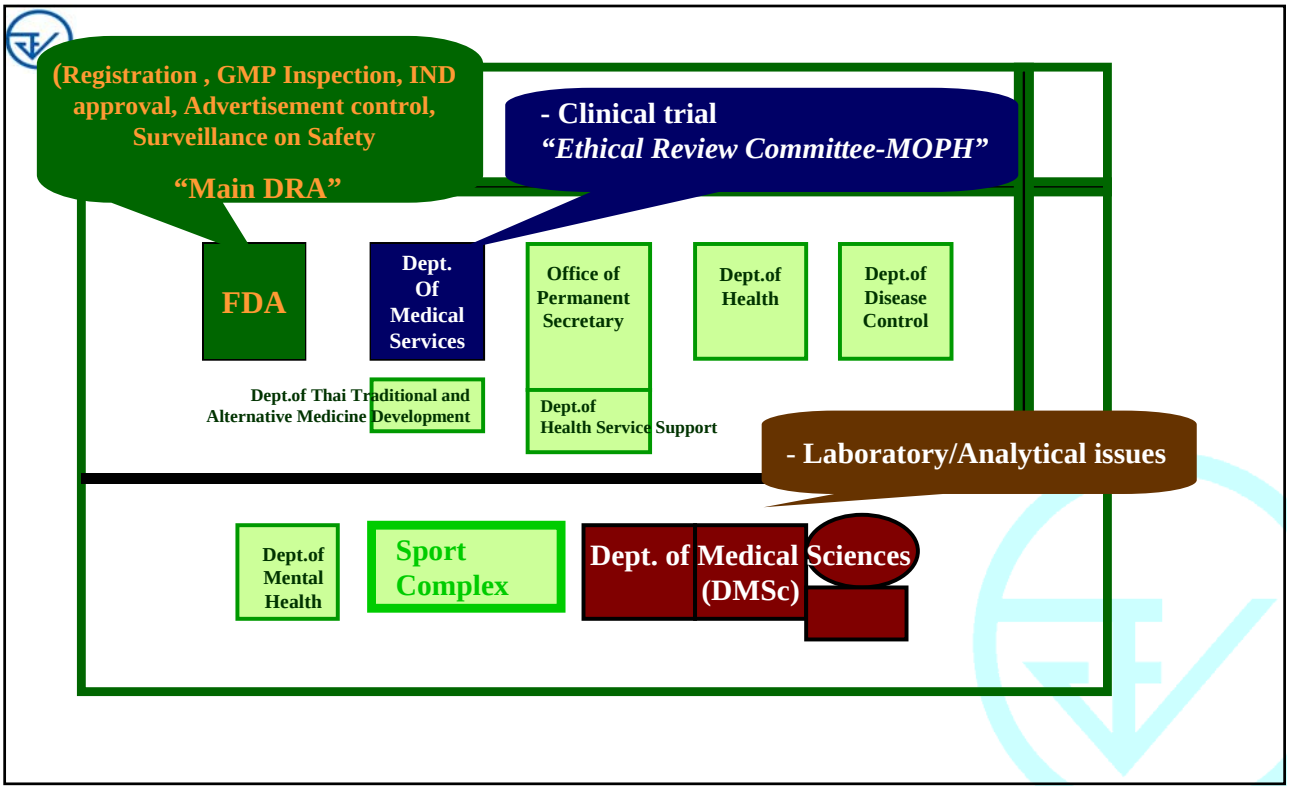
http://www.cde.org.tw/ct_taiwan/index.htm

Thank You for Your Attention

Status of *Clinical Trial Environment* in Thailand

Outline:

- Organization
- Law and Regulation
- Importation of Drug product for Clinical Trial



TFDA

Organization

Secretary-General(1)

Deputy Secretary-General(3)

Experts(11)

Committees

Health Product Control Div.

- Drug Control div.
- Narcotic Control div.
- Medical Devices Control div.
- Import & Export Inspcetion div.
- Cosmetic & Hazardous Substance Control Bureau
- Food Control div.

Supportive Div.

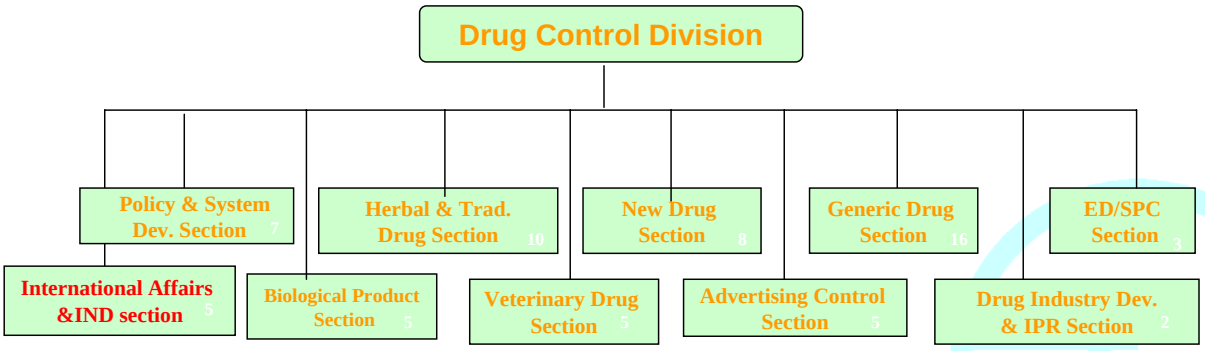
- Office of Secretary
- Technical & Policy Administration div.
- Consumer Affairs div.
- Rural & Local Consumer Health Product Protection Promotion div.

Additional Group

-IT Center
-Legal Affairs Task gr.
-Internal Audit Task gr.
-Administrative Dev. Task gr.

TFDA

The Organization Chart



TFDA

The current laws and regulations

The Drug Act B.E. 2510 (A.D.1967)

amended by

- *Drug Act (No.2) B.E. 2518 (1975)*
- *Drug Act (No.3) B.E. 2522 (1979)*
- *Drug Act (No.4) B.E. 2527 (1984)*
- *Drug Act (No.5) B.E. 2530 (1987)*

Ministerial Notification
No.14 (A.D.1989)

The drugs, which are intended to import into the Kingdom on following purpose, are exempted from registration;

- -Clinical trial/study,
- -Analysis,
- -Exhibition, *or*
- -Donation

➔ **Authorization NEEDED!**
➔ **only to the "rightful Organization/Person"**
➔ **need Application + attached Documents**

Importation of Drug product for Clinical Trial (1)

Regulation/Rule Requirement

- **Application form**
- **Attached Documents**
  - **Labeling**
  - **Drug Leaflet**
  - **Clinical Trial Report**
  - **Certificate of Free Sale / CPP / or EC Approval Certificate**
  - **Clinical Protocol & Investigator's Brochure**

Importation of Drug product for Clinical Trial (2)

Regulation/Rule Requirement

Application form

- Date
- Applicant's name & title
- Organization's name & address
- Detail of the Drug product(s) intended to import
  - *name*
  - *quantity*
  - *strength*
  - *packing*
- Signature

Importation of Drug product for Clinical Trial (3)

Regulation/Rule Requirement

Labeling

- Name / Code of the drug product
- Protocol Code No. (or Title)
- "For Clinical Use Only"
- Manufacturing name & address

Importation of Drug product for Clinical Trial (4)

Regulation/Rule Requirement

IEC/IRBs's Acceptance

- Ethical Review Committee of MOPH (~ national IEC)
- 8 IRB of Medical Faculty's Hospitals (all Government)

➔ only 1 "IEC-MOPH" for all Sites

➔ for "accepted IRB", needed from each Site !

Importation of Drug product for Clinical Trial (5)

Regulation/Rule Requirement

Procedure for Authorization

- check on
  - *completeness of the Application Form*
  - *rightful applicant?*
  - *correctness Attached documents/Label/EC approval….*
- evaluate the "amount requested" appropriateness
- provide Comment/Recommendation
- authorized Officer 'final review', and 'sign' for approval (in special stamp made on Application)

➔ target timeline = 10 working days *(with stop-clock)*

Importation of Drug product for Clinical Trial (6)

Regulation/Rule Requirement

Authorization

call 'Applicant'
to get following Documents
at our Office

- ***approval Application***
- ***informed Letter***

Importation of Drug product for Clinical Trial (7)

Regulation/Rule Requirement

Informed Letter

informed the Authorization,
and following orders….

- **use 'drug product' for Clinical trial ONLY !**
- **maintain on Quality + administer the Drug appropriately**
- **Comply to the ICH-GCP**
- **Report 'SAEs' within the specific timeline**
- **Submit Final Report of 'finished' / or 'terminated' protocol**
- **Destroy or re-export all remained drug, and submit report To Drug control div. within 1 mths.**

GCP situation

- **GCP adopted in 2000**
- **~ 6,000 trainees on GCP(y.2002-7)**
- **- active and closely cooperation**
- **- regular *Annual Seminar***
- **- willing & ready for participate –**

“Global Drug Development”

GCP Inspection Experience

- Training on GCP audit/inspection
  - by industry
- Observe other DRA’s inspection in Thailand
  - US FDA in 2006
  - MHRA, (EU) in 2006

The Overall Plan on Changing

- new Roadmap
- IND Trial approval and monitoring
-Strengthening & Networking “Stakeholder”

→ Healthy & Powerful Clinical Research in Thailand

Thank You

ขอบคุณค่ะ

Sawasdee from Vietnames Delegations

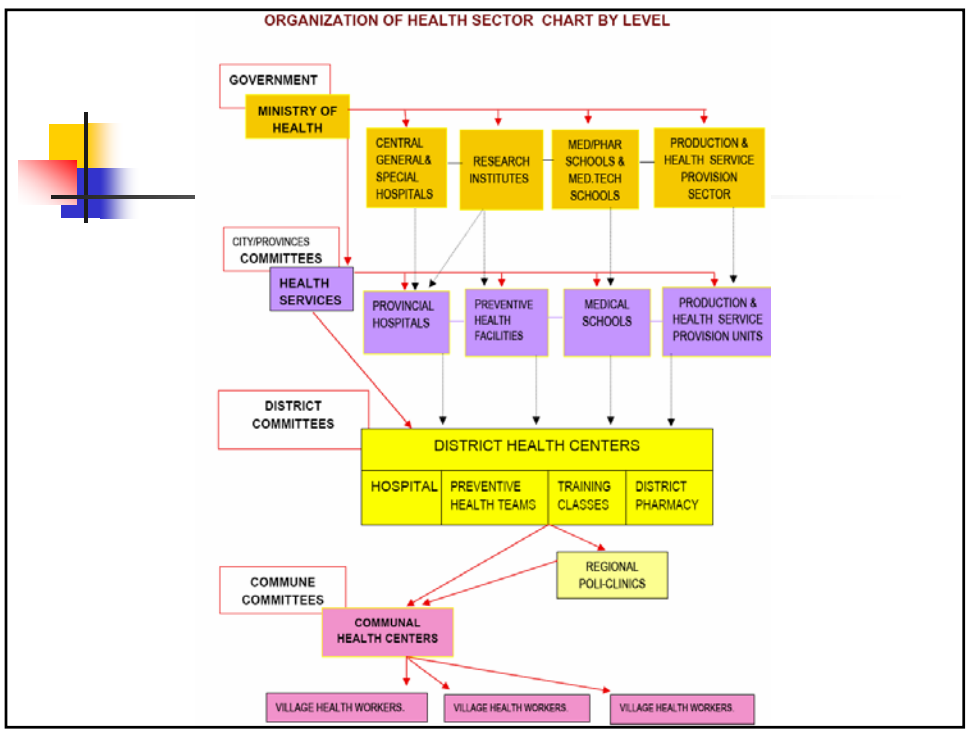
Ministry of Health
Vietnam

GCp system in vietnam

Department of Science and Training
Ministry of Health
(DST- MoH)
T: +84 4 273 2249
F: + 84 4 273 2243

- Square: 332,600 Km2
- Population : 82,727,400
- Urban: 50,8% Female, 25,1% Male
- Annual growth rate: 1,32%.
- Life expectancy (years): 71,3
- Ethnic group 54 (87% Viet or Kinh)
- Two main religions : Buddhism & Catholicism
- City and Province : 65
- Capital: Hanoi
- The biggest city: HoChiMinh
- Districts: 673
- Communes: 12,753
- GDP per capita: 580 US$

(Source: Statistics office 2006)



Basement…

1. GCP ICH – E6 (International Conference on Harmonization regulations).
2. WHO guideline on Ethical Committee's activities in biopharmaceutical research (Ethical Review Board Guideline).
3. Ethics Committee's regulation.
4. Clinical trial regulation (Decision N^0 01/2007/QĐ-BYT dated 11/01/2007).
5. GCP Guideline (Decision No 799/QDD-BYT dated 7/3/2008)
6. The necessary and harmonization of clinical trial system in Vietnam at present (US, EU, France, Sweden, Netherlands, Australia, Asian...)

Objective

Establish the standard system to **review, approval, conduct, inspection, monitoring and deployment of clinical trial study** on medicines, vaccines, biologicals and traditional medicines in Vietnam in order to comply with International clinical trial guidelines, applicable laws and regulations in Vietnam, International Harmonization basing on GCP Guideline/ICH.

.

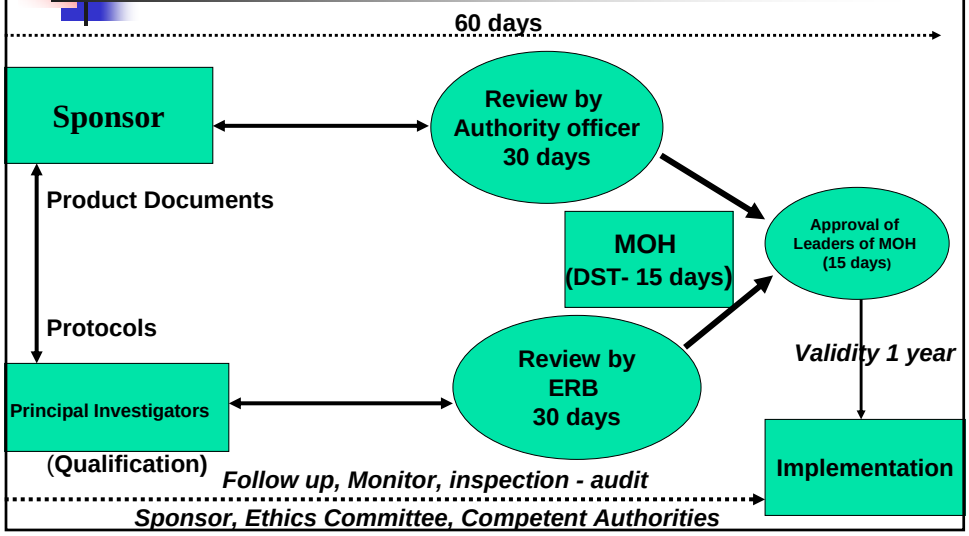
GCP System in Vietnam

- ERB/MoH
- ERB/Hospitals, Institutes
- CRUs : 11 Hospitals an Institutes
- Clinical Trial regulation
- GCP Guideline
- GCP Training.

General regulation

All biomedical researches (Incl. Clinical trials) conducted in Vietnam must be reviewed on ethical and science aspect by the Ethical Review Board (ERB-MoH).

Reviewing process



Plan to develop GCP System in Vietnam

- **1- To improve the awareness and implementation of GCP and ethical quality standards among investigators in Vietnam institutes-hospitals.**
- **2- To establish a monitoring and inspection system for clinical researches in compliance with GCP standard.**

Plan to develop GCP System in Vietnam

- 3- To develop a CRUs (Institutes–hospitals) which meet GCP requirements in conducting a clinical researches.
- 4- To improve the management capacity of the functional department (Department of Science and Training-DST-MoH) and set up a data management system for clinical researches in Vietnam.
- To establish the CRCs in Vietnam.

Our Team ....

1- Prof.Dr. Van Do Duc- Vice Chairman of ERB-MoH

2- Dr. Quang Nguyen Ngo – Expert of DST-Secretary of ERB- MoH.

3- Ms. Tu Nguyen Le – DAV- MoH

4- Ms. Vinh Nguyen Tran – DAV- MoH

Thank you for your attention!

Overview of GCP Laws/ Regulations in Saudi Arabia

Abdulmohsen H. AL Rohaimi,
DDS, APC, MSc, Ph.D
Director of Research and Publication
27 –30 MAY2008
GCP/Clinical Research Inspection Workshop
Bangkok - Thailand

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Objectives of my talk

- Give an insight GCP Laws/ Regulations in Saudi Arabia.
- Current initiatives.
- What are the challenges in GCP regulations in Saudi Arabia?

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Food and Drug Authority (SFDA)

The SFDA : Recently established, 2004

Vision

- To be the leading regional regulatory authority for food, drugs and medical devices with professional and excellent services that contributes to the protection and advancement of the health in Saudi Arabia.

Mission

- To ensure the safety of food; the safety, quality and efficacy of drugs; and the safety and effectiveness of medical devices, by developing and enforcing an appropriate regulatory system.

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

SFDA Guidelines

- Regulations implemented with two main objectives:

  – strengthen protections for human research subjects

  – increase R & D investment in clinical trials in Saudi Arabia

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

SFDA Guidelines

Protection of Trial Subjects Guidelines

- IRB, Investigator and sponsor responsibilities .
- Manufacturing, Packaging, Labeling, and Coding of Investigational Product.
- Clinical Trial Protocol

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Basic goal of GCP

- Unified standard to facilitate the mutual acceptance of clinical data by different Regulatory Authority .

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

An insight of GCP Laws/ Regulations in Saudi Arabia

- Institutional review board: done independently in each institution e.g.:

Tertiary Hospitals -. King Faisal Specialist Hospital & Research Center

- King Abdulaziz City for Science & Technology

- Ethics committee : NATIONAL COMMITTE
- -responsibility
- composition – function – operations – procedure - Records

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

The Current Efforts for GCP Laws/ regulation in Saudi Arabia

MOH : The Central Committee For Research Ethics

- **Governmental Hospitals :** Local Ethical committees- IRB

- **National committee For Research Ethics**
- - informed consent : predictable side effects and risk
  - protect research subject from unethical risk

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

The Current Efforts for GCP Laws/ regulation in Saudi Arabia … continue

Working to build a regulatory framework that…

- Incorporates essential elements of Good Clinical Practices
  - –Sound research protocol
  - – Informed consent of research subjects
  - – Obtain IRB approval and continuing oversight
  - – Appropriate qualifications of investigator and staff
  - – Monitor and report serious, unexpected, adverse drug reactions through Saudi vigilance center
  - – Maintain accurate records
  - • Gives the authority clear vision to reject, suspend or cancel the authorization of a clinical trial

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Opportunity & Needs

Infrastructure
- Med.Hospital Faculty =200
- Resources ; trainees on GCP.

training

-info. Exchange

-Capacity building a network to all Stakeholder
-research collaboration

Outcome :
- Clinical Research Center – GCP Approved

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Need for GCC Directive on clinical trail

- Some studies are complex and often multistate .
- Rationalization of requirement for starting of trails
- Minimum standard for conducting of the clinical trails have been captured
- Protection of patient- application to start trail- ethics –handling of the PV data- investigational medicinal products

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Need for GCC Directive on clinical trail

- Need central database to share information within country and b/w member states

-trail submission details

- any amendments
- all ethics approval
- end of trail notification
- GCP inspection conducted

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Ongoing Initiatives

- – Implementation of Saudi Vigilance System for the management of ADRs
- – Research Ethics: development of standards for Research ethic board .
- –Clinical Trials Registration and Disclosure

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Trend & Plan - SFDA

- Sponsor & CRO
- internal Auditing
- provide Training:

  - to improve Quality & Speed of the Trial
  - to work in New highly technology (i.e. Snip,
  - enhancing the contribution to the R&D

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Understanding the challenges and opportunity context

- Politics,
- Funding, - Research
- Interagency support,
- Competing organizations,
- Competing interests,
- Social and economic conditions,
- And history (of the program, agency, and past collaborations).

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Thank you

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Review of GCP:
Goals /Principles/ Roles/Responsibilities

David A. Lepay M.D., Ph.D., and
Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 27, 2008

What This Lecture will Address/Review

- Key Activities in a Clinical Trial
  - The Process Approach
- Brief History of GCP (U.S. and international)
- Goals and Principles of GCP
- Roles and Responsibilities Under GCP
  - Investigators
  - Sponsors/Contract Research Organizations
  - Ethics Committees

Inspector's View of a Clinical Trial

- Premise: A clinical trial can be viewed as a series of key activities
  - WHO Handbook for GCP identifies 15 key activities in conducting a single clinical study
    - The order of these activities may vary
    - Activities may be completed simultaneously
  - Multiple parties (including the investigator --- but also the sponsor, ethics committee[s], and regulator[s]) are responsible for the success of each of these activities

Key Activities and The Process Approach

- Thesis: To achieve quality of the clinical trial as a whole, quality must be defined, controlled, and assured for each key activity
- An inspection should address each of the key activities that take place at the inspected site and for which the inspected party is responsible

Thinking Like an Inspector: Questions to Ask -1-

- What are these 15 key activities ?
- Which of these 15 are the responsibility of the party I am inspecting ?

The 15 Key Activities in a Regulated Clinical Trial -1-

1. Development of the Study Protocol
2. Development of Written Standard Operating Procedures (SOPs)
3. Development of Support Systems and Tools
4. Generation and Approval of Study-Related Documents
5. Selection of Study Sites and Qualified Investigators

The 15 Key Activities in a Regulated Clinical Trial -2-

6. Ethics Committee Review and Approval of the Protocol
7. Review by Regulatory Authorities
8. Enrollment of Subjects: Recruitment, Eligibility, and Informed Consent
9. The Investigational Product(s): Quality, Handling, and Accounting
10. Conducting the Study: Study Data Acquisition

The 15 Key Activities in a Regulated Clinical Trial -3-

11. Safety Management and Reporting
12. Monitoring the Study
13. Managing Study Data
14. Quality Assurance of Study Performance and Data
15. Reporting the Study

Thinking Like an Inspector: Questions to Ask -2-

- What information do I have about each key activity before I start the inspection ?
- What do I ask/review on-site to assess each key activity ?
- What are the inspected party's responsibilities in each key area and what is the standard I use to evaluate these ?

GCP: Origins in the Successes and Failures of Research

- Successes
  - Scientific Method and Evidence-Based Medicine
  - Principles of Conduct (Hippocratic Oath and beyond)
- Failures
  - Ethical Atrocities (War-time research; others)
  - Scientific Fraud
  - Preventable Research Deaths/Injury

GCP in the U.S.: A Brief History -1-

- In contrast to GMP (Good Manufacturing Practices) and GLP (Good Laboratory Practices: for animal toxicology studies), the term “Good Clinical Practice” (or GCP) does not appear in U.S. law or FDA regulations
- But FDA has a long history of regulating and inspecting clinical research

GCP in the U.S.: A Brief History -2-

- 1960’s
  - Requirement for “adequate and well-controlled clinical investigations” to support marketing applications
  - Requirement for research permits (IND) to conduct human subjects research with investigational products
  - First FDA inspections of clinical investigators

GCP in the U.S.: A Brief History -3-

- 1970's
  - FDA regulations for each of the parties involved in clinical research
    - Clinical Investigators
    - Sponsors/Monitors/ Contract Research Organizations
    - Ethics Committees (IRBs/IECs)
  - Comprehensive Bioresearch Monitoring (BIMO) Program of inspections: Inspecting each party
  - Extension of law/regulations to medical devices

GCP in the U.S.: A Brief History -4-

- 1980's
  - Acceptance of non-U.S. studies in support of a U.S. marketing application
    - A marketing application (NDA; PMA) can be submitted to the U.S. with only foreign studies --- no requirement for a U.S. study
  - FDA began inspection of clinical investigators and sponsors outside of the U.S.

FDA CI International Inspections*

Algeria**	1	Gabon	1	Peru	6
Argentina	19	Germany	59	Philippines	4
Australia	9	Greece	2	Poland	29
Austria	6	Guatemala	2	Portugal	2
Bahamas	1	Hong Kong	5	Romania	1
Belgium	26	Hungary	10	Russia	35
Brazil	13	India	6	Serbia	3
Bulgaria	1	Ireland	1	Singapore	1
Canada	151	Israel	5	Slovenia	1
Chile	8	Italy	36	South Africa	26
China	7	Japan	3	Spain	17
China, Taipei	3	Kenya	1	Sweden	28
Colombia	1	Latvia	5	Switzerland	2
Costa Rica	8	Lithuania	2	Thailand	4
Czech Republic	7	Malawi	1	Turkey	6
Croatia	3	Malaysia	4	U. K.	91
Denmark	13	Mexico	14	Ukraine	4
Dominican Rep.	1	Netherlands	24	Venezuela	2
Ecuador	1	New Zealand	4	Yugoslavia	3
Egypt	1	Nigeria**	1	Zambia	1
Estonia	5	Norway	5		
Finland	15	Panama	2		
France	51				

*Conducted for FDA/CDER from 1980 through 08/8/07; total: 810
**data reviewed in U.S.

GCP in the U.S.: A Brief History -5-

- 1990's:
  - International GCP harmonization through ICH (International Conference on Harmonization)
    - Harmonization between industry and regulators in U.S., European Union, and Japan
    - First "formal" use of the term GCP at FDA
    - Resulted in ICH GCP (E6) Consolidated Guideline
      - Published in the U.S. in May 1997 as official FDA "guidance"

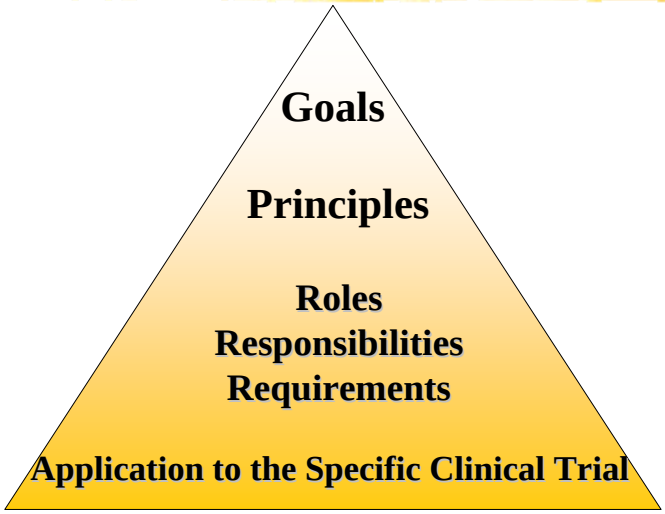
GCP in the 21st Century

- Beyond Drugs/Biologics
  - ISO 14155-1: Clinical Investigation of **medical devices** for human subjects: General requirements (2002)
  - Global Harmonization Task Force (GHTF)
- Globalization
  - PAHO/PANDRH "Good Clinical Practices: Document of the Americas" (2004)
  - WHO "Handbook for Good Clinical Practice (GCP): Guidance for Implementation" (2005/2006)
- Global Acceptance and Expectation
  - FDA proposed "new" rule for acceptance of non-U.S. studies: expects compliance with international GCP

GCP: Overarching Themes

- Responsibility(-ies)
- Attention to Detail
- Documentation
- Quality
  - Data/Scientific Quality; Ethical Quality; Process Quality
- Risk and Risk Management
- Validation/Verification/Inspection

The Hierarchy of GCP



The Goals of GCP –1-

- Protecting Research Subjects
  - Subject safety
  - Rights as subjects (research ethics)
    - Right to be informed
    - Right NOT to participate
    - Right to withdraw at any time
    - Right to protection of privacy
    - ... and other Rights

The Goals of GCP –2-

- Ensuring the quality and integrity of research data for regulatory decision-making
  - Based on a scientifically sound protocol that is designed to meet its stated objectives
  - Based on the quality conduct and oversight of the clinical study

The Goals of GCP –3-

- Assuring the existence and operation of "quality systems"
  - Including but not just for the current study
  - By each party (investigator, sponsor, IEC, and regulatory authority)
  - Based on written procedures
  - Assured through self- and cross-evaluation
  - Leveraged: Regulatory authority can't do it all

The Principles of GCP

- The identification of Principles of GCP was/is a major achievement of ICH GCP carried through to all other international GCP guidelines (ISO, PAHO, WHO...)
- Each of the 13 Principles can be linked to one or more of the goals of GCP
- The GCP Principles reflect internationally accepted ethical and quality principles found in other internationally accepted documents
- Achieving a Principle requires that each party and all parties together meet their corresponding responsibilities

A Listing of the Principles

- #1: Trials should be conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki.
- #2: Before a trial is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified.

A Listing of the Principles

- #3: A trial should be initiated and continued only if the anticipated benefit(s) for the individual trial subject and society clearly outweigh the risks.
  - Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial subjects.

A Listing of the Principles

- #4: The trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
- #5: Approval of trials of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

A Listing of the Principles

- #6: A trial should be scientifically sound, and described in a clear, detailed protocol.
- #7: Freely given informed consent should be obtained from every subject prior to trial participation in accordance with national culture(s) and requirements. When the subject is mentally or legally incapable, consent should be obtained from a legally acceptable representative.

A Listing of the Principles

- #8: Qualified medical personnel (i.e., physician or, when appropriate dentist) should be responsible for the medical care of trial subjects, and for any medical decision made on their behalf.
- #9: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

A Listing of the Principles

- #10: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
- #11: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A Listing of the Principles

- #12: Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.
- #13: Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Goals and Principles of GCP: Thinking Like an Inspector

- Violations so serious as to compromise the goals and principles of GCP:
  - Are the most important to detect in inspection
  - Are most likely to result in official (enforcement) action
  - Must be most thoroughly documented

Roles and Responsibilities: The Framework of the Inspection

Responsible Parties

- Study sponsor/contract research organization (CRO)
- Clinical investigators (CIs)
- Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

Shared Responsibilities

- Responsibilities overlap – system of checks and balances
- Non-compliance by any party does not eliminate need for other parties to be compliant
- FDA regulations and ICH GCP definitions – similar and include/imply responsibilities

SPONSORS

Sponsor -1-

- Definition: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial
- Includes: commercial (pharmaceutical and device) companies, government funding agencies, private foundations, and individuals
- Sponsor-investigators – must comply with both sponsor and investigator responsibilities

Sponsor -2-

- GCP requires certain direct communications and interactions between the sponsor and the regulatory authority

Contract Research Organization (CRO)

- A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions
- FDA's pharmaceutical regulation covers transfer of regulatory responsibility; not addressed in device regulation
- Sponsor ultimately responsible for the conduct of the study

Monitor

- Employee of the sponsor (or CRO) who works to oversee the progress of a clinical study through on-site visits and other means
  - To ensure that the study is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP and the applicable regulatory requirement(s). (Quality control)

Medical Expert ("Medical Monitor")

- Employee of the sponsor (or CRO) who is readily available to advise on trial-related medical questions or problems
  - If necessary, outside consultant(s) may be appointed for this person

Independent Data Monitoring Committee (DMC; DSMB)

- A committee established by, but acting independent of, the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial
  - Every study needs safety monitoring; but not every study requires a DMC/DSMB

Sponsor Responsibilities -1-

- Obtain regulatory approval, where necessary, before initiating a study
- Manufacture and label investigational products appropriately
- Initiate, withhold, or discontinue studies as required
  - Includes protocol development, often in consultation with one or more clinical investigators

Sponsor Responsibilities -2-

- Refrain from commercialization of investigational products
- Control the distribution and return of investigational products
  - Detailed records
  - Proof of IEC/IRB approval before initial shipment
- Select qualified clinical investigators
  - Credentials can vary by study & country requirements
  - “1572” commitments for pharmaceutical studies
  - Investigator agreements for medical device studies

Sponsor Responsibilities -3-

- Disseminate appropriate information to investigators
  - Commonly = Investigator’s Brochure for pharmaceutical studies
  - Update as necessary
- Select qualified persons to monitor the conduct of the studies

Sponsor Responsibilities -4-

- Adequately monitor clinical studies
  - Written SOPs desirable (required by FDA device regulation)
  - Requires access to site and subject records (privacy laws applicable)
  - Provides quality control – for assurance of subject protections and data integrity
  - Enables assurance of clinical investigator compliance

Sponsor Responsibilities -5-

- Evaluate and report adverse experiences
- Maintain adequate records
  - Retention according to regulatory requirements
- Submit all reports, including safety reports, annual/progress and final reports, as required

Financing/Compensation

- FDA regulations
  - Do not address the financing of clinical studies or compensation to research subjects
  - Are silent on liability for injury to subjects in a clinical study
  - Address financial disclosure by investigators and other study staff
- ICH GCP recommends
  - The financial aspects of the study be documented in an agreement between the sponsor and investigator
  - Compensation, insurance, and any costs of treatment in the event of study-related injury be addressed in the sponsor's policies

CLINICAL INVESTIGATOR

Clinical Investigator

- ICH GCP definition: A person responsible for the conduct of the clinical trial **at a trial site**
- Suggests an investigator at each site; multisite study may have a coordinating investigator, but there should be a responsible party at each site
- The investigator is
  - THE contact with study subjects
  - Responsible for study site compliance with GCP

Subinvestigator(s)

- FDA does not specifically define
- ICH GCP: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or make important trial-related decisions

Investigator Responsibilities -1-

- Personally conduct and/or supervise the study
  - Cannot contract out any responsibilities; is entirely responsible for study conduct at site
  - Needs to ensure qualifications and training of anyone delegated study duties and meet with study staff on a regular basis
  - SOPs for site's conduct of studies and handling of problems

Investigator Responsibilities -2-

- Communicate with the IEC/IRB
  - Initial approval before initiation of study
  - Amendments/progress reports/continuing review
  - "Safety" reports
- Ensure proper informed consent process
  - IEC/IRB approved form
  - Documented prior to any study-related activities
  - If delegated, only to appropriate study staff

Investigator Responsibilities -3-

- Protocol compliance
  - No deviation without prior sponsor and IEC/IRB approval – unless to eliminate an **immediate** hazard to subjects
  - Protocol should be designed to facilitate compliance
- Control of investigational products
  - Detailed records – receipt, use, & disposition
  - Proper storage and handling – as defined in the protocol

Investigator Responsibilities -4-

- Maintenance of randomization and blinding; unblinding only for medical emergencies and then fully documented
- Safety reporting
  - Recognizing and reporting all adverse events
  - Special attention to serious and unexpected events – reporting to sponsor and IEC/IRB and regulatory bodies as required

Investigator Responsibilities -5-

- Recordkeeping
  - Accurate and complete case histories for each study subject – both those to whom investigational product was administered and controls
  - Includes
    - Source documents (Hospital charts, clinical laboratory reports, x-rays, ECGs, subject diaries, pharmacy records)
    - Case report forms
    - Correspondence
    - Other study-related documents – e.g., protocol, with all amendments; Investigator's Brochure, screening logs

Investigator Responsibilities -6-

- Recordkeeping (cont.)
  - Quality and integrity of data essential
  - Maintained as required by applicable regulations

Investigator Responsibilities -7-

- Reporting
  - Safety reports
  - Progress reports
    - To sponsor
    - To IEC/IRB for continuing review
  - Final report

Investigator Responsibilities -8-

- Medical care of study subjects (ICH/WHO)
  - Ensure access to reasonable standard of care
  - Investigator or other medically qualified member of study team
  - Recommends informing subject's primary physician of participation in the study

IEC (U.S. = IRB)

References

- ICH Good Clinical Practice Consolidated Guideline (E6), 1996, Section 3
- Operational Guidelines for Ethics Committees that Review Biomedical Research, World Health Organization, 2000 (TDRPRDEthics2000.pdf)
- Surveying and Evaluating Ethical Review Practices: A complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research, World Health Organization, 2002 (TDRPRDEthics2002.pdf)

Role of an Independent Ethics Committee (IEC) -1-

- Safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants
- Providing **independent**, competent, and timely ethical review of the proposed study
- Considering both the scientific and ethical aspects of the study – since scientifically unsound research is not ethical

Role of the IEC -2-

- To ensure
  - Risks to subjects are minimized
  - Risks are reasonable in relation to anticipated benefits
  - Selection of subjects is equitable
  - Informed consent is appropriately conducted and documented
  - Subject safety is adequately monitored
  - Subject privacy is adequately addressed

Rights of Research Subjects

- Subjects have the right to
  - Be informed
  - NOT participate
  - Withdraw at any time
  - Protection of their privacy
- Declaration of Helsinki – "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."

IEC Responsibilities -1-

- Membership – must be diverse and independent
  - At least 5 members
  - At least one from nonscientific area
  - At least one independent of institution/study site
  - Non-voting experts invited as necessary

IEC Responsibilities -2-

- Obtain and review pertinent documents
  - Protocols and amendments
  - Proposed informed consent document
  - Subject recruiting materials
  - Investigator's Brochure
  - Available safety information
  - Investigator's curriculum vitae, including all active studies
  - Other – as pertinent to specific study and IEC requirements

IEC Responsibilities -3-

- Schedule and document meetings
  - Time for adequate review by all members
  - Maintenance of detailed minutes
- Written procedures
  - Establishment of IEC authority
  - Definition of membership requirements and terms
  - Meeting schedule and quorum requirements
  - Details of initial and continuing review processes
  - Recordkeeping requirements
  - Procedures to minimize conflict of interest

IEC Responsibilities -4-

- Perform ethical reviews
  - Ensure proper expertise for scientific review
  - Review target subject population to ensure adequate inclusion/exclusion criteria and proper recruiting
  - Review investigator's qualifications and ability to supervise and conduct the study at the site
  - Review proposed compensations to investigator and subjects
  - Consider subject privacy and data confidentiality
  - Review issues that may raise community concerns
  - Ensure proposed informed consent process and form are appropriate

IEC Responsibilities -5-

- Decision-making
  - Normally at a convened meeting where a quorum is present
  - Method for reaching decision should be predetermined in written procedures (approval, disapproval, modifications requested, suspension/termination of previously approved study)
  - No one with a conflict of interest should participate
  - Non-members excluded from deliberations and vote

IEC Responsibilities -6-

- Communicating decisions
  - In writing to investigator, including responsibilities an approval entails
  - Suggestions for revision when modifications are required
  - Reasons for disapproval or termination/suspension of prior approval

IEC Responsibilities -7-

- Continuing review
  - As appropriate to risk of study, but at least annually
  - Substantive and at a convened meeting
- Documentation and archiving
  - Retention of all pertinent study documents and related correspondence
  - Maintained at least 3 years after completion of study

The IEC: Closing Perspectives

- The credibility of the IEC will affect the credibility (and acceptability) of clinical studies and study sites
- Developing “high quality” clinical trials depends on developing “high quality” IECs
- Developing methods to assess their adequacy is an important consideration for regulatory bodies

Regulator's Role in GCP

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 27, 2008

Objectives of this Talk

- Review the roles and responsibilities of the regulatory authority under GCP
- Identify within our respective countries:
  - Which functions are already well-established within the national authority
  - Which functions have yet to be established
  - Which functions could be strengthened --- and how

ICH GCP: The Role of the Regulator

- ICH GCP does not contain a separate chapter on the roles and responsibilities of the regulator or regulatory authority
  - But does mention “applicable regulatory requirements” and “regulatory authority” in Definitions, in Principles, and in sections on the IRB/IEC, the Investigator, the Sponsor, and the Essential Documents

International GCP: The Role of the Regulator

- The WHO (World Health Organization) “Guidelines for GCP” (1995) and Handbook for Implementation (2005) does include separate sections on the role of the Drug Regulatory Authority
- And the PAHO (Pan American Health Organization) “GCP Document of the Americas” includes a chapter on “GCP Compliance Monitoring by Regulatory Authorities” and an Annex: “Guide to Clinical Investigator Inspections”

An Important Distinction

- Role of government
- Role of the regulatory authority

Role of Government in Clinical Studies

- Establish a legal framework for GCP
  - Protect rights and safety of subjects (including requirements for informed consent and IEC review)
  - Ensure quality of studies/data, quality of regulatory decisions, and implementation of quality systems
  - Sanctions/penalties for violators
- Licensure of medical professionals
  - Qualifications of clinical investigators/staff
- Provide mandates to the regulatory authority

Role of Regulatory Authority in Clinical Studies –1-

- Must act according to laws to implement and enforce the laws

Role of Regulatory Authority in Clinical Studies –2-

- In general, the regulatory authority bears responsibility for:
  - Allowing a protocol to proceed
  - Ensuring the quality of the investigational product
  - Ensuring subject rights and safety during a study
  - Assuring and using quality study data for regulatory decision-making

Role of Regulatory Authority in Clinical Studies –3-

- Inspecting the parties who conduct or oversee the study
- Receiving and acting on complaints about a clinical study
- Educating the parties who conduct or oversee the study

Allowing a Protocol to Proceed

- Should ensure that both scientific and ethical review have been performed
  - Regulatory Authority's Review
    - May include inspection of non-clinical (animal toxicology) studies/facilities supporting the protocol
  - Independent Review(s)
    - Expert review(s); Ethics Committee review
- Should include authority for the regulator to NOT allow the protocol to proceed or to require modification of the protocol before proceeding

Ensuring the Quality of the Investigational Product

- In accordance with national/local laws and regulations, regulators may
  - Establish Good Manufacturing Practice (GMP) requirements for investigational products
  - Review manufacturing data submitted in support of research permits
  - Inspect manufacturing facilities
  - Establish requirements for the import of investigational products

Ensuring Subject Rights and Safety during the Study

- Should include the regulator's receipt and review of safety information (especially serious and unanticipated adverse experiences) during the study
- Should include knowledge by the regulator of safety concerns with the investigational product in other studies of the product
- May include the regulator's requesting or requiring independent data and safety monitoring boards (DSMBs) for the study

Ensuring Subject Rights and Safety during the Study

- Should include assurance to the regulator that informed consent and ethical (IEC) review is conducted prior to initiating the study and continued during the study
- Regulatory authorities also need to be alert to the issue of subject confidentiality and any applicable national/local laws and regulations for handling private medical information
- Regulators should have the authority to stop a study if they find that subjects are or will be exposed to an unreasonable risk

Establishing a System of Ethical Review

- States should promote the establishment of Ethics Committees (WHO)
  - Promote development of independent ethical review within a country
  - Ensure clear and efficient communication between committees
  - Ensure ongoing education of IEC members
  - Establish procedures for the review of protocols carried out at more than one site in a country or in more than one country

IEC: Regional Organizations

- Regional organizations or forums can encourage the exchange of information among IECs and assist in the development of high quality ethics committees
  - FERCAP (Forum of Ethics Review Committees of Asia-Pacific): Asia-Pacific forum initiated by WHO-TDR

Study Data -1-

- Regulators must be able to rely on the study data in making regulatory decisions
  - Allowing other studies of that investigational product to proceed
  - Approving the product for marketing
  - Labeling of the product

Study Data -2-

- Regulators, regardless of their specific job (reviewer, inspector, educator, administrator), should understand and be able to assess and apply the basic elements of data quality and integrity

Inspecting -1-

- Regulators should have authority to inspect on-site each of the parties under GCP
  - Investigators and site staff
  - Sponsors/monitors/contractors
  - IECs
- Inspections should be conducted in accordance with written procedures
- Inspections may be carried out routinely, randomly, and/or for specific reasons

Inspecting -2-

- The regulator's authority should include direct access to the subject's original medical records for verification of clinical study procedures and/or data
  - Subjects should be made aware of this provision (required element of informed consent)
  - Regulatory authorities should handle private information with respect for subject confidentiality

Receiving and Acting On Complaints

- Subjects and others involved in clinical studies should be able to report complaints (concerning subject safety, subject rights, data quality/integrity, or other aspects of study conduct) to the regulatory authority
- The regulatory authority should implement procedures to receive, review, evaluate, and as appropriate, follow-up (e.g., by inspection) on any such complaints

Ensuring GCP Compliance

- Regulators should be promptly notified when a sponsor identifies serious and/or persistent GCP noncompliance on the part of an investigator or institution
- Regulators should have enforcement options and authority when serious and/or persistent GCP noncompliance is observed and confirmed through due process

Written Procedures

- The regulatory authority should develop SOPs and quality systems for internal regulatory activities, including
  - Reviewing product applications and safety reports
  - Conducting GCP inspections
  - Communicating findings to inspected/ regulated parties
  - Establishing an infrastructure for due process and imposing sanctions on parties who violate laws/regulations

Regulatory Authority: Educational Role

- Regulators have a role in educating those parties that conduct or oversee regulated clinical studies
  - What is expected/required under national and local laws/regulations
  - Internationally recognized standards (GCP)
- Regulatory review and inspection should serve an educational as well as a compliance/enforcement function

Capacity-Building: Where is Capacity Still Needed ?

- For the inspector:
  - Recognizing which of the regulatory responsibilities for GCP are strongest and which still need strengthening
- For the regulatory authority/inspectorate
  - Commitment
  - Prioritization
  - Planning/Coordination
  - Implementation/Assessment

Informed Consent

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 27, 2008

Overview

- Background
- FDA regulations
- ICH GCP guidance
- Basic (Essential) elements
- Additional elements

Background -1-

- Nuremberg Code – 1947
- Declaration of Helsinki – 1964
- United States
  - Belmont Report – 1979
  - 21 CFR Parts 50 and 56 – 1980 & 1981
  - The Common Rule – 45 CFR Part 46 – 1991
- ICH GCP – 1997

Background -2-

- Belmont Report: 3 Ethical Principles
  - Respect for persons
    - Individual autonomy
    - Protection of individuals with reduced autonomy
  - Beneficence
    - Maximize benefits and minimize harms
  - Justice
    - Fairness in selection of subjects and distribution of burdens and benefits

Background -3-

- Informed consent
  - Sufficient information
  - Comprehension
- Legally authorized representative
- Free of coercion and undue influence

Informed Consent

- Not a single event
- Not simply a form to be signed
- Educational process that starts by informing a potential study subject and continues throughout the study
- Requires disclosure of information, adequate comprehension, and a voluntary decision to participate

FDA's Regulation

- 21 CFR Part 50 - requires
  - Use of IRB/IEC approved document
  - Voluntary participation, after sufficient time is allowed for consideration
  - Minimization of coercion and undue influence
  - Understandable information
  - No exculpatory language

Exculpatory language

- Language that waives or appears to waive
  - any of the subject's legal rights

    or
  - releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence

ICH GCP

ICH GCP definition (1.28)

"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form."

Basic Elements -1-

The following elements of information must be provided to all study subjects

- A statement that the *study involves research*, an explanation of the *purpose* of the research, the expected *duration* of the subject's participation, and a description of the *procedures* to be followed

Basic Elements -2,3,4-

- A description of any *foreseeable risks or discomforts* to the subject
- A description of any *benefits to the subject or to others* which may be reasonably expected from the research
- A disclosure of appropriate *alternative procedures* for courses of treatment, if any, that might be advantageous to the subject

Basic Elements -5-

- A statement describing the extent to which *confidentiality of records* identifying the subject will be maintained [specifically noting regulatory authorities – FDA – may inspect the records]

Basic Elements -6-

- For research involving more than minimal risk, an explanation whether any *medical treatments or compensation* are available if any injury occurs and, if so, what they consist of or where further information may be obtained

Basic Elements -7-

- An explanation of *whom to contact* for answers to pertinent questions about the research or research subjects' rights or in the event of a research-related injury or adverse occurrence

Basic Elements -8-

- A statement that *participation is voluntary*, that *refusal to participate* will involve *no penalty or loss of benefits* to which the subject is otherwise entitled, and that the subject *may discontinue participation at any time without penalty or loss of benefits* to which the subject is otherwise entitled

Additional Elements -1,2-

When appropriate, the following elements must also be provided to subjects

- A statement that the research may involve *risks to the subject that are currently unforeseeable*
- Anticipated circumstances under which the subject's *participation may be terminated* without regard to the subject's consent

Additional Elements -3,4-

- Any *additional cost to the subject* that may result from participation
- The *consequences of a subject's decision to withdraw* from the research and procedures for orderly termination of participation by the subject

Additional Elements -5,6-

- A statement that *significant new findings* developed during the course of the research which may relate to the subject's willingness to participate will be provided to the subject
- The *approximate number of subjects* involved in the study

Interactive Exercise

Introduction to FDA's Clinical Research Review Process

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 27, 2008

What This Talk Will Cover

- Basics of FDA application review
- FDA's regulatory expectations for acceptance of non-U.S. clinical studies
- Some problems encountered by FDA reviewers
- The interface between regulatory review and clinical trial inspection

FDA Oversight of Clinical Research Occurs at Two Levels

- Review Process
- On-Site Inspections
  - Manufacturing (GMPs)
  - Bioresearch Monitoring (GLPs, GCPs)

In the United States, FDA Review is Required:

- To Obtain a Research Permit for human study
  - Investigational New Drug Application (IND)
  - Investigational Device Exemption (IDE)
- During research under that permit
  (IND: Phases 1, 2 and 3; IDE: pilot and pivotal studies)
- To Obtain a Marketing Permit
  - New Drug Application (NDA)
  - Premarket Approval (PMA) or Premarket Notification [510(k)] for devices
- During (or post-) marketing under that Marketing Permit

Where are Drug Applications Reviewed?

- Within CDER (Center for Drug Evaluation and Research), there is an Office of New Drugs
  - 17 Review Divisions (grouped in 6 Offices of Drug Evaluation)
  - Approximately 60 staff per Review Division
  - Organized by Therapeutic Area

and an Office of Generic Drugs

Where are Device Applications Reviewed?

- Within the Center for Devices and Radiological Health (CDRH) – 2 Offices
  - Office of Device Evaluation (ODE)
  - Office of In Vitro Diagnostic Evaluation and Safety (OIVD)
- ODE = 5 Divisions, approximately 350 reviewers
- OIVD = 3 Divisions, approximately 60 reviewers
- Branches organized by therapeutic/diagnostic area

Reviews are Conducted by Teams of Specialists

For CDER:

- Medical Officer
- Consumer Safety Officer/Project Manager
- Statistician
- Chemist
- Pharmacologist(s)
- Human Biopharmaceutics specialist
- Bioresearch Monitoring (BIMO) reviewer
- A single review team will generally follow a drug from its IND application through the NDA "approval" decision and into post-marketing

Reviews are Conducted by Teams of Specialists

For CDRH:

- Lead reviewer
- Medical/clinical reviewer
- Engineer (Material, Mechanical, Electrical)
- Statistician
- Patient labeling reviewer
- Manufacturing reviewer
- Bioresearch Monitoring (BIMO) reviewer
- Others as appropriate (e.g., toxicology, microbiology, biocompatibility, software, human factors, optics)

Bioresearch Monitoring (BIMO) Reviewer

- Part of the review team in CDER/CBER/CDRH
  - Represents Center's "Office of Compliance"
  - Advises the review team on
    - Oversight of the study (e.g., monitoring plans)
    - Subject protection/GCP-related issues
    - When/what to inspect
  - Translates any identified "GCP concerns" into the inspection assignment
  - Reports back to the review team during/after the inspection

IND and IDE Review

- The focus of the IND and IDE reviews is on safety and on ensuring that the study will provide useful information once completed
- Review teams can recommend:
  - Stopping a study ("clinical hold" for drugs; refusal or withdrawal of an IDE for devices)
  - Changes to the study protocol or Investigator's Brochure
  - Additional examinations or laboratory tests
  - Limits to the number of subjects or number of sites (or increases in the number of subjects)

Review of IND and IDE Applications

- Review team has 30 days to review the initial IND/IDE application
- No News = Good News

Product Development Under an IND or IDE

- Review Team Monitors
  - New Protocols (IND amendments; IDE supplements and 5-day reports)
  - Safety reports
  - Annual reports
  - Additional chemistry/bench, animal toxicology, microbiology data, device biocompatibility data
- Review team is available to consult/meet with sponsors: advise on protocol design, advise on drug/device development plan

Under the IND: If Problems..

- "Clinical Hold"
  - Legal order to delay or stop the study in the U.S.
  - May be imposed at any time/phase of study if:
    - Subjects would be exposed to unreasonable risk (includes manufacturing problems)
    - Investigator's Brochure is misleading, erroneous, or materially incomplete
    - Investigator is not qualified
    - The study is not designed to achieve its stated objectives
  - An inspection may be assigned

Marketing Applications: Science from Source Data

- The focus of FDA NDA and PMA review is on the data itself and on data analyses, NOT on expert reports or summary statements
  - Ability to independently review and analyze primary data
  - Primacy of data quality and integrity
  - Perspective that can reveal the failings of summary reports and even peer-reviewed publications

Marketing Application Review

- Standard for Approval:
  - Drugs = Substantial evidence of safety and effectiveness from adequate and well-controlled investigations
  - Devices = Valid scientific evidence of safety and effectiveness
- Output: Application decision and product label

Non-U.S. Studies -1-

- FDA has no absolute requirement that there be a U.S. study(-ies) to support a U.S. drug marketing application (NDA) or device marketing application (PMA) or submission [510(k)] in the U.S.
- Applications/submissions can and have been entirely supported by non-U.S. studies
- Non-U.S. studies must meet criteria for acceptance by FDA

Non-U.S. Studies -2-

- The application must be signed by an attorney, agent, or other authorized official who resides or maintains a place of business within the U.S.

Non-U.S. Studies -3-

- FDA can accept non-U.S. data for purposes of FDA review in two ways:
  - For drugs, if the non-U.S. studies/sites voluntarily operate under a U.S. research permit (IND) as designated by the sponsor
  - Under FDA regulations for accepting non-U.S. data in support of NDAs and PMAs

Non-U.S. Studies -4-

- FDA regulations for accepting "Foreign Studies Not Conducted Under an IND" have been in place since 1975
- Finalization of an update has just occurred (Apr '08)
  - FDA's regulatory expectation for non-U.S. studies submitted in support of an NDA is now linked to compliance with internationally recognized GCP
- FDA will require not just certification but also certain documentation supporting GCP compliance
- FDA is planning to revise the PMA regulation to mirror the proposed change to the IND regulation

Required Documentation Reflects FDA's Risk-Based Approach

- Investigator's qualifications
- Description of the research facility(-ies)
- Information about the IEC(s)
- A summary of the IEC's decision
- A description of how informed consent was obtained
- A description of what incentives, if any, were provided to subjects to participate

Required Documentation Reflects FDA's Risk-Based Approach

- A description of how the sponsor monitored the study
- A description of how investigators were trained to comply with GCP
- Protocol, product and study summary information
- Provision (and authority) for FDA to validate the data through an on-site inspection

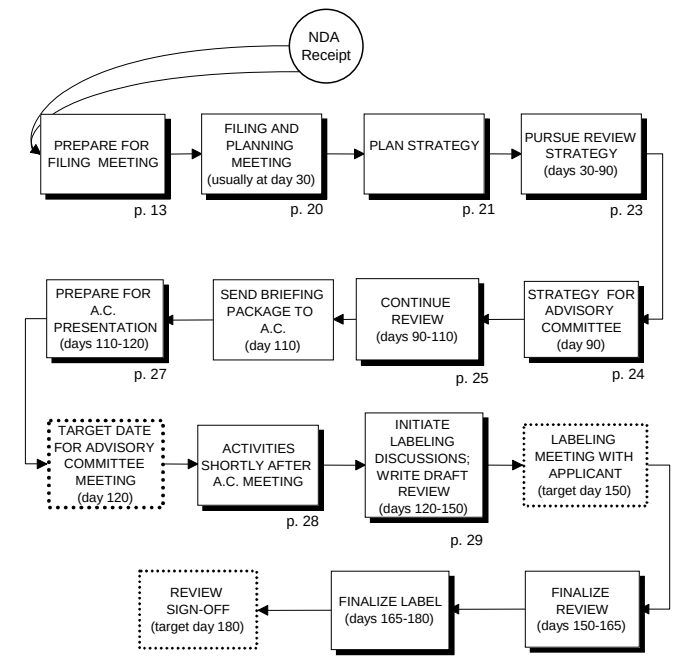
Non-U.S. Studies -5-

- If/once non-U.S. studies/data are accepted for FDA review, they are reviewed to the same standards as studies/data from the U.S.

Review Teams are Guided by "Good Review Practices"

- SOPs and standard review formats are available for FDA reviewers to assist in conducting their application reviews
- FDA has also developed diagrams of how CDER review teams do their work and meet timeframes
- Good Review Management Principles and Practices – April 2005, available at http://www.fda.gov/cder/guidance/5812fnl.htm

REVIEW PROCESS AFTER RECEIPT OF NDA



Some Problems Reviewers Encounter -1-

- Failure of studies to meet statutory requirements for establishing safety/efficacy
  - Unsuccessful drug/device
  - Poor study design
  - Bias in the design or execution of the study
- Failure to follow GCP
  - Compromise to data integrity and/or human subject protection

Some Problems Reviewers Encounter -2-

- Failure of the sponsor to follow the protocol and/or its predetermined plan for data analysis
- Underreporting of adverse events
- Selective reporting of studies, study data and/or study analyses

Interactive Exercise

The Interface Between Review and Inspection

Review Team

Bioresearch Monitoring Reviewer

Inspection Team

- The Bioresearch Monitoring Reviewer is part of both the Review Team and the Inspection Team

On-Site Inspections Complement In-House Review

- Through the Bioresearch Monitoring Reviewer, GCP Inspections are closely coordinated with FDA's in-house review
- Both processes (review and inspection) seek to ensure protection of research subjects and the quality of studies and data

Reviews Must be Completed On Schedule

- Schedules are addressed in U.S. law for both drug/biologics reviews and for medical device reviews
  - This includes time to assign and complete pre-approval GCP inspections

Review Teams make use of Advisory Committees

- Each review division has an associated advisory committee available to consult on New Drug Applications and Premarket Approvals
  - Members are appointed for specified terms
  - Non-FDA employees
  - Scientific experts; community representative
- Committees are purely advisory; FDA review team makes the decisions

Review Decision

- For NDA or PMA, action may be:
  - Approval
  - Approvable
  - Not Approvable
- For 510(k),
  - Substantially Equivalent (SE)
  - Not Substantially Equivalent (NSE)

Review continues after a product is approved...

- Phase 4 (Post-approval) commitments
- Advertising and promotional material
- Field alert reports (drug quality or labeling problems)
- Annual reports
- Spontaneous adverse event reporting

Review of Day 1

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

Day 1: What Was Covered ? -1-

- Clinical Research Process
  - 15 key activities involved in the conduct of a clinical study
  - Inspection should address each of the key activities for which the inspected party is responsible
- History, Goals, and Principles of GCP
  - Violations that compromise GCP Goals and Principles are the most important to detect and thoroughly document on inspection

Day 1: What Was Covered ? -2-

- Investigator, Subinvestigator(s), Site Staff
- Investigator Responsibilities under GCP: Targets for Inspection
  - 1. Personally conducting or supervising the study
  - 2. Communication with the ethics committee
  - 3. Informed consent of each study subject
  - 4. Compliance with the protocol

Day 1: What Was Covered ? -3-

- Investigator Responsibilities (Continued)
  - 5. Control of the investigational product(s)
  - 6. Maintaining randomization and blinding
  - 7. Safety reporting
  - 8. Recording, handling, and maintaining clinical study information
  - 9. Required reporting
  - 10. Medical care of study subjects

Day 1: What Was Covered ? -4-

- Sponsors, Contract Research Organizations (CROs), Monitors, Sponsor's Medical Expert
  - Sponsor Responsibilities under GCP
- Independent Ethics Committee (IEC)
  - IEC Responsibilities under GCP
  - Some important considerations for IECs
    - Protecting the rights of research subjects
    - Independent review and operating independently
    - Ethical vs. scientific review
    - Decisional authority
    - Substantive continuing review of ongoing research

Day 1: What Was Covered ? -5-

- Regulator's role in GCP
  - Allowing a protocol to proceed
  - Ensuring quality of the investigational product
  - Ensuring subject rights and safety
  - Assuring data quality for decision-making
  - Responding to complaints
  - Inspecting (as feasible) and educating
- Operating transparently: SOPs and due process
- Assessing strengths/weaknesses "at home"; building capacity

Day 1: What Was Covered ? -6-

- Informed Consent
  - Eight Basic (Essential) Elements
    - "RESEARCH" including explanation of purpose, duration and procedures
    - Foreseeable risks/discomforts to the subject
    - Reasonably expected benefits to the subject or others
    - Appropriate alternatives and their advantages, if any
    - Extent of confidentiality of records; possibility of inspection
    - Available treatment/compensation if injury
    - Contacts: about the research; subject rights; if injury
    - Participation is voluntary; no loss of rights/benefits for refusal or for withdrawal

Day 1: What Was Covered ? -7-

- Informed Consent (Continued)
  - Additional Elements
  - Process and Documentation
  - Regulator's Role in Informed Consent
    - Recognizing Deficiencies

Day 1: What Was Covered ? -8-

- FDA's clinical research review process
  - Applications, review, and review teams
    - Research permits (INDs; IDEs)
    - Marketing permits (NDAs; PMAs)
  - Acceptance of non-U.S. studies for FDA review
  - "Good review practices"; Focus on data
  - Some problems FDA reviewers encounter in applications
  - Linking application review and inspection
    - Centers' Bioresearch Monitoring Reviewers

Today

- Anatomy (Overview) of a GCP Inspection
- Preparing for an Inspection
  - Protocol Review
  - Review of Inspection SOPs
  - The Record Inventory
  - Developing an Inspection Plan
- Opening Interview
  - Developing Interview Skills
- Auditing Clinical Data

Anatomy of a GCP Inspection

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

FDA has a Long History of GCP Inspecting

- First inspections in the 1960's
- Formal bioresearch monitoring (BIMO) program since 1979
- Inspections of Ethics Committees since 1980
- First international inspections in 1980

GCP Inspectional Activity

- FDA conducts approximately 1100 GCP (BIMO) inspections per year
  - Clinical Investigators (600-700/year)
  - IRBs/Ethics Committees (200-300/year)
  - Sponsors/Monitors/CROs (50-100/year)
  - Bioequivalence facilities (50-100/year)
- Approximately 80 of these investigator inspections (per year) are outside of the U.S.

BIMO Inspections Completed FY 2007

Center	CI	IRB	Spon/Mon	GLP	Total
CBER	77	28	12	13	130
CDER*	367	101	23	46	537
CDRH	183	92	40	8	323
CFSAN	0	0	0	3	3
CVM	9	na	0	9	18
All Centers	636	221	75	79	1011

*** +** 122 **BEQ** inspections (CDER specific) = 1133 total

FDA's Authority to Inspect

- FDA has regulatory authority to inspect studies conducted under a U.S. IND or IDE (research permit)
  - Addressed as an element of informed consent
- FDA's ability to inspect is a criterion for accepting non-U.S. non-IND studies in support of a U.S. IND or NDA and non-U.S. data to support an IDE, PMA, or 510(k)

Bioresearch Monitoring (BIMO) -1-

- Specific group in each Center to oversee BIMO program
  - Bioresearch Monitoring Branch/Division of Inspections and Surveillance/Office of Compliance – CBER
  - Division of Scientific Investigations (DSI)/Office of Compliance - CDER
  - Division of Bioresearch Monitoring (DBM)/Office of Compliance – CDRH

Bioresearch Monitoring (BIMO) -2-

Headquarters BIMO staff:

- Interact with Center reviewers
- Issue inspection assignments (GCP & GLP)
- Interact with FDA's BIMO investigators
- Review and classify inspection reports
- Issue post-inspectional correspondence
- Take part in regulatory actions
- Provide staff for BIMO investigator training
- Provide speakers for outreach activities

Inspection Assignments

- Most generated upon receipt of marketing application/submission
  - Supporting study(ies) usually completed
- "For cause" inspections
- "Real time" surveillance inspections – vulnerable populations; unique products
- FDA presently issues most IRB (IEC) inspections at the start of the fiscal year – as surveillance inspections

Focus of GCP Inspections

- When assigned on receipt of marketing applications, the main focus is the data audit
- BIMO reviewers who issue assignments
  - Coordinate with FDA's application reviewers – to identify sties and special issues or concerns
  - Supply FDA investigators with relevant material contained in the marketing application
  - Include data line listings for essential data – commonly that supporting primary and secondary endpoints and documenting adverse events

Site Selection -1-

- Application-related assignments
  - Cover one or more study sites
  - May include a sponsor inspection, depending on the issuing Center and the reason for the inspection

Site Selection -2-

- Study site selection generally based on
  - Subject enrollment
  - Data concerns
  - Adverse events
  - Site compliance history
  - Study specific issues, such as sub-studies performed at only a limited number of sites

Timeliness of Inspections

- Most FDA Centers have User Fees, requiring goals for the timing of marketing decisions
- These timeframes include time to
  - develop the inspection assignment (including site selection and compilation of appropriate data to audit)
  - conduct the inspection
  - review, report and analyze the inspection
  - provide appropriate feedback to the application reviewer

Support for FDA GCP Inspections

- BIMO reviewers and application reviewers are available to support FDA's investigators
  - Either as part of the on-site team or as consultants
  - Includes support for primary data audit including ECG's, laboratory tests, X-rays, and pathology/ radiology reports

Qualifications/Training of FDA Field Investigators

- Field Investigator
  - Minimum 4-year college degree
    - Biologic/Health Science or related degree
  - FDA training: Formal BIMO courses and supervised on-the-job BIMO training
- Headquarters Scientists
  - Physicians and PhDs provide additional scientific and medical support

Planning and Preparation -1-

- Center BIMO reviewer issues assignment – to the District Office closest to the site (or to the international coordinator)
- An FDA Investigator/Inspector is usually assigned from the receiving District Office (or from the international cadre)
- FDA investigator often a GCP/BIMO "specialist"
- Investigator assigned conducts assignment alone or as part of an inspection "team"
  - Another FDA investigator
  - BIMO and/or application reviewer

Planning and Preparation -2-

- The FDA investigator/inspector
  - Reviews CPGM (inspection SOPs), study protocol, and assignment specifics
  - Communicates with the party to be inspected – inspections are pre-announced, unless possibly "for cause" (international inspections require sponsor assistance to arrange)
  - Confirms will have access to all required records/essential documents, as provided by regulations

Planning and Preparation -3-

- FDA Investigator/Inspector (continued)
  - May request additional site-specific information from the investigator or the study sponsor
  - Plans the Inspection
    - Scientific Preparation
    - Audit Plan
    - Inventory of Records
    - Opening Interview

Conduct of Inspection -1-

- Notice of Inspection and presentation of inspector's credentials to inspected party
- Opening Interview (45-60 minutes) with clinical investigator (CI) (or most responsible person for sponsor and IRB inspections)
  - Requests to meet periodically (e.g., end of each day) and at close of inspection with CI (or most responsible person)
  - Inspections generally last 5 days

Conduct of Inspection -2-

- Secondary interviews of key study personnel
  - Plan for these at the outset of the inspection
  - Consider additional interviews during the inspection

Conduct of Inspection -3-

- Getting Started
  - Knowledgeable site personnel should guide the inspector through a complete hospital/clinic chart and associated case report form (CRF) for one subject
  - Identify all study-related source documents and source data and determine how these relate to the CRF
  - Identify who collected data and completed records at the site and how this is documented

Conduct of Inspection -4-

- Inventory the study records
  - Are essential documents available ? (ICH GCP Section 8)
  - Are any essential documents missing ?
- The Data Audit – strongly emphasized by FDA, particularly for inspections triggered by marketing submission
- Both will be discussed in more depth later today

Conduct of Inspection -5-

- Research subject protection (ethics)
  - Informed consent
    - Verify that informed consent was obtained for 100% of subjects
    - Verify that the Informed Consent Form contains required elements
    - Understand the informed consent process

Conduct of Inspection -6-

- Research subject protection (ethics)
  - Ethics Committee Review
    - Identify the IEC name, location
    - Were required approvals obtained and documented by the clinical investigator ?
      - Were approvals obtained in advance of study initiation and in advance of any changes to the protocol ?
    - Were required reports made to the IEC ?

Conduct of Inspection -7-

- Test Article (Investigational Product) Accountability
  - Verify receipt, use, and final disposition of test article
  - Confirm that the test article was administered only by authorized personnel
  - Inspect the test article storage (and preparation) area(s)

Conduct of Inspection -8-

- Supporting laboratories and diagnostic testing facilities
  - Identify nature and location
  - If on-site, consider inspection to:
    - Verify availability of required equipment
    - Confirm authenticity of lab/diagnostic data

Conduct of Inspection -9-

- Document objectionable findings (deviations from GCP)
  - Collect study records (“exhibits”) to support each observation
    - Protect subject confidentiality in records collected

Conduct of Inspection -10-

- Concluding the inspection
  - Verify objectionable findings
    - Discuss and confirm with the clinical investigator or site staff during the inspection if possible
  - Develop a written list of objectionable findings (the Form FDA 483)
  - Close-out Discussion: more later

Reporting and Documentation -1-

- The list of objectionable findings (Form FDA 483) is **NOT** a final FDA report
- The FDA inspector(s) prepares an Establishment Inspection Report (EIR)
  - Detailed report with exhibits
- FDA headquarters reviews the 483, EIR with exhibits, and any follow-up correspondence from the inspected party before assigning a compliance classification and issuing a close-out letter

Reporting and Documentation -2-

- An abbreviated report can be generated when there are no objectionable findings
- But when very serious GCP violations are found, the enforcement process requires even further communications and opportunities for the inspected party to respond to FDA

FDA International GCP Inspections -1-

- Non-U.S. Investigator sites may be inspected
  - IF there are substantial or exclusively non-U.S. data to support an application (i.e., there are insufficient or no adequate and well-controlled U.S. studies) OR
  - IF U.S. and non-U.S. data show conflicting results pertinent to decision making OR
  - IF there is a serious issue to resolve (e.g., suspicion of fraud, significant subject protection concerns/violations)

FDA International GCP Inspections -2-

- Inspections must address the specific questions and needs of FDA's review team for that specific application and clinical trial as well as assure overall compliance with GCP
- The procedures for inspecting are the **same** whether for a U.S. or non-U.S. site

FDA International CI Inspections*

Algeria**	1	Gabon	1	Peru	6
Argentina	19	Germany	59	**Philippines**	4
Australia	9	Greece	2	Poland	29
Austria	6	Guatemala	2	Portugal	2
Bahamas	1	**Hong Kong**	5	Romania	1
Belgium	26	Hungary	10	Russia	35
Brazil	13	**India**	6	Serbia	3
Bulgaria	1	Ireland	1	**Singapore**	1
Canada	151	Israel	5	Slovenia	1
Chile	8	Italy	36	South Africa	26
China	7	**Japan**	3	Spain	17
China, Taipei	3	Kenya	1	Sweden	28
Colombia	1	Latvia	5	Switzerland	2
Costa Rica	8	Lithuania	2	**Thailand**	4
Czech Republic	7	Malawi	1	Turkey	6
Croatia	3	**Malaysia**	4	U. K.	91
Denmark	13	Mexico	14	Ukraine	4
Dominican Rep.	1	Netherlands	24	Venezuela	2
Ecuador	1	**New Zealand**	4	Yugoslavia	3
Egypt	1	Nigeria**	1	Zambia	1
Estonia	5	Norway	5		
Finland	15	Panama	2		
France	51				

*Conducted for FDA/CDER from 1980 through 08/8/07; total: 810
**data reviewed in U.S.

CDRH International BIMO Inspections (since 1991)

Sponsor inspections:

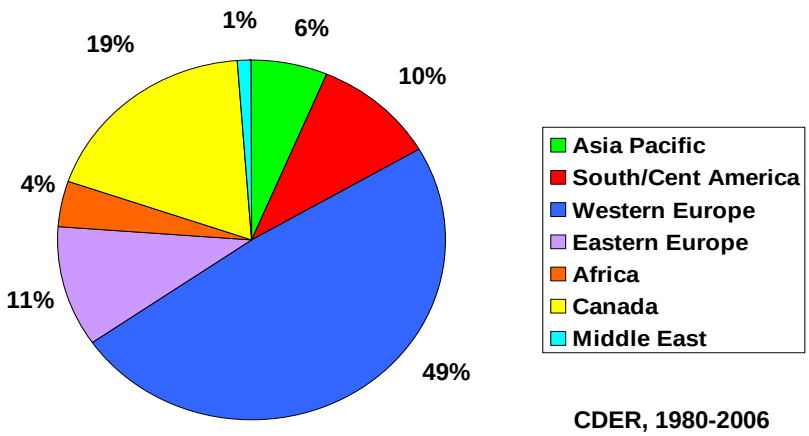
Australia
Austria
Canada
Finland
France
Israel
Italy
Netherlands
Sweden
Switzerland
United Kingdom

CI inspections:

Austria
Belgium
Canada
Denmark
France
Germany
Israel
Italy
Mexico
Netherlands
Spain
Sweden
Switzerland
Brazil
Thailand
China, Taipei
United Kingdom

(2 Sponsor and 9 CI inspections in FY'07)

FDA Experience in Asia/Pacific is Still Very Limited



CDER, 1980-2006
n=727

International GCP Inspections Completed: FY 2007

Center	Total
CBER	3
CDER	104
CDRH	11
Totals	118

Preparation for the Inspection: The Protocol and the Science

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

A Good Inspection is Built on the "Scientific Method"

- Ask yourself questions/generate hypotheses
- Seek answers/test hypotheses
- Develop new questions from these answers

To Start: Why Was this Site Chosen for Inspection ?

- Are there scientific reasons ?
  - Drives key efficacy or safety analyses ?
  - Significant data outlier(s) ?: Safety or efficacy
  - Unusual patterns or trends in the data ?
  - Significant missing data ?
  - Potential for bias ?
  - Any reports or complaints of scientific misconduct ?

Why Was this Site Chosen for Inspection ?

- Are there scientific questions that can be uniquely addressed on site ?
  - Data that can be acquired and/or better understood through interview with the clinical investigator and site staff

What Should You Know About the Investigational Product ?

- Are there other approved indications or other indications under study ?
- Is there approved product labeling for this or other indications ? What does this tell about the product ?
  - FDA product labels for earlier approved indications can be obtained at: www.fda.gov/cder; “Google” search on product name

What Should You Know About the Investigational Product ?

- What is the product’s known or suspected adverse event profile ?
  - Potentially serious or life-threatening events
  - Important expected (vs. unexpected) adverse events
- Are there important known drug/drug interactions ?

What Should You Know About the Disease Under Study ?

- At least basic information
  - Background section of the protocol
  - Study rationale
  - Search on references if more information is needed/desired

Inclusion/Exclusion Criteria

- Validating these is always an important part of the data audit/inspection
- Understand what purpose each inclusion/exclusion criterion serves in the study

Inclusion/Exclusion Criteria

- Possible purpose(s)
  - Ensuring subject has the disease/ condition under study
    - Ruling out other diseases/conditions with similar signs or symptoms
  - Ensuring that study endpoints have not already been met
  - Ensuring the safety of study participants
  - Ensuring the ethics of the study
  - Avoiding confounding drug/drug interactions

Study Endpoints

- Validation is a critical part of the data audit
- Identify and understand primary endpoints
  - Is efficacy the focus of these primary endpoints ?
  - Which are related to efficacy ? To safety ?
- Identify and understand secondary endpoints

Study Endpoints

- Laboratory Values: What are they measuring ?
- Special Tests or Diagnostic “Scores”
  - Is there subjectivity ?
- Signs/Symptoms of Disease or Disease Progression
  - How are they measured ?
  - Is there subjectivity ?

Blinding and Randomization

- Understand if the study is blinded and how randomization is handled
- What could unblind the study ?

Allowed and Disallowed Concomitant Medications

- Understand why a concomitant medication might be allowed or disallowed ?
  - Subject safety ?
  - Can the concomitant medication confound the interpretation of study results/study drug effects ?

Investigational Product Handling and Administration

- Is there the potential to enhance or reduce investigational product effects (efficacy or safety) through alternate handling or mishandling of the investigational product or through variation in investigational product administration ?

Study Visits

- What is supposed to be done at each ?
- Purpose of each test, measurement, or observation
  - Scoring for an endpoint ?
  - Assuring subject safety ?
  - Recognizing confounders ? (e.g., concomitant medication use)
- Identify subjective vs. objective data measurements (Is bias minimized ?)

Study Visits

- Is there a window (timeframe) in which each study visit should or must occur ?

Laboratory Values and Determinations

- Which values will be determined locally, centrally, or both ?
- How are interlaboratory variations handled ?

Protocol Definitions

- Always review any protocol definitions of:
  - Adverse event
  - Serious adverse event (experience)
  - Serious and unexpected adverse experience
- Recognize protocol-defined/protocol-specific adverse events that do not qualify as serious and unexpected (which may include study endpoints)

The Data –1-

- Look at any available data listings before arriving at the site
  - Anything suspicious ?
  - Fraud is more often detected through careful preparation and then corroborated during the on-site inspection

The Data –2-

- Be attentive to any premature discontinuations (withdrawal of subjects) that may actually represent undocumented endpoints or undocumented serious/unexpected adverse experiences

Study Plan Summary

- Always review Study Plan Summary Tables
- Understand what each procedure aims to measure or accomplish

Inspector's Preparation for a CI Inspection: FDA Compliance Program & the Records Inventory

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

Compliance Program Guidance Manuals (CPGMs) -1-

- FDA's SOPs for the conduct of inspections
- Developed and periodically updated by agency work groups
- Describe
  - Preparation and planning
  - Conduct of the inspection
  - Report and documentation of findings
- Allow FDA investigator/inspector flexibility to expand the inspection dependent on observations

CPGMs -2-

- BIMO CPGMs cover
  - Clinical investigators
  - Sponsors/Monitors/Contract Research Organizations (CROs)
  - IRBs/IECs
  - Bioequivalence (and bioavailability) studies
  - Nonclinical laboratories (GLPs)

CI CPGM

- Current version available at http://www.fda.gov/ora/ftparea/compliance/48_811.pdf
- Includes
  - Objectives & administrative authority
  - Assignments
  - Conduct of inspection -- including specifics of what and how to inspect (with product-specific information)
  - Reporting
  - Administrative and regulatory follow-up
  - Pertinent references and contacts

Conduct of the Inspection

- Clinical investigator inspections are usually study specific
- Compliance program describes minimal scope; assignment specifics may augment; inspectional findings may require further expansion
- Majority of on-site inspection time consists of records review
- Need to determine early in the inspection what study records are available on site – determine if any essential records need to be “retrieved”

Records Inventory -1-

- FDA inspectional emphasis = data audit
- Essentially an assessment of data quality and integrity
- Includes confirmation of adherence to study protocol and regulatory compliance
- Inspectional approach – comparison of source data with CRFs, and data submitted in support of marketing application when appropriate

Records Inventory -2-

- Identification of source data and source documents
- Copy of completed CRFs
- Safety reports, if applicable
- Identify what should be there --- and what is available for each subject

Records Referenced in FDA's CI Compliance Program

- Agreement with sponsor (Form FDA 1572, investigator agreement)
- IEC/IRB and sponsor correspondence
- Protocol and amendments
- Subject case histories – source documents and case report forms (CRFs) – includes informed consent documents
- Investigational product accountability
- Required reports

ICH E6 As a Guide to Records Inventory

- Section 8 of the ICH E6 guideline defines “Essential Documents” that should be retained at the investigator (and sponsor) sites
- Lists documents to be available at the initiation of the study, during the conduct of the study, and after completion of the study

Clinical Investigator (CI) Records -1-

- Investigator’s Brochure, including updates
- Protocol, amendments, revisions
- Information given to the study subjects
  - Informed Consent form – revisions, if appropriate
  - Any other written information
- (Financial aspects of the study)
- (Insurance statement – where required)

CI Records -2-

- Signed agreements between involved parties
  - Investigator and Sponsor
- Dated, documented IEC approval(s)
  - Protocol
  - Amendments
  - Informed Consent form
  - Other written information to subjects
  - Recruitment materials
  - Subject compensation

CI Records -3-

- (IEC composition)
- (Regulatory authority authorization[s])
- Curriculum vitae
  - Clinical Investigator
  - Subinvestigators/site staff (List of duties)
- (Laboratory information; normal values at study initiation, with any necessary updates during the course of the study)

CI Records -4-

- Shipping records for investigational product and study-related materials
- Appropriate labeling of investigational product
- Instructions for handling investigational product
- Decoding procedures for blinded studies
- (Study initiation monitoring report, monitoring visit reports, close-out report)

CI Records -5-

- Relevant communications with sponsor
  - Letters
  - Meeting notes
  - Records of calls
- Signed and dated Informed Consent forms
- Source documents
- (Signed) completed CRFs
- Documentation of CRF corrections

CI Records -6-

- Notification to sponsor (and IEC) of serious adverse events
- Notification by sponsor to CI re: important safety information
- Interim reports to IEC
  - Supporting IEC's continuing review
  - Timeliness

CI Records -7-

- Subject Screening "Log"
- Subject Enrollment "Log"
- Investigator product accountability at the site
  - Documentation of return or destruction at end of study
- (Signature sheet: Authorized signatures)
- Study reports

The Opening Interview

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

Background

- The opening interview is the first contact with the clinical investigator (or for sponsor/IEC inspections, the person of responsibility for sponsor/IEC administration and operations)
- The interview will typically last 45-60 minutes
- While others may be present (at the discretion of the inspector), the interview is conducted as a one-on-one dialogue

Setting the Tone -1-

- Communicating the purpose of the regulator's bioresearch monitoring program and the purpose and logistics of this on-site inspection
  - Assuring GCP compliance
  - In-depth data and record review
  - Speaking to study site staff
  - Learning of site experiences with the protocol/study and any problems encountered

Setting the Tone -2-

- The most successful interviews are conversational but purposeful
  - Genuine interest on the part of the inspector vs. assertion of authority
  - Open-ended questions
  - Educational vs. confrontational

Orientation to the Site

- Query the layout of the facility
  - Where records are kept
  - Where subjects are seen
  - Where procedures (if any) are performed
- Understand the investigator's level of personal involvement in the study
  - Competing commitments
- Identify key staff members and the roles they perform

International Inspections

- For inspections in countries where a different language is spoken (e.g., "non-English speaking" countries for FDA inspections), ensure the availability of a skilled translator who is familiar with medical/scientific terminology

Confidence-Building

- In a routine (surveillance) inspection, approach the interview from a neutral position
- Let the investigator's answers build your confidence that the study was conducted properly
- If you don't feel confident from an investigator's answer(s), probe further

Some Typical Questions in an Opening Interview -1-

- How did the investigator become involved with this study ?
- How many clinical studies has he/she conducted prior to this one? How many for commercial sponsors?

Some Typical Questions in an Opening Interview -2-

- What is the investigator's prior education/ specialty training? Has he/she had any formal clinical research (or GCP) training? Where and how long ago?
- Did the sponsor provide any training for this study?
- How did the investigator receive information about the investigational product? Were any updates provided by the sponsor during the study?

Some Typical Questions in an Opening Interview -3-

- Who else is working for the investigator on this study?
  - How did the investigator select them?
  - Are they still working for the investigator?
  - Did the investigator train them?
  - Would we be able to meet with them?

Some Typical Questions in an Opening Interview -4-

- Delegation of authority
  - Who, when, where: Informed Consent of subjects
  - Who, when, where: Screening of subjects
  - Who, when, where: Interpreting screening results/admitting to the study
  - Who, when, where: Receipt of test article; handling; administration; return. Can we visit the (pharmacy)?

Some Typical Questions in an Opening Interview -5-

- Delegation of authority (Continued)
  - Who, when, where: Collecting data
  - Who, when, where: Reporting (including safety reporting) /transcribing data
  - Who, when, where: clinical laboratory. Can we visit the laboratory?
  - Who, when, where: Archiving the data?
- Does the investigator have regular meetings with his/her staff?

Some Typical Questions in an Opening Interview -6-

- How did the investigator identify subjects for the study? How many of these were the investigator's own patients? Did the investigator have any problems with subject recruitment?
- When did the investigator enroll his/her first subject? When did the investigator enroll his/her last subject?

Some Typical Questions in an Opening Interview -7-

- What ethics committee did the investigator use? (Is there an ethics committee here at the hospital?)
- Were there changes to the informed consent? Did the investigator take these to the ethics committee for approval?
- Does the investigator have required documentation from the Ministry of Health?

Some Typical Questions in an Opening Interview -8-

- Were there any problems with subjects coming in for visits?
- Were there any problems with blinding of the study? Did the investigator believe that he/she knew which subjects were on which study arm?

Some Typical Questions in an Opening Interview -9-

- Does the investigator have copies of the protocol and its amendments available?
- Were there any amendments to the inclusion/exclusion criteria during the investigator's conduct of the study?
- Did the investigator have to request any exceptions to inclusion/exclusion criteria in enrolling subjects?

Some Typical Questions in an Opening Interview -10-

- Did the investigator (have to) reconsent any subjects?
- Did the investigator provide or need to provide updates to subjects about the study? the progress of the study? any safety issues during the study?

Some Typical Questions in an Opening Interview -11-

- Did the investigator have any serious and unexpected adverse events occur at his/her site during the study?
- (Was the investigator informed of serious and unexpected adverse event(s) from any other sites during the study?)

Some Typical Questions in an Opening Interview -12-

- Did the sponsor come to monitor the site? How often? Did the monitor(s) leave any log or record of their visits? Did they provide the investigator with any feedback from their monitoring visits?
- Were any computer systems used in recording data at the site?

Some Typical Questions in an Opening Interview -13-

- Who organized the files we will be looking at? Is the person available today? Would the investigator be available later today if we have some questions about these files or any other questions?

Concluding the Interview -1-

- The investigator should be provided the opportunity to ask questions about the logistics of the inspection (for example, the expected length of the inspection; when the inspector will arrive each day)
- The inspector should request a quiet work area and should identify who he/she can go to with any questions about records, record-access, and site procedures

Concluding the Interview -2-

- The inspector should indicate that the investigator need not be physically present throughout the entire day during the inspection but should be available to meet periodically (e.g., at the end of each day) and at the close of the inspection

Auditing Clinical Data

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 28, 2008

Assessing Data Quality and Integrity

- Evaluation of the agreement of data found in source documents with that on CRFs and in regulatory submissions
- Determination of adherence with the study protocol
- Determination of conformity with human subject protections

FDA Record Requirements

- CI retains all relevant information regarding the study as conducted at his/her site – paper and electronic
- Records be complete, accurate, and current
- Records be retained for at least the minimal timeframe indicated in pertinent regulation

Elements of Quality Data

- Accurate
- Legible
- Complete and contemporaneous (recorded at time activity occurred)
- Original
- Attributable (to person who generated data)

Data Integrity

- **C**redible
- Internally **C**onsistent
- Independently verifiable (**C**orroborated)

The Data Audit -1-

- Critical Points
  - Did subjects exist; did they show up for study visits as reported ?
  - Did subjects meet inclusion/exclusion criteria ?
  - Did subjects receive the test article per protocol (frequency and dose) ?
  - Is all significant safety/efficacy data corroborated in source data/documents and completely and accurately reported per protocol ?

The Data Audit -2-

- Are all source documents available?
- Are data corrections properly made? – original information visible, "corrector" properly identified, rationale included?
- Do results appear too good?
- Are data repeated identically in one or more files?

The Data Audit -3-

- Are entries out of chronological order or data squeezed between the lines?
- Do laboratory reports, consultations, charts, ECGs, or other test results appear to be photocopies?
- Do any signatures on informed consent documents appear similar to one another?
- Does any other required signature appear not to match that of the person identified?

Be On the Lookout

- Shadow Charts
  - What is really the source data here ?
- Pre-Signed data sheets or CRFs
- Inconsistencies
- Anything suspicious

Review of Day 2

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 29, 2008

Day 2: What Was Covered ? -1-

- Anatomy of a GCP Inspection
  - On-site inspections complement in-house application review
  - Discrete steps in an inspection
    - Planning and preparation
    - Conducting the inspection
    - Reporting and documentation

Day 2: What Was Covered ? -2-

- Preparation for the inspection
  - Review of the assignment
  - Review of the protocol
  - Compliance Program Guidance Manuals: SOPs for conducting an FDA GCP inspection
  - Essential documents
  - Developing an audit plan

Day 2: What Was Covered ? -3-

- Conducting the Inspection
  - Opening Interview
    - Features of an Opening Interview
    - Some typical questions to ask
    - Difficulties that might be encountered and how to overcome these
  - Auditing clinical data

Day 2: What Was Covered ? -4-

- Data quality: Essential characteristics (ALCOA)
  - Accurate
  - Legible
  - Complete and contemporaneous (recorded at time activity occurred)
  - Original
  - Attributable (to person who generated data)

Day 2: What Was Covered ? -5-

- Data integrity
  - The body of data should be:
    - **C**redible
    - Internally **C**onsistent
    - Independently verifiable (**C**orroborated)

Day 2: What Was Covered ? -6-

- Data and GCP noncompliance
  - Investigator/site “ignorance”
  - Sloppiness

Today

- Common CI Inspectional Findings
- Research Misconduct: Fraud/Falsification
- Documenting an Inspection
- Assessing Sponsor and Ethics Committee Compliance from the CI Inspection
- Site Visit

Common Investigator Deficiencies

Jean Toth-Allen, Ph.D.

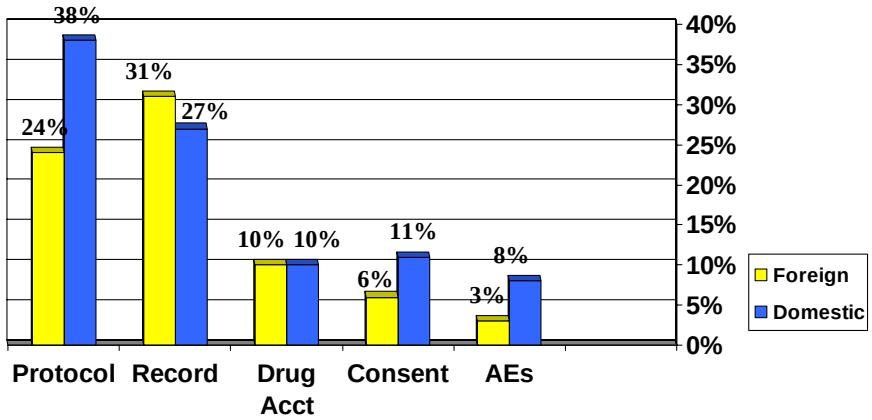
APEC GCP Inspection Workshop

May 29, 2008

Most Common CI Deficiencies

- Failure to follow the investigational plan
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate subject protection – including informed consent issues

CI Deficiencies
CDER Inspections - FY 2007

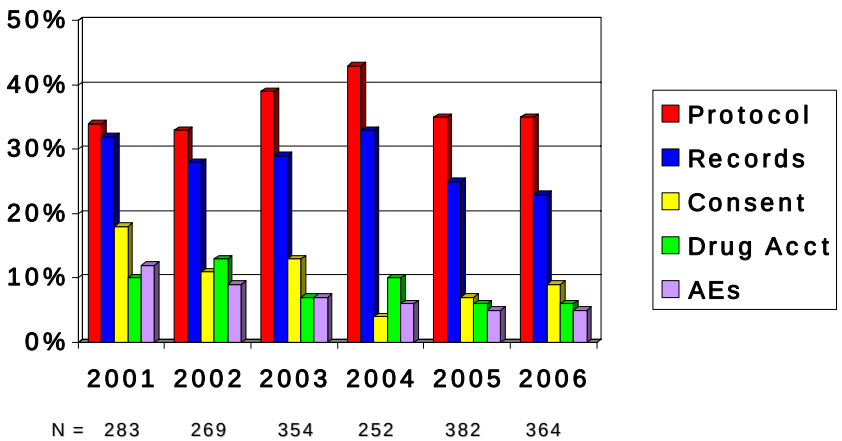


*Based on Letter Date

Foreign n = 104*
Domestic n = 244*

2/28/08

CDER CI Deficiencies
FY 2001 - 2006



Device CI Deficiencies Fiscal Years 1999 - 2006

	1999	2000	2001	2002	2003	2004	2005	2006
Failure to follow investigational plan/regs	**46%**	**47%**	**44%**	**44%**	**51%**	**54%**	**50%**	**44%**
Protocol deviations	**8%**	**26%**	**40%**	**20%**	**38%**	**16%**	**9%**	**22%**
Inadequate subject protection/IC	**19%**	**21%**	**28%**	**21%**	**21%**	**24%**	**29%**	**20%**
Inadequate device accountability	**17%**	**21%**	**27%**	**26%**	**18%**	**14%**	**7%**	**15%**
Lack of FDA &/or IRB approval	**9%**	**11%**	**5%**	**8%**	**13%**	**13%**	**10%**	**7%**

FDA and TURBO

- Computerized system for recording observations (FDA Form 483) and preparing establishment inspection reports (EIRs)
- Initiated in early 2000s
- Presently used for most GCP inspections

TURBO: Purposes -1-

- To aid the investigator in preparing and electronically storing FDA 483s and EIRs
- To improve the quality of the FDA 483 by linking citations to underlying regulations and statutes
- To streamline and enhance uniformity, appearance, and fitness for use of the EIR

TURBO: Purposes -2-

- To allow on-line access to inspectional findings from throughout FDA
- To streamline FDA's process for making 483s and EIRs publicly available
- To allow for easier capture and analysis of data on specific types of violations

TURBO Cites: Restricting Inspection

Drugs

- Failure to permit an authorized officer or employee of FDA to [have access to] [copy] [verify] records or reports. Specifically, ***

Devices

- Authorized FDA employees were not permitted to enter and inspect an establishment where records of results from use of devices are kept. Specifically, ***
- Authorized FDA employees were not permitted to [inspect] [copy] all records relating to an investigation. Specifically, ***

TURBO Cites: CI Agreement – Drugs

- An investigation was not conducted in accordance with the [signed statement of investigator] [investigational plan]. Specifically***
- Broad use for non-compliance with/deviation from general investigational plan – which includes the study protocol

TURBO Cites: CI Agreement – Devices

- An investigation was not conducted according to the [signed agreement] [investigational plan] [applicable FDA regulations]. Specifically, ***

TURBO Cites: CI Oversight

Drugs

- A study drug was [administered to subjects] [provided to persons] not under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. Specifically, ***

Devices

- An investigational device was used for subjects not under the supervision of an authorized investigator. Specifically, ***

TURBO Cites: IEC Approval

Drugs

- Failure to assure that an IRB [complying with applicable regulatory requirements] was responsible for the initial and continuing review and approval of a clinical study. Specifically, ***

Devices

- Subjects were allowed to participate in an investigation prior to obtaining [IRB] [FDA] approval to conduct the investigation. Specifically, ***

TURBO Cites: Progress Reports

Drugs

- Not all investigational progress reports were furnished to the drug study sponsor. Specifically, ***

Devices

- Progress reports on the investigation were not submitted [at the required intervals] [at least yearly] to the [sponsor] [monitor] [reviewing IRB]. Specifically, ***

TURBO Cites: Informed Consent - Drugs

- Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to [drug administration] [conducting study-related tests]. Specifically***
  - 21 CFR Part 50 – FDA's regulation regarding informed consent

TURBO Cites: Informed Consent - Devices

- Written informed consent of potential subjects to participate in an investigation was obtained prior to obtaining [IRB] [FDA] approval to conduct the investigation. Specifically, ***
- Records documenting that informed consent was obtained for each subject prior to participation in the study are not all [accurate] [complete] [current]. Specifically, ***

TURBO Cites: Safety Reports - Drugs

- Failure to report [promptly] to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Specifically, ***

TURBO Cites: Safety Reports - Devices

- A complete and accurate report of an unanticipated adverse device effect was not prepared and submitted [within 10 working days after first learning of the effect] to [the sponsor] [the reviewing IRB]. Specifically, ***

TURBO Cites: Case Histories

Drugs

- Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent]. Specifically, ***

Devices

- Records of each subject's [case history] [exposure to the investigational device] are not all [accurate] [complete] [current]. Specifically, ***

TURBO Cites:

Investigational Product Control – Drugs

- Investigational drug disposition records are not adequate with respect to [dates] [quantity] [use by subjects]. Specifically, ***
- Unused supplies of an investigational drug were not [returned to the sponsor] [disposed of in accordance with sponsor instructions]. Specifically, ***

TURBO Cites:

Investigational Product Control – Devices

- Devices under investigation were not properly controlled. Specifically, ***
- An investigational device was supplied to a person not authorized to receive it. Specifically, ***
- Records of [receipt] [use] [disposal] of a device that relate to the [type and quantity] [dates of receipt] [batch number or code mark] of the device are not all [accurate] [complete] [current]. Specifically, ***
- The remaining supply of investigational devices was not disposed of as the sponsor directed upon [completion] [termination] of a clinical investigation or part thereof. Specifically, ***

TURBO Cites:
Labeling – Drugs

- Investigational drug (label) (labeling) [bears a statement that is false or misleading] [represents that the investigational drug is safe or effective for the purposes for which it is being investigated.] Specifically, ***

TURBO Cites: Record Retention - Drugs

- Investigational records were not retained for a period of two years following [approval of a drug's marketing application] [discontinuance of the investigation and notification of FDA]. Specifically, ***

TURBO Cites: Record Retention - Devices

- Required records were not all maintained [during the investigation] [for a period of two years after the date on which an investigation was terminated or completed] [for a period of two years after the date that the records were no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol]. Specifically, ***

TURBO Cites: Labeling – Devices

- The labeling for an investigational device bears a statement that is [false] [misleading]. Specifically, ***
- The labeling for an investigational device misrepresents that the device is [safe] [effective] for the purposes for which it is being investigated. Specifically, ***

TURBO Cites: Other – Drugs

- Representations were made in a promotional context that the investigational drug is [safe] [effective] for the purposes for which it is under investigation. Specifically, ***
- The investigational new drug was [commercially distributed] [test marketed]. Specifically, ***
- Charges were made for the investigational drug without the prior written approval of FDA. Specifically, ***

TURBO Cites: Other – Devices

- An investigational device was [promoted] [test marketed] prior to FDA approval/clearance. Specifically, ***
- An investigational device was commercialized by charging the [subjects] [investigators] a price larger than that necessary to recover costs of manufacture, research, development, and handling. Specifically, ***

Misconduct in Research: Detecting Falsification

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 29, 2008

Noncompliance and Research Misconduct

- An honest difference of opinion or an honest error can result in the occurrence of isolated GCP noncompliance. This is NOT research misconduct
- Misconduct requires deliberate **or** repeated noncompliance with GCP requirements
- Even here there is a gradation of concern...

The "Misconduct" Scale

- Innocent Ignorance
- Sloppiness
- Malicious Intent: Falsification/Fraud

Malicious Intent: Falsification/Fraud

- Worst case scenario
- Generally a deliberate action to deceive or mislead
- Broad implications
- Low incidence, but great risk to GCP and the research enterprise
- Hard to detect/Hard to manage

Ways That Data is Falsified

- Creating data that were never obtained
- Altering data that were obtained by substituting different data
- Recording or obtaining data from a specimen, sample, or test whose origin is not accurately described or in a way that does not accurately reflect the data
- Omitting data that were obtained and ordinarily would be recorded

Who Does It ?

- Anyone at the investigator's site who has access to data
  - Principal Investigator
  - Subinvestigators
  - Study Coordinators
  - Study Nurses
  - Monitors sent from the Sponsor

Types of Data Falsified

- ECGs
- Blood Pressure Data
- Physical and lab examinations
- Biological Specimens
- Subject Identities
- Drug Compliance Records
- Most any other data...

Omitting Data: Where Have the Source Documents Gone ?

- “They were destroyed in a hurricane”
- “They were lost in a boating accident”
- “They were lost in the mail”
- “The mover threw them out”
- “They were stolen”

Why is Data Falsified ?

- Reasons are not always known or clear
  - To qualify ineligible subjects to enroll or continue on the study ("good of the subject")
  - To please the sponsor by filling in the blanks and making the source documents match the Case Report Form
  - To save time or to make a profit

Consequences of Falsification -1-

- If falsification takes place during a clinical study, it places all subjects in that study at possible **safety risk**
- Falsification jeopardizes the **reliability** of submitted and/or published data and undermines the regulatory authority's mission to protect and promote public health
  - False basis for product approval; inaccurate information in the product label

Consequences of Falsification -2-

- Falsification may also have a far-reaching negative impact on clinical research
  - Decreasing public confidence and willingness to participate as subjects
  - Tendency for “falsifiers” to work on multiple studies involving multiple investigational products and often multiple sponsors

FDA Applications and Sponsors Associated with Violative CIs

CI	Applications	Sponsors
A	91	47
B	49	25
C	43	21
D	21	17
E	12	6
F	6	6

Dealing with Falsification

- Prevention
  - Identify and eliminate/minimize risk factors for falsification
- Detection
  - Monitor and recognize signs of falsification
- Correction
  - Promptly investigate and report falsification

A CASE STUDY:

Lessons for Detecting Falsification

Outcome of the Case

- Guilty: Making false statements in a matter within the jurisdiction of the FDA
- Guilty: Conspiracy to commit an offense against the United States
- Penalties
  - Clinical Investigator sentenced to 15 months in prison
  - Fined US$ 800,000

Background to the Case

- CI conducted over 200 studies for as many as 47 drug companies beginning in the early 1990's
- Bought bacteria from a commercial supplier to create qualifying cultures
- Diluted urine from staff member with benign proteinuria to qualify other subjects
- Pulled pages from patients' medical charts making reference to disqualifying conditions

Media Attention

- National (U.S.) and international press coverage
- New York Times Article
  - "Research for Hire: A Doctor's Drug Studies Turn Into Fraud"

From the New York Times -1-

- Letter from one of the testing company's study monitors:
  - "CONGRATULATIONS on meeting your enrollment deadline !" the monitor wrote in a letter. "I performed a 100 percent source document verification (x-rays) and found no outstanding issues."

Lessons Learned -1-

- To detect falsification, it is necessary to **get technical**
  - Read and evaluate x-rays, ECGs, laboratory results
  - Don't just inventory the source documents

From the New York Times -2-

- "When a monitor hired by (XXX) asked to see the patient's medical chart, a study staff member quickly fetched the patient's medical chart, and pulled out every page that made reference to the disqualifying lung disease. Then, according to investigative documents, she turned the remaining records over to the monitor. The violation went undetected."

Lessons Learned -2-

- Question missing dates, times, information
- Question missing or out-of-sequence records
- Offer to retrieve records yourself

From the New York Times -3-

- "Even when his employees spelled out their suspicions (to monitors) about what was happening, it wasn't that he was particularly adept at dodging their questions. Rather, they *seemed reluctant to challenge such a prominent figure* in the drug-testing business."

Lessons Learned -3-

- Don't be intimidated
- You may need to challenge or confront the investigator
  - See if and what he/she tries to cover up when challenged

From the New York Times -4a-

- "Several former coordinators for [Dr. F] said they had reported his unethical conduct to an independent study monitor working with (XXX). The study monitor sharply challenged [Dr. F] and his staff in her reviews of their paperwork. [Dr. F] chafed at the challenges, feigning outrage."

From the New York Times -4b-

- " 'Our integrity and reputation for performing high-quality clinical trial work has been injured, and we are justifiably upset,' [Dr. F] wrote in a letter to the sponsor, complaining about the monitor's demand. He insisted the sponsor 'have a new monitor assigned to our site immediately.' "

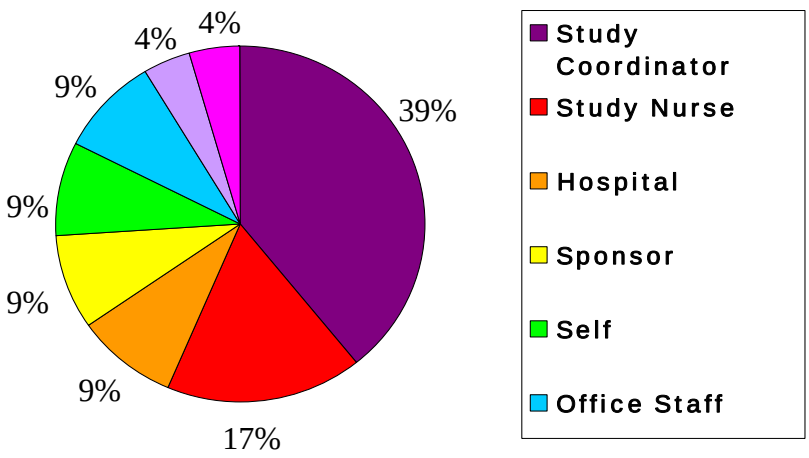
Lessons Learned -4-

- Believe the monitor and others who may come forward with complaints or suspicions
- Put the burden of proof on the clinical investigator

From the New York Times -5-

- "[Dr. F] replied that they were going to blame the study nurse for all of the problems, and he was going to say he had no knowledge of what was going on."

Lessons Learned –5a- Blame is Often Shifted



n (parties blamed) = 23
n (cases) = 20

Lessons Learned -5b-

- Be suspicious of blame shifting
- Tell the clinical investigator that he/she is responsible for the conduct of the study and is accountable for the results

From the New York Times -6-

- “Why was [Dr. F] able to fool the monitors so easily ? Because the oversight system is mostly designed to catch errors, not fraud.”

Lessons Learned -6-

- Expect fraud
- Start from the assumption that the records are bogus and the study is fraudulent, and work back
- Let the records and your inspection restore your confidence that the work is NOT fraudulent

From the New York Times -7-

- “The FDA investigators asked [Dr. F] ...what could the watchdogs have seen that would have allowed them to detect his fraud.”
- “ ‘**Nothing’**, [Dr. F] replied. Had it not been for a disgruntled former employee, he would have still been in business.”

Lessons Learned -7-

- Cultivate “whistleblowers”
- Establish rapport with the study staff
- Be approachable and available; listen to grievances; observe working conditions

From the New York Times -8-

- “Avoiding Detection: The FDA Ignores an Early Warning”
- “The government had its first solid lead on what was happening in [Dr. F’s] office fully 17 months before Ms. X exposed his crimes to an FDA auditor.”

Lessons Learned -8-

- Have a system (with procedures) in place to capture, document and deal with complaints of misconduct in a timely fashion
- All complaints should be assumed to be credible unless demonstrated to the contrary after thorough evaluation and supervisory review
- The receipt, follow-up, and action on all complaints should be documented so that all decisions and actions can be reconstructed

Falsification / Fraud: More Case Examples

Falsified Subjects

- Same subject enrolled more than once under two different names and identities
- Nonexistent subjects created
- Subjects fabricated from names in the obituary column of the local newspaper

Falsified Specimens

- Genetic analysis of sputum samples from 26 subjects showed only 3 distinct profiles

Falsified ECG's

- Continuous ECG strip run on one patient then torn in half and represented as coming from two subjects
- Preprinted subject identifying information altered or obliterated
- Multiple subjects with identical ECG's ("Dr. Xerox" will see you now...)

Falsified Outcome Data

- "The case report for patient #20 indicates he died in June 1985. The hospital medical records for this patient as of April 1996 indicate he swims and goes to the gym twice a week."

Perfect Results: Healing Esophageal Erosions

Subject #	Baseline Endoscopy	Healed Week4
1	3	0
2	3	0
3	3	0
4	3	0
5	3	0
↓	↓	↓
40	3	0

Even Worse ?

- Clinic has no endoscope/endoscopy suite to perform the procedures

Vital Sign Determinations

Subject #	Study Day	Heart Rate	Blood Pressure
1	1	100	110/70
	9	100	110/70
	18	100	110/70
	26	100	110/70
	38	100	110/70
3	1	80	100/70
	11	80	100/70
	18	80	100/70
	25	80	100/70
	39	80	100/70

If you can't believe it, it is probably not true...

Subject #	Study Day	Heart Rate	Blood Pressure
8	1	120	70/50
	10	120	70/50
	21	120	70/50
	23	120	70/50
9	1	100	120/70
	7	100	120/70
	19	100	120/70
	47	100	120/70

Documenting an Inspection

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 29, 2008

FDA's Investigations Operations Manual (IOM)

- Includes information and general instructions regarding inspections
- Speaks to documenting inspectional findings
  - How to develop the report
  - What to include as exhibits and how to identify them
- Available at
  http://www.fda.gov/ora/inspect_ref/iom/ChapterText/5_10.html#SUB5.10

Establishment Inspection Report (EIR) -1-

- Factual, objective, and free of unsupportable conclusions
- Concise, while covering the necessary information
- Free of opinions about administrative and/or regulatory follow-up
- Written in the first person
- Signed by all who participated in the inspection

Establishment Inspection Report (EIR) -2-

- Includes
  - Narrative report
  - Exhibits
  - Attachments – usually include the inspection assignment and any Form FDA 483 issued

Inspector's Diary

- Each inspector should maintain a diary
  - Record information throughout the inspection
  - Diaries should be written in ink and identify when the entry was made
  - Any changes to the diary should not obliterate the original entry and should identify when the change was made, why, and by whom
  - Identify when, where and from whom exhibits were obtained, and that any photocopy is a true copy of the original document

Exhibits -1-

- Copies of records (exhibits) supporting any observations noting deviations from GCP
- Include when, where, and from whom copies were obtained and that it is a true copy of a source document – investigator inspection diary should make note that the authenticity of source copied was verified
- Confidentiality essential and FDA maintains, but subject identifiers often are essential – reason for essential element in informed consent

Exhibits -2-

- Exhibit pages are identified with an exhibit number, name of inspected party, date(s) of inspection, and FDA investigator's initials
- Identifying information must not cover, deface, or obliterate any data on the record/document
- Narrative of the EIR references supporting exhibit(s) by number

Form FDA 483 -1-

- Commonly referred to as a "483"
- Listing of observations
- Not a final report
- Issued to and discussed with the inspected party at the close of the inspection
- Observations significant and based on pertinent FDA regulations

Form FDA 483 -2-

- Observations should not reference guidance
- Should not be issued when there are no significant GCP deviations
- Inspected party may respond orally, in writing, or both

Narrative Report

- May be a “Summary of Findings” if no violative conditions were found
- Same basic areas covered, just more abbreviated
  - Reason for inspection
  - What was inspected
  - Administrative information
  - Individual responsibilities
  - Inspectional findings
  - Discussion with investigator or most responsible person

Reason for Inspection

- Identify who requested/initiated the assignment
- State the Purpose of the Inspection
  - Support review of a product application
  - Real time surveillance of the study
  - External or internal complaint or concern

What Was Covered

- FDA Application [IND or NDA; IDE, PMA or 510(k)] number
- Name of Investigational Product
- Study Sponsor
- Protocol Title and Number
- Dates of Study (overall; at site)
- Location of Study Site Inspected

Administrative Procedures

- Name, title, and authority of the person to whom credentials were shown and any Notice of Inspection was issued
- Persons interviewed
- Who accompanied during the inspection
- Who provided relevant information
- Prior inspectional history
- Other regulated studies performed by the clinical investigator
- Identity of the ethics committee

Individual Responsibilities

- Identify study personnel and summarize their responsibilities relative to the study
- Comment on who obtained informed consent and how it was obtained
- Identify who monitored the study and how often

Inspection Findings -1-

- Statement about comparison of data (recorded on the Case Report Form and/or in line listings supplied to FDA) with the clinical investigator's source documents
- State what records were covered
  - Clinic Charts
  - Hospital Records
  - Laboratory slips; Radiology/Pathology Reports
  - Other Source Documents (ECGs; X-rays)

Inspection Findings -2-

- Number of files and CRFs Reviewed (out of the total site and study population)
- Statement that investigational product accountability records were or were not sufficient
- Discussion of "483" (inspectional) observations
  - Reference the exhibits/documentation collected

Inspection Findings -3-

- State whether there was evidence of under-reporting of adverse events
  - Make a special note of any under-reporting (or significant delays in reporting) of serious and unexpected events which would trigger IND safety reports or device unanticipated adverse device effect (UADE) reports

Discussion with Management

- Summarize the discussion of “483” observations and non-483 observations
  - Include identification of who was present at this closing interview
- Summarize the investigator’s response to these observations

EIR: Other Issues

- Include a copy of the protocol actually used, unless identical to the one in the assignment and have assigner's concurrence to omit
- Include a copy of the consent form(s) actually used by the clinical investigator
- Include more detail (including exhibits) where violations are observed
- Provide considerable detailed documentation for highly violative inspections
  - May include affidavits, where appropriate

EIR Review

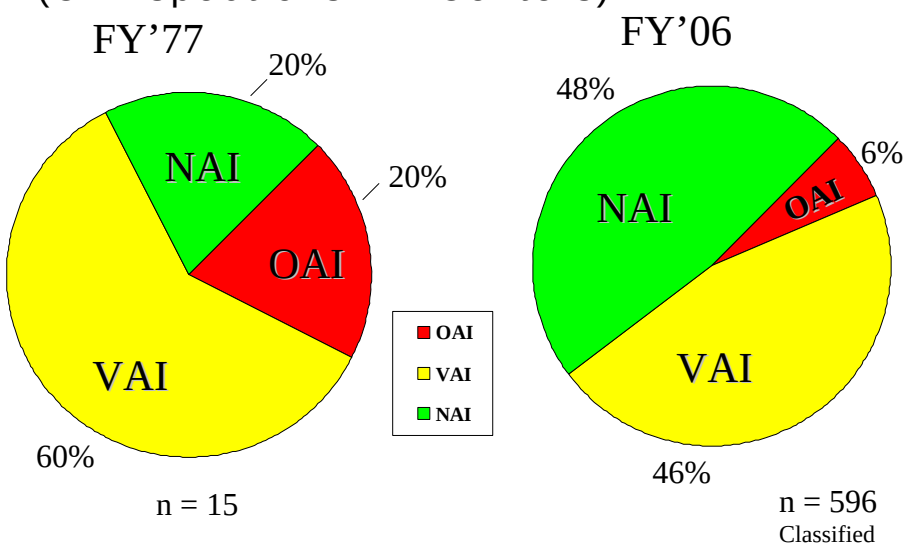
- The complete, signed EIR is forwarded to FDA headquarters for further review
- This review will assure that any cited GCP deficiencies are violations of FDA regulations and are supported by exhibits
- The review will also include any response (including additional information or documentation) provided by the inspected party

Compliance Classification

- Based on headquarters review of the “483”, EIR, and any response from the inspected party, a compliance classification will be assigned
  - NAI: No Action Indicated
  - VAI: Voluntary Action Indicated
  - OAI: Official Action Indicated

GCP Compliance Has Improved Over Time

(CI Inspections: All Centers)



Close-Out/Follow-Up

- For VAI and most NAI inspections, FDA headquarters will issue a close-out letter to the inspected party
  - The VAI letter will cite those deficiencies for which voluntary action should be taken
- For more seriously violative inspections, official action (which may include sanctions) will be initiated by FDA

Assessing Sponsor and IEC Compliance from CI Inspection

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 29, 2008

Objectives of this Talk

- Review sponsor and IEC Roles and Responsibilities
  - To the clinical investigator and at the clinical trial site
- Identify Essential Documents and other information at the CI/trial site that suggest the sponsor and IEC are/are not meeting their regulatory responsibilities

Sponsor Responsibilities: CI Site Perspective -1-

- Study (protocol) Design
  - Availability of protocol, amendments, and revisions at the site
  - Investigator's perspective on implementing the protocol
    - Any barriers to compliance inherent in the protocol
    - Dialogue between sponsor/investigator on protocol design and implementation

Sponsor Responsibilities: CI Site Perspective -2-

- Managing the Study
  - Standard Operating Procedures
    - Sponsor-provided
    - ? Site-developed/site-specific
    - Any conflicts ?
  - Trial-related documents
    - Case report forms (including sample CRF)
    - ? Worksheets; ? Other sponsor-supplied forms
  - Sponsor-supplied equipment

Sponsor Responsibilities: CI Site Perspective -3-

- Selecting sites/qualified investigators
  - Any evidence that the investigator lacks education, training, or experience to perform the study/study procedures ?
  - Any evidence that the study site lacks essential equipment or personnel to perform study-related procedures ?
  - Documentation of curriculum vitae (CI; subinvestigator[s]) and list of duties

Sponsor Responsibilities: CI Site Perspective -4-

- Informing the Investigator
  - Availability of Investigator's Brochure
  - Documentation of Relevant Communications between the sponsor and investigator
    - Including notification by sponsor re: any important emerging safety information
  - Query of investigator on contact/adequacy with sponsor

Sponsor Responsibilities: CI Site Perspective -5-

- Financing and Compensation
  - Not specifically queried on CI inspection, BUT
  - Evidence of completion/submission of any required financial disclosure information by CI and, as applicable, subinvestigator(s)
  - (Essential) documentation of “agreements” between sponsor and CI

Sponsor Responsibilities: CI Site Perspective -6-

- Required submissions to/approval by regulatory authorities
  - (Essential) documentation of any regulatory authority authorization[s] at the CI site
  - Note: A “for cause” inspection may be assigned to document performance of regulated clinical research without a required IND/IDE application to FDA

Sponsor Responsibilities: CI Site Perspective -7-

- Assuring access to study records and data
  - Evidence of (written) agreement between sponsor and investigator/(institution) assuring sponsor access to study-related records
  - Evidence in the signed informed consent document(s) of the basic (essential) element re: direct access to subject medical records
  - Querying the CI on any barriers to access of subject records
  - Querying/reviewing the handling of records with respect to subject privacy/confidentiality

Sponsor Responsibilities: CI Site Perspective -8-

- Investigational Product (IP): Handling/Storage and Accounting
  - Instructions/SOPs for handling/storing the IP
  - Adequacy of storage facilities
    - Temperature/conditions of storage
    - Security of the IP
  - Availability of shipping and disposition records
  - Return or destruction of unused IP
  - Investigator's perspective on study blinding

Sponsor Responsibilities: CI Site Perspective -9-

- Safety Management and Reporting
  - Availability of safety information from the sponsor
    - Investigator's Brochure
    - Notification by sponsor re: any important emerging safety information
      - For any adverse experience that was both serious and unexpected, did the investigator receive a "copy" of the written safety report filed with the regulatory authority ?

Sponsor Responsibilities: CI Site Perspective -10-

- Monitoring the Study
  - Log of on-site monitoring visits
    - Frequency of visits and by whom
    - Purpose of visits: Extent and nature of monitoring
  - Communication of findings
    - Monitoring reports; other communications with CI
    - Notification of problems; prompt corrective action
  - Documentation of CRF corrections
    - ? Any changes to source documents/CRF by monitor without review/approval of CI

Sponsor Responsibilities: CI Site Perspective -11-

- Sponsor Recordkeeping; Managing Study Data; Reporting the Study
  - ? Any discrepancies between source data/CRF and sponsor line-listings/study reporting

Sponsor Responsibilities: CI Site Perspective -12-

- General sponsor oversight of the CI/site
  - For any serious findings on regulatory inspection of the clinical investigator
    - Consider why these were missed by the sponsor during site training/monitoring/auditing/data management
      - Degree of difficulty to detect
      - ? Reflection on individual sponsor staff
      - ? Reflection on sponsor's systemic processes

Learning about the IEC
from a CI Inspection

IEC Responsibilities: CI Site Perspective -1-

- Membership/Independence
  - Relationship of CI to the IEC
    - ? Member; ? Institutional official/ administrator; ? Invited Expert
    - Any conflicting interest(s) ?
    - Recusal, if appropriate
  - (Documentation of IEC composition at CI site)

IEC Responsibilities: CI Site Perspective -2-

- Evidence of IEC Procedures (SOPs) for ensuring prompt reporting to the IEC of:
  - Changes in the research activities
  - Any unanticipated problems involving risks to human subjects in the study

IEC Responsibilities: CI Site Perspective -3-

- Communication with the CI
  - Dated, documented IEC approval(s), including any stipulations
    - Protocol and Amendments
    - Informed Consent form
    - Other written information to subjects
    - Recruitment materials
    - Subject compensation

IEC Responsibilities: CI Site Perspective -3a-

- Communication with the CI (Continued)
  - For any serious and unexpected adverse experience(s) at the site: evidence of notification(s) by CI to IEC

IEC Responsibilities: CI Site Perspective -4-

- Informed Consent
  - Inclusion of all basic (essential) elements of consent in the IEC-approved informed consent document in use at the trial site

IEC Responsibilities: CI Site Perspective -5-

- Vulnerable subject populations
  - (? Any additional protections/procedures imposed by the IEC on the CI/study site for research involving vulnerable subject populations)

IEC Responsibilities: CI Site Perspective -6-

- Evidence of IEC Continuing Review
  - (Essential) documentation of interim reports from the CI to the IEC
  - (Interim communications between the IEC and CI)

Take Home Messages from this Talk

- A great deal can be learned about sponsor and IEC compliance from a CI inspection
- FDA most often assigns a CI inspection “first”
  - Evidence of sponsor or IEC non-compliance on CI inspection may lead to a follow-up inspection of the sponsor or IEC
  - Information learned at the CI site can help “focus” the sponsor or IEC inspection which is otherwise more “systems”-oriented

The Close-Out Discussion

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 30, 2008

The On-Site Component of the Inspection is Complete

- CI [and any relevant study staff] have been interviewed
- Records have been inventoried
- Data audit has been conducted
- Relevant facilities have been “visited”
- Objectionable findings have been identified and documented
  - Inspector’s diary entries
  - Exhibits

Close-Out Discussion -1-

- Final meeting with the clinical investigator
  - Others may be present at the inspector's discretion
    - Shouldn't interfere with the dialogue and discussion between inspector and CI
  - Explain what was inspected

Close-Out Discussion -2-

- Present the written list of objectionable findings (FDA Form 483)
  - Discuss and explain each finding, including any supportive exhibits
  - Understand and be able to explain the context and relevance of each objectionable finding
    - Regulatory violation as well as relevance to the goals and principles of GCP

Close-Out Discussion -3-

- Discuss and explain any additional findings that were not included on the written list
  - Be sure to clearly distinguish regulatory violations from any “comments” on non-violative observations
  - This includes any references to FDA guidance documents which represent FDA’s “best thinking”, but are not enforceable as regulation

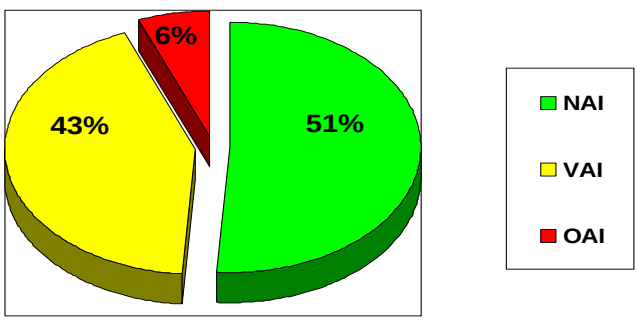
Close-Out Discussion -4-

- Provide the CI with an opportunity to respond to the findings orally or in writing
  - Capture any oral response in inspector’s diary at the time of the close-out discussion
  - Indicate that the CI can also respond in writing
    - Contact information for a written response
  - Include any CI response (written or oral) in the EIR

Close-Out Discussion -5-

- Explain that “FDA headquarters” will evaluate findings before making any final decisions
- Summarize the close-out discussion in the Establishment Inspection Report (EIR)

“Correctable” GCP Violations are Identified in > 40% of CI Inspections



CDER Assigned CI Inspection with Final Classification* in FY 2007; n = 348

***Based on Letter Date** **02/28/08**

Closing Perspectives

- Maintaining cordiality
- Identifying, discussing and explaining objectionable findings
  - Including context
- Assuring due process
- Educational as well as compliance focus

Clinical Investigator Inspecting: In Summary

David A. Lepay, M.D., Ph.D.
Jean Toth-Allen, Ph.D

APEC GCP Inspection Workshop

May 30, 2008

Any Questions ? -1-

- Planning and Preparation
  - Site Selection
  - Inspection Assignment
  - Protocol Review
  - Inspection SOPs (CPGMs)
  - Inspection/Audit Plan

Any Questions ? -2-

- Conducting the Inspection
  - Credentials/Notice of Inspection
  - Opening Interview
  - Inventory of Essential Documents
  - Clinical Data Audit
    - Elements of Data Quality/Data Integrity
  - Facilities Tour; Additional Interviews
  - Close-Out Discussion

Any Questions ? -3-

- Recognizing GCP Deficiencies
- Misconduct: Fraud/Falsification
  - Recognizing and Preventing Misconduct

Any Questions ? -4-

- Documenting and Reporting the Inspection
  - Investigator's Diary
  - Exhibits
  - Inspectional Observations ("483")
  - Establishment Inspection Report (EIR)

Any Questions ? -5-

- Due Process for the Inspected Party
- Secondary (Headquarters) Review of Inspection Reports/Responses
  - Final compliance classification
  - [Enforcement strategies: Later this afternoon]
- Indicators of Sponsor and IEC Compliance/ Non-Compliance in a CI Inspection

Inspecting Sponsors and Contract Research Organizations

Jean Toth-Allen, Ph.D.

APEC GCP Inspection Workshop

May 30, 2008

Sponsors -1-

- Responsible for general conduct of clinical trials – important to understand process and quality controls
- In direct communication with regulatory authorities and must provide adequate information to investigators
  - Required communication must be accurate, timely, and complete

Sponsors -2-

- Handle study data – from time it leaves the investigator site until it is communicated to regulatory authorities
- Handle and account for investigational product – including control of shipping and receipt by investigator(s)

Sponsors -3-

- Duties and functions can be contracted to others – commonly Contract Research Organizations (CROs)
- FDA regulation governing investigational pharmaceuticals (drugs and biologics) addresses transfer of regulatory responsibilities
- FDA device regulation does not include such language
- Sponsor ultimately responsible for conduct of studies

Sponsor/CRO Inspections -1-

- FDA SOPs in compliance program – http://www.fda.gov/ora/compliance_ref/bimo/7348_810/48-810.pdf
- May be issued
  - On receipt of marketing application/submission
  - Upon receipt of a complaint/concern
  - For general surveillance
- Usually study-specific
- Usually pre-announced

Sponsor/CRO Inspections -2-

- Inspection includes
  - Notice of inspection and credentials
  - Opening interview (and secondary interviews as appropriate)
  - Records inventory and audit
    - Data audit – where appropriate
    - Records of research subject protection
    - Control of investigational product(s)
  - Documentation of objectionable findings (exhibits)
  - Close-out discussion

Elements of a Sponsor/CRO Inspection -1-

- Organization and Personnel
  - Key research processes: Where and by whom (organizational structure and staffing) are these conducted by the sponsor
  - What (if any) sponsor duties and functions are contracted
    - Contracted to whom
    - Written documentation (contract)
    - Sponsor oversight of contracted duties

Elements of a Sponsor/CRO Inspection -2-

- Selection of/communication with investigators
  - Criteria for evaluating investigator qualifications and training
  - Correspondence with and provision of adequate information to investigator(s)
    - Investigator's Brochures; safety updates, etc.
  - Identification of any GCP noncompliant investigators and corrective actions taken to secure compliance or terminate

Elements of a Sponsor/CRO Inspection -3-

- Monitors and Monitoring
  - List of all monitors for the selected study
  - Qualifications, selection, training of monitors
  - SOPs for study monitoring (FDA investigational device regulation requires written SOPs; also in ICH E6 5.18.6)
  - Review of monitoring/site-visit reports
  - Follow-up to corrective actions identified in monitoring reports

Elements of a Sponsor/CRO Inspection -4-

- Adverse event reporting
  - Review of systems for tracking adverse events, ensuring the receipt of information from investigators and relay to regulatory authorities (and other study sites/IECs as required)
- Data handling/data audit
  - SOPs for data handling; following these SOPs
  - Audit of data quality/integrity from source (investigator site) through data listings/analysis to submission in applications/reports

Elements of a Sponsor/CRO Inspection -5-

- Control of investigational product(s)
  - Integrity from manufacture to receipt by the investigator, including integrity of “blinding”
  - Accountability through final disposition
- Review of automated (computerized) processes
  - Procedures
  - Validation; change controls
  - System security
  - Audit trails

Elements of a Sponsor/CRO Inspection -6-

- Recordkeeping
  - Record storage and security
  - Availability of records for inspection
- Multiple regulated studies
  - While the inspection assignment is usually focused on a single selected study, additional regulated studies may be identified and reviewed during the course of a sponsor/CRO inspection
  - Emphasis is on process implementation and quality

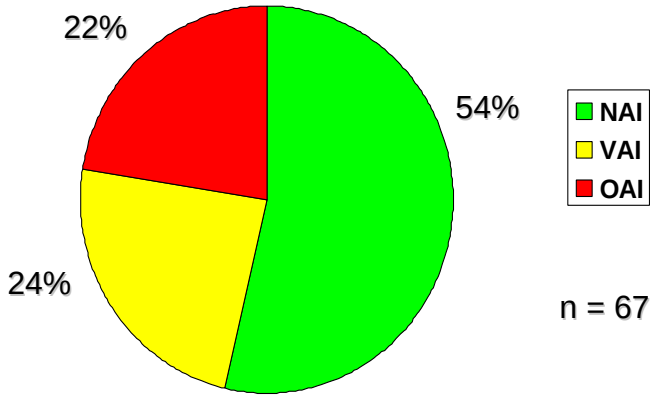
Most Common Deficiencies

- Inadequate monitoring
  - Lack of qualified monitors
  - Lack of documentation of monitoring visits
  - Lack of adequate procedures
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product

FY'07 Sponsor Inspections Classified

	NAI	VAI	OAI
CBER	7	0	1
CDER	18	4	2
CDRH	11	12	12
CFSAN	0	0	0
CVM	0	0	0

FY'07 Sponsor Inspections Classified – All Centers



Sponsor Exercise

Ethics Committee (IEC) Inspections

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 30, 2008

References

- FDA Compliance Program Guidance Manual Program 7348.809: Institutional Review Board (http://www.fda.gov/ora/compliance_ref/bimo/7348_809/irb-cp7348-809.pdf)
- Surveying and Evaluating Ethical Review Practices: A complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research, World Health Organization, 2002 (http://www.who.int/tdr/cd_publications/pdf/ethics2.pdf)

Role of the Ethics Committee: Brief Summary

- Safeguarding the dignity, rights, safety, and well-being of all actual or potential research participants
- Providing **independent**, competent, and timely ethical review of the proposed study
  - Initial review
  - Continuing review

Products of an Ethics Committee -1-

- Decision/opinion on the research protocol before commencement of the protocol
  - Special attention to any enrollment of vulnerable subject populations; additional protections
  - Consideration of the investigator's qualifications and the adequacy of the study site
- Review of informed consent and approval/favorable opinion of the informed consent form and process

Products of an Ethics Committee -2-

- Review of any payments to subjects
- Regular evaluation of the ethics of ongoing studies that received a positive decision
  - Affirming that the study is ethical to continue
  - Determining that information provided to subjects in the informed consent is still accurate and current OR updating the information provided to subjects and, where appropriate, renewing the informed consent of each subject

Ethics Committee (IEC) Inspections

Ethics Committee Inspections

- FDA performs approximately 200 Ethics Committee (IRB/IEC) inspections per year
- Duration of inspection is 2-5 days
  - Inspections are generally pre-announced
- IEC Compliance Program is available at:
  - http://www.fda.gov/ora/compliance_ref/bimo/7348_809/irb-cp7348-809.pdf

Conduct of Inspection

- The general approach to IEC inspection is similar to inspections at investigator sites --- although more systems-oriented vs. data-driven
- Inspection consists of:
  - Interviews with responsible IEC staff
  - In-depth review of SOPs, files, and records
  - Review of active studies to assess IEC operations

Ethics Committee Inspectional Considerations -1-

- FDA views (properly operating) IECs as allies in protecting research subjects
- The focus of an IEC inspection is to ensure the IEC's proper constitution and its proper and independent operation
  - Including written procedures, documentation of activities/decisions, and communication with investigators
  - Including conduct of substantive initial **and** continuing review

Ethics Committee Inspectional Considerations -2-

- FDA inspections do not question the IEC's decision/opinion on a study, but do review the process by which a decision is made, the authority of the IEC to render an independent decision, and the documentation and communication of the decision/opinion
- FDA inspections also seek to establish the IEC's knowledge of the informed consent process that will be used and that required elements of informed consent are included

Selection of IECs for Inspection

- FDA conducts routine surveillance inspections of IECs (Target: Every 5 years)
- More frequent inspection if:
  - Deficiencies are identified in previous inspection
  - High volume IEC
  - New IEC
- Complaints can also trigger an inspection
- FDA has authority to inspect non-U.S. IECs as a criterion for accepting studies, but this is very rare

FDA Is Not Alone in Auditing/Inspecting IECs

- Institutions receiving U.S. research grants/funds (for example, U.S. NIH grants) are required to maintain a “Federal Wide Assurance” [FWA] that certifies compliance with IEC and institutional requirements
- The U.S. Department of Health and Human Service’s Office for Human Research Protections (OHRP) is responsible for ensuring compliance with the Federal Wide Assurance and can inspect to ensure such compliance

Elements of an IEC Inspection: IEC Membership Review

- Required representation
  - Terms of appointment
- Quorum requirements
- Alternate members
  - Advance appointment
  - Listing on the roster
  - Identification of primary member(s) for whom each alternate may substitute
  - Recording in the minutes when an alternate serves
- Recusal (when conflicting interests)

Elements of an IEC Inspection: Identification of Regulated Studies

- Review of IEC's study inventory/roster
- Selection of active FDA-regulated study(-ies) for in-depth assessment/inspection
  - Pre-selection: Confirmation of jurisdiction
  - Selection of additional regulated studies
- Review any FDA-granted waivers of IEC review

Elements of an IEC Inspection: Review of Written SOPs -1-

- Availability of required SOPs describing:
  - Conduct of initial and continuing review
    - Establishing timeframes for continuing review
  - Reporting of findings and actions to CIs/institution
  - Prompt reporting to the IEC of changes to the research
    - Ensuring that changes may not be initiated without IEC review and approval except where necessary to eliminate immediate hazard to subjects

Elements of an IEC Inspection: Review of Written SOPs -2-

- Availability of required SOPs describing:
  - Prompt reporting to the IEC, institutional officials, and regulatory authority of unanticipated problems involving risks to subjects
  - Prompt reporting to the IEC, institutional officials, and regulatory authority of any serious or continuing noncompliance
  - Prompt reporting to institutional officials and regulatory authority of any suspension/termination of IRB approval

Elements of an IEC Inspection: Affirm IEC Authority

- Establish (through interview/documentation) whether the IEC has the authority to approve, modify, or disapprove proposed studies and to modify or terminate approval of ongoing studies
- Determine whether the institution overrides or can override a negative or restrictive IEC decision

Elements of an IEC Inspection: Materials for Initial IEC Review

- Inventory and review materials submitted by the clinical investigator to the IEC for selected study(-ies)
  - Proposed protocol
  - Consent form
  - Investigator's Brochure
  - Instruction summaries given to subjects
  - Advertising materials; payment schedules (if applicable)
  - Translations of "non-English" consent forms

Elements of an IEC Inspection:
Review of IEC Meeting Minutes -1-

- Assess the availability and adequacy of IEC meeting minutes
- Track IEC handling and review of selected study(-ies) from documentation provided in IEC meeting minutes
  - Distribution of materials to IEC members
  - Assignment/responsibilities for review
  - Discussion at (a) convened meeting(s); voting

Elements of an IEC Inspection:
IEC Reporting to the CI/Institution

- Determine that the IEC notifies the investigator and institution in writing of IEC actions
  - Review IEC correspondence
  - Opportunity for CI to respond to a disapproval
- Determine that the CI is notified of responsibilities for subsequent reporting to the IEC
  - Inclusion in IEC decision letter or
  - By providing the CI with copies of IEC handbook or procedures that describe reporting responsibilities

Elements of an IEC Inspection: Materials for Ongoing IEC Review

- Inventory and review materials submitted by the clinical investigator to the IEC for selected study(-ies)
  - Any protocol amendments/revised consent forms
  - CI Progress Reports
  - Reports of unanticipated problems involving risk to subjects
  - Reports of serious or continuing noncompliance

Elements of an IEC Inspection: Review of IEC Meeting Minutes -2-

- Track IEC handling and continuing review of selected study(-ies) from documentation provided in IEC meeting minutes
  - Process for reviewing progress reports and other reporting
  - Assurance of required substantive continuing review

Elements of an IEC Inspection: Review of Informed Consent

- Consent Form
- Required Elements
- IEC Approval
- Consent Process
  - Authority of IEC to observe the consent process

Elements of an IEC Inspection: Areas for Additional Assessment

- Expedited Review
- Medical Device Studies
  - Significant/Non-Significant Risk Determinations
- Pediatric Studies
  - Additional protections/procedures
- Emergency Review
  - Review of Emergency Use of an Investigational Product
  - Review of Emergency Research where there is special provision for an exception from informed consent

Elements of an IEC Inspection: Areas for Additional Assessment

- Agreements between IECs
  - Centralized or cooperative review of multicenter studies
- IEC record retention
  - At least 3 years after completion of the research

Documents Collected by the Inspector -1-

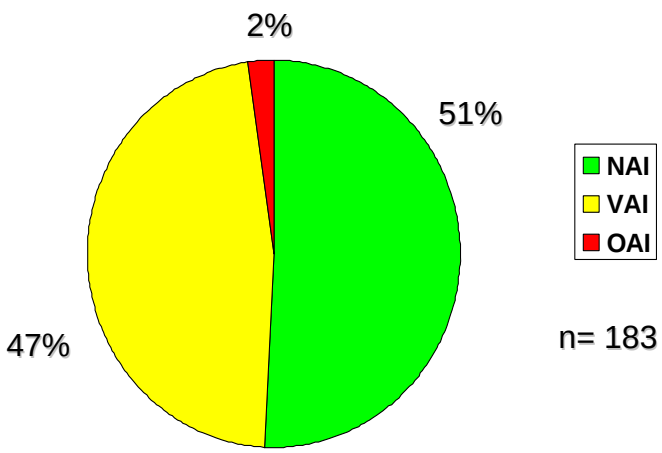
- IEC Membership Roster
- IEC Written Procedures
- Copies of IEC Minutes to illustrate adequacy of minutes and to demonstrate
  - Recent IEC Practices
  - Violative Procedures
  - Approval and Follow-Up on Tracked Studies

Documents Collected by the Inspector -2-

- Records of Tracked Studies
  - Protocol and consent form (original and final approved versions)
  - Investigator's Brochure
  - Correspondence between the IEC and the CI

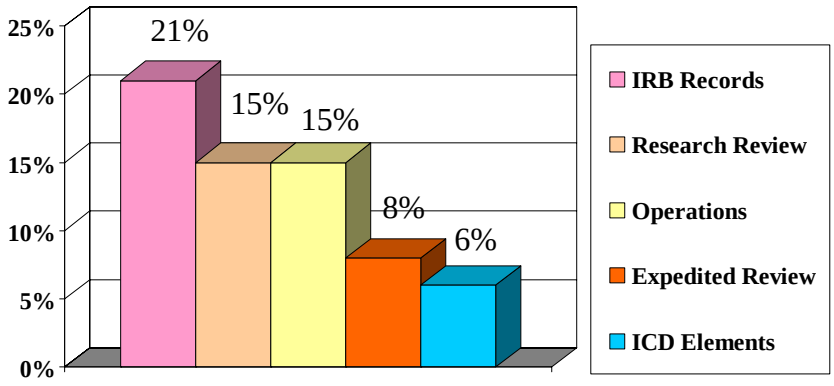
IRB/IEC Compliance

Inspections Classified: FY'07 All Centers



IRB/IEC Deficiencies

FY 2006



CDER Assigned Inspections

Official Action Results from Multiple Serious Problems

- Analysis of 15 IEC OAI Inspections
  - Failure to prepare and/or follow written procedures (n=14)
  - Failure to adequately document activities (n=13)
  - Failure to conduct adequate continuing review (n=10)
  - Failure to fulfill requirements for expedited review (n=9)
  - Failure to fulfill the requirements of informed consent (n=7)

Educating the IEC:
How to Prepare for Inspection -1-

- Prior to Inspection
  - Know what the regulatory requirements are
  - Obtain and be familiar with the compliance program (SOPs) for IEC inspection
  - Retain all records necessary to completely reconstruct IEC activities and findings

Educating the IEC:
How to Prepare for Inspection -2-

- During the Inspection
  - Have the most responsible personnel available as needed (e.g., IEC Chair; IEC Administrator; Institutional Officer)
  - Have all records available and organized for review and possible copying by inspectors
  - Be available throughout the inspection to answer questions and explain records

Educating the IEC:
How to Prepare for Inspection -3-

- During the Inspection (Continued)
  - Have records up to date, organized and available, including:
    - Inventory of ongoing research and status
    - IEC SOPs
    - IEC membership rosters, current and past
    - IEC meeting minutes
    - Records of tracked studies (Protocol, consent forms, IEC correspondence, etc.)

IEC Registration vs. Accreditation in the U.S.

- FDA will soon require (by regulation) that U.S. Ethics Committees register with FDA
  - This is for identification purposes only
  - Registration does not imply regulatory compliance or quality of the IEC
- Private, non-governmental groups are currently accrediting IECs/institutions in the U.S.
  - Effort to improve subject protection and IEC quality
  - FDA does not require and has no formal opinion on IEC/institutional accreditation by such groups

IEC Case Study Exercise

FDA GCP Enforcement Strategies and Options

David A. Lepay, M.D., Ph.D.

APEC GCP Inspection Workshop

May 30, 2008

FDA Compliance Classifications: A Review

- NAI: No Action Indicated
- VAI: Voluntary Action Indicated
- OAI: Official Action Indicated
- The focus of this talk will be “sanctions” -- when official action is indicated

Sanctions in Regulated Research

- Purpose of Sanctions
- Focus of Sanctions
- Types of Sanctions Applied
- Issues

Purpose of Sanctions: General

- To protect and promote the integrity and quality of the drug/medicinal product development and approval process
- To ensure that the rights and welfare of research subjects are adequately protected

Purpose of Sanctions: Methods

- Exclude data found to be of questionable quality and integrity
- Restrict or exclude participation by investigators (sponsors, IECs) that seriously violate GCP
- Notify those affected by violators to take appropriate actions

Focus of Sanctions

- Individuals, companies, and institutions involved in regulated research
  - Clinical Investigators
  - Sponsors; CROs
  - Ethics Committees (IECs)
- Applications and data submitted to FDA

Clinical Investigator Sanctions

- Clinical Hold
- Warning Letter
- Formal Disqualification
- Consent (Voluntary) Agreements
- Debarment
- Prosecution

Clinical Hold

- Order issued by FDA (CDER/CBER) to the sponsor to
  - Delay a proposed clinical investigation
  - Suspend an ongoing investigation
    - No new subjects may be recruited to the study
    - Patients already in the study should be taken off investigational therapy unless specifically permitted by FDA in the interest of patient safety

Clinical Hold

- Most often applied to entire studies or applications by an FDA review team
  - Subjects would be exposed to unreasonable risk
  - Investigator's Brochure is misleading or materially incomplete
  - Investigators are not qualified
  - Study is not designed to achieve its stated objectives

Clinical Hold: Single Investigator/Site

- May also be imposed on a single clinical investigator/site as an outcome of inspection
  - Repeated or deliberate failure to obtain adequate informed consent
  - Serious protocol violations that put subjects at increased risk
  - Failure to report serious or life-threatening adverse events
- Clinical hold may be applied to an investigator/ site "quickly" and in advance of other sanctions

Clinical Hold

- The Clinical Hold remains in effect until removed by FDA

Warning Letter

- “Least severe” of available FDA actions following classification of an inspection as “OAI” (Official Action Indicated)

Warning Letter

- Advisory letter communicating need for correction of serious deviations
  - Publicly available
  - Only applies to studies under U.S. FDA jurisdiction
  - Further action is required to assess and ensure corrections

Warning Letter

- Not viewed as a “final” agency action
  - Resources will be required by FDA (as well as the clinical investigator and sponsor) to address and ensure correction of deviations
  - “More severe” action may be taken if correction is not carried out

Formal Disqualification

- Ineligibility to receive investigational products as determined through a regulatory hearing process
  - Repeated or deliberate failure to comply with regulations or submission of false information
- Does not affect ability to practice medicine
  - Medical licensing is regulated by individual states, not by the U.S. federal government

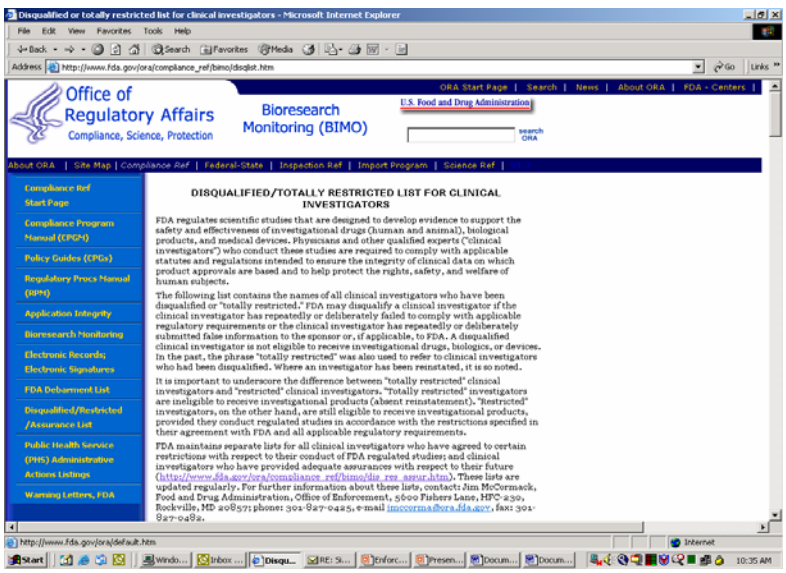
Formal Disqualification: A Lengthy Process

- NIDPOE letter issued
  - Response ***or***
  - Informal Conference
- Evaluation
- NOOH letter issued
  - Response
- Evaluation
- Separation of Powers
- Counsel assigned
- Review by Counsel
- Presiding officer assigned
- Formal Hearing
- Presiding officer's report
- Comment period
- Commissioner's decision

Formal Disqualification

- Typical case may take 2-4 years
- Investigator can continue to conduct studies (unless clinical hold is imposed: separate process)
- List of Disqualified Clinical Investigators is posted on FDA's website

Website for List of Disqualified CIs



Consent Agreement

- Voluntary agreement between FDA and the investigator
- Offered as an expedited alternative from the ***outset*** of the formal disqualification process
  - Disqualification by consent
  - Lesser restrictions (separate website posting)
    - Restriction on number of studies or subjects
    - Oversight by another investigator
    - Third party verification of data

Debarment

- Applies to an individual (or firm) convicted of a crime related to the drug/product development or approval process
- Debarred person can **not** work in any capacity for a pharmaceutical firm
- FDA will not accept or review applications involving debarred persons or companies

Prosecution

- Individuals (or firms) can be criminally prosecuted under Title 18 of the U.S. Criminal Code for
  - Fraud and False Statements
  - Conspiracy
  - Mail Fraud

Sanctions for Sponsors*

- Resulting from Problems
  - With Submissions to FDA
  - At the Clinical Site

- *Sponsor sanctions would also apply to CROs that assume sponsor responsibilities or functions

Sanctions for Sponsors

- Exclude Data or Delay Approval
- Prosecution
  - Criminal Misconduct
- Debarment
  - FDA will not accept or review applications from debarred individuals or companies
- Application Integrity Policy

Application Integrity Policy (AIP)

- Where there is a pattern or practice of wrongful acts
- A validity assessment (acceptable to FDA) will be required for ALL applications from that sponsor where integrity might be in question
- Application review is deferred and marketing applications will not be approved and may be withdrawn

Sanctions for Ethics Committees (IECs)

- Warning Letter/Reinspection
- Lesser Administrative Sanctions
  - Withhold approval of new studies
  - No new subjects to ongoing studies
  - Terminate ongoing studies
- Disqualification
  - FDA will not approve a research permit (e.g., IND) for a clinical investigation that is to be under review of a disqualified ethics committee

Sanctions: Issues

- Targeted to parties regulated under GCP
  - Clinical investigator is responsible for actions of site staff
- FDA regulations are less explicit than ICH GCP in some areas
  - Sponsor monitoring of trials
- For FDA: How to act quickly while maintaining due process

Part III.
Summary of Round Table Discussion

Round Table Discussion :
Identifying Specialized Topics and Defining Objectives and Approaches for the Advanced GCP Inspection Workshop

The participants were informed that the APEC Project "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)" was approved by APEC on 18 April 2008. The recently approved project will support the activities of 2 advanced workshops: (1) Review of Drug Development in Clinical Trials and (2) GCP Inspection, continuing forward from the 2 basic/preliminary workshops of the first approved project.

A round table discussion at the close of the Basic GCP Inspection Workshop provided an opportunity for open comments or suggestions from all participants to identify specialized topics and define objectives and approaches for the advanced GCP inspection workshop.

Expected dates

The advanced workshop is planned to be conducted over 5 days during 2-6 March 2009

Expected instructors and mentors

Instructors and mentors will be identified from US FDA (Dr David Lepay and his colleague), Health Canada, other experienced drug regulatory agencies, and PhRMA. The expected number of mentors will be at least 5 (from both public and private sectors). Dr Lepay also suggests asking for EMEA's cooperation in providing a GCP inspection expert, so the participants will also learn from EMEA's perspective

Target participants

It is highly recommended that the participants who have attended the basic workshop on 27-30 May 2008 be the same, target participants for the advanced workshop.

Format of the advanced workshop

Presentations, experience sharing, questions and answers, discussions, and 2-day on-site mock inspection exercise.

The first day of the workshop should be devoted to a review of key topics from the 'Basic Workshop on GCP/ Clinical Research inspection' and follow up discussion on economies'

progress in implementing GCP and GCP inspection programs. Subsequent days of the advanced workshop will focus on a mock inspection exercise as well as new and specialized topics in GCP/GCP inspection. For the 2 day on-site mock inspection exercise, the participants will be divided into 4-5 groups depending on the number of participating sites/clinical trials (selected by Thai FDA in cooperation with PhRMA). Each group will be accompanied by a mentor, who will instruct and assist the participants during the exercise. The last day of the workshop will be devoted to inspection report presentations, discussions of findings, Q&A, and conclusions of the workshop, which may suggest or lead to the next steps for continuing communication and cooperation in clinical research inspection or regulations among APEC members.

Suggested specialized topics

Participants were asked to suggest specialized topics to be included in the advanced workshop. The suggested specialized topics are listed as follows:

- Hands-on training and more focus on inspection process, including a more complete mock inspection exercise
- Provision of examples of more technical documents involved in GCP e.g. evaluation of forms would be more informative
- Use of Electronic/Computerized processes in Clinical Trials e.g. eCRF
- GCP inspection for Bioequivalence studies, supporting generic drug applications
- Standardization of laboratories for clinical trials
- GCP inspection for clinical trials involving vulnerable populations e.g. special considerations, additional protections, industry approaches to quality assurance, etc.
- Identifying appropriate protocol objectives, end points, and data management
- How to inspect diagnostic data in a clinical trial and evaluate the Lab results e.g. EKG, etc
- Inspection report writing
- Data auditing
- How to inspect drug accountability and considerations
- Turbo inspection reporting software (in use at FDA)
- GCP inspection for medical devices
- More detailed case studies, and discussions

Thailand has collected all recommendations and comments to further develop the workshop agenda together with our consultants. It is obvious that 5 days will not be enough to cover

all suggested topics. However, Consulting economies and Thailand will do our best to accommodate the requests in developing the workshop agenda.

Part IV.
Participants

List of Participants

1. Name :	Dr Abdulmohsen Al rohaimi
Organisation/Affiliation:	Saudi Food & Drug Authority (SFDA) – DRUG SECTOR
Address:	3292 Northern Ring Rd – Al Nafal District
	Riyadh 13312 – 6288
	Saudi Arabia
Daytime Phone:	+69912759222
Fax:	+96612757195
Email:	ahrohaimi@sfda.gov.sa

2. Name:	Benjamin Ing-Tiau Kuo, MD, DrPH, CIP
Organisation/Affiliation:	Joint IRB - Taiwan
Address:	#201 Shih-Pai Rd Taipei, Chinese Taipei
Daytime Phone:	+886-2-28757633
Fax:	+886-2-28737136
Email:	benjamin_kuo@jirb.org.tw

3. Name:	Chao-Yi Wang
Organisation/Affiliation:	Department of Health/ Chinese Taipei
Address:	11F, No. 100 Aiguo E. Rd., Taipei, Chinese Taipei, R.O.C.
Daytime Phone:	+886-2-23210151 Ext, 418
Fax:	+886-2-23971548
Email:	pajoyce@doh.gov.tw

4. Name:	CHERRY ROSE ROLDAN CRUZ
Organisation/Affiliation:	BUREAU OF FOOD & DRUGS
(DEPARTMENT OF HEALTH)	
Address:	CIVIC DRIVE, FILINVEST CORPORATE CITY, ALABANG, MUNTINLUPA CITY
Daytime Phone:	+632 8070726 / +6329179590466
Fax:	+6328070751
Email:	cherry13232003@yahoo.com

5. Name:	Foo Yang-Tong
Organisation/Affiliation:	Health Sciences Authority
Address:	11 Biopolis Way #11-03, Helios, Singapore 138667

Daytime Phone:	+65 6866-3442
Fax:	+65 6478-9034
Email:	Foo_Yang_Tong@hsa.gov.sg

6. Name:	MR. HARY WAHYUT
Organisation/Affiliation :	NATIONAL AGENCY OF DRUG AND FOOD CONTROL, REPUBLIC OF INDONESIA
Address:	JL. PERCETAKAN NEGARA 23, JAKARTA, INDONESIA
Daytime Phone:	62.21.42885459 EXT. 115
Fax:	62.21.42885404
Special Dietary Needs:	HALAL FOOD
Email:	penilaianobat@pom.go.id

7. Name:	Mrs Jamilah Metussin
Organisation/Affiliation:	Department of Pharmaceutical Services, Ministry of Health Brunei Darussalam
Address:	2nd Floor Ministry of Health Building, Commonwealth Drive, Bandar Seri Begawan 883910, Brunei Darussalam
Daytime Phone:	+673 223 0001 / +673 223 0041
Fax:	+673 2 230 001 / + 673 2 230 041
Special Dietary Needs:	Halal meal
Email:	Jamilah_metussin@yahoo.com

8. Name:	Mrs. Lela Amelia
Organisation/Affiliation:	National Agency of Drug and Food Control - Indonesia
Address:	Jl. Percetakan Negara No. 23 - Jakarta
Daytime Phone:	+62-21-4245459 (116)
Fax :	+62-21-42885404
Special Dietary Needs:	Halal Food (no pork)
Email:	penilaianobat@pom.go.id

9. Name:	Luong Thu Vinh
Organisation/Affiliation:	Drug Administration of VietNam
Address:	138 A Giang Vo, Ba Dinh, Ha Noi
Daytime Phone:	084 04 8235812
Fax:	084 04 8234758
Email:	nhocmaiyeu@yahoo.com

10. Name: MIGUEL GONZALEZ GUERRA
Organisation/Affiliation: INSTITUTO DE SALUD PUBLICA DE CHILE
Address: AVENIDA MARATON 1000 ÑUÑOA SANTIAGO
Daytime Phone: 56 – 2-3507638
Fax: 56-2-3507574
Email: magonzalez@ispch.cl

11. Name: Nguyen Thanh Tu
Organisation/Affiliation: The Drug Administration of Vietnam (The DAV)
Address:.. 138A Giang Vo street,
Daytime Phone: 84-4-8230794
Fax: 84-4-8234758
Email: tuxinhvoL2@yahoo.com

12. Name:. MS NORSHIDA KASIM
Organisation/Affiliation: NATIONAL PHARMACEUTICAL CONTROL BUREAU, MINISTRY OF HEALTH MALAYSIA
Address: LOT36 JALAN UNIVERSITI, 46200 PETALING JAYA, SELANGOR, MALAYSIA
Daytime Phone: +60378835583
Fax: +60379551030
Special Dietary Needs: MUSLIM FOOD
Email: shida@bpfk.gov.my.

13. Name: QUANG NGUYEN NGO
Organisation/Affiliation: DEPARTMENT OF SCIENSE AND TRAINING- MINISTRY OF HEALTH- SECRECTARY OF ETHICAL COMMITEE – MoH of Vietnam
Address 138 A GIANGVO- HANOI- VIETNAM
Daytime Phone: +84 91455 8118
Fax: +84 4 273 2243
Email: quangbyt@yahoo.com

14. Name: VAN DO DUC
Organisation/Affiliation: HANOI MEDICAL UNIVERSITY – VICE CHAIRMAN OF OF ETHICAL COMMITEE – MoH of Vietnam
Address 138 A GIANGVO- HANOI- VIETNAM

Daytime Phone:	+84 903289155
Fax:	+84 4 273 2243
Email:	ddvan@fpt.vn

15. Name:	Wenzel Cabotage Asprec
Organisation/Affiliation:	Bureau of Food and Drugs (BFAD) – Department of Health
Address:	Civic Drive, Filinvest Corporate City, Alabang, Muntinlupa City, Philippines
Daytime Phone:	+63 2 8070726 or +63 917 4905627
Fax:	+63 2 8070751
Email:	wenzel_asprec@yahoo.com

16. Name:	ZARIL HARZA ZAKARIA
Organisation/Affiliation:	NATIONAL PHARMACEUTICAL CONTROL BUREAU, MINISTRY OF HEALTH MALAYSIA
Address:	JALAN UNIVERSITI, P.O BOX 319, 46730 PETALING JAYA, SELANGOR, MALAYSIA
Daytime Phone:	603-78835582
Fax:	60379551030
Special Dietary Needs:	HALAL FOOD
Email:	zaril@bpfk.gov.my

17. Name:	Ms Akanid Wapeewuttikorn
Organisation/Affiliation:	International Affairs and Investigational Drug Section Drug Control Division Food and Drug Administration, Thailand Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone :	+66 2 – 590 7061
Fax :	+66 2 – 591 8390
Email :	akanid@fda.moph.go.th

18. Name:	Ms Charunee Krisnaphan
Organisation/Affiliation:	International Affairs and Investigational Drug Section Drug Control Division Food and Drug Administration, Thailand

	Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone :	+66 2 – 590 7061
Fax :	+66 2 – 591 8390
Email :	charunee@fda.moph.go.th

19. Name:	Mr Pramote Akarapanon
Organisation/Affiliation:	Biologics Section
	Drug Control Division
	Food and Drug Administration, Thailand
	Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone:	+66 2-5907029
Fax :	+66 2 - 5918463
Email :	pramote@fda.moph.go.th

20. Name:	Dr Pravan Suntharasamai
Organisation/Affiliation:	Faculty of Tropical Medicine
	Mahidol University, Bangkok, THAILAND
Email :	**tmpst@mahidol.ac.th**

21. Name:	**Mrs Tasanee Lorchaivej**
Organisation/Affiliation:	Biologics Section
	Drug Control Division
	Food and Drug Administration, Thailand
	Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone:	+66 2 - 5907028
Fax:	+66 2 - 5918463
Email:	**nang@fda.moph.go.th**

22. Name:	**Dr. Tharnkamol Chanprapaph**
Organisation/Affiliation:	New Drug Section
	Drug Control Division
	Food and Drug Administration
	Ministry of Public Health

Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone:	+66 2 - 5907196
Fax:	+66 2 -5907204
Email:	**tankamol@fda.moph.go.th**

23. Name :	**Mrs Yaowapa Srabua**
Organisation/Affiliation:	International Affairs and Investigational Drug Section
	Drug Control Division
	Food and Drug Administration, Thailand
	Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone :	+66 2 – 590 7167
Fax :	+66 2 – 5918390
Email :	**yaobuna@fda.moph.go.th**

24. Name:	**Dr Yuppadee Javroongrit**
Organisation/Affiliation:	International Affairs and Investigational Drug Section
	Drug Control Division
	Food and Drug Administration, Thailand
	Ministry of Public Health
Address:	Tiwanont Road, Mueng, Nonthaburi 11000, THAILAND
Phone :	+66 2 – 590 7061
Fax :	+66 2 – 5918390
Email :	**yuppbkk@fda.moph.go.th**

Observers

1. Name:	MICHAEL CHAPNICK
Organisation/Affiliation:	APEC SECRETARIAT
Address:	35 Heng Mui Keng Terrace, Singapore 119616
Daytime Phone:	65 6891 9600 / 6891 9603
Fax:	65 6775 0424
Email:	mc@apec.org / ms@apec.org

2. Name:	Dr Yupin Lawanprasert
Organisation/Affiliation:	Senior Advisor in Safety, Effectiveness, and Use of Health Product Thai Food and Drug Administration Ministry of Public Health Nonthaburi
Phone:	+66 2 590 7150
Fax:	+66 2 591 8446

Part V.
Questionnaire Survey Results

Questionnaire Survey Results

Project Code:	CTI24/2007
Project Title:	Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice
Workshop	Basic Workshop on Good Clinical Practice(GCP)/ Clinical Research Inspection

Bangkok, Thailand 27-30 May 2008

Part A for Trainees

Number of respondents was 17 among 24 trainees.

Question (a): How have you or your economy benefited from the project?

- In terms of standardized GCP inspection procedure which at the end would lead to better quality of data as well as drugs being produce in my economy. This will leads to a boost in economy in terms of manufacturers/foreign investor to invest in our country
- The officers have been trained on GCP issues, which will support the development of human subject protection and drug development in the region
- The GCP is ongoing setup in my economy. For this course, we received many useful information concerning GCP to conduct inspection
- To use new information and knowledge to improve the system
- To match the requirements for a new drug or device to be marketed in US.
- How to refine quality of Clinical Trials for drugs and device
- We realize the status of other economies and country about GCP inspection. We can exchange information, experience, and learn a lot from FDA. We also want to improve our GCP inspection skill through this workshop
- This workshop will help to built model for GCP in my country. We just started and there are over 65 clinical trials going on right now.

- As my economy has no procedure yet in place for GCP Inspection. This workshop gives a great opportunity for me to learn about the elements that are involved that shall be shared with the relevant officers involved in GCP
- From this project, I gain a lot of knowledge or information about GCP inspection from the USFDA speaker and also from other participated economies and country. I also can share an experience in GCP Inspection with others.
- The project can increase number of global clinical trials, which be conducted in my economy and the project can in crease our division
- It enhances our knowledge on how to conduct Clinical Trial Inspection. Although we are not inspecting clinical trials right now but it will be useful since our agency is planning to regulate clinical trials
- With the knowledge, technique, and skill that I have strengthened, I can be an effective member of BA/BE inspection team, particularly on GCP compliance.
- We can ensure that our organization will follow and conform with internationally recognized guidelines.
- GCP Inspection improves the quality of Clinical Trials.
- I already got knowledge in GCP inspection and GCP related matters and I will generate them with my colleague

Question (b):What new skills, knowledge, or value have you gained?

- How to inspect a clinical trial for Good Clinical Practice compliance by learning from theory and practice exercises (hand-on skills)
- The workshop provided a comprehensive knowledge about elements involved in GCP e.g. key activities, how to develop procedures related to it, etc
- How to review clinical trial data that has been presented during the inspection
- GCP Inspection of Ethic Committee
- The visit to the trial site was also a new and informative experience, where I was able to obtain a clearer picture of what is involved in a GCP inspection of Clinical Trial site.
- Everything needs to have a law or regulation, if you want to put penalty on either CI or sponsor
- Sharing experiences has given us ideas on how we can develop or improve our system

- About sequences in inspection that starting from the beginning of the inspection, Often I missed this activity due to limited time we had but now I realize that it is the important activity that should be done
- Knowledge about other economies' systems and particularly US system, activity protocol of IEC and IRB, activities of clinical trials, GCP inspection
- Knowledge of International guidelines & regulations being implemented enforced by the USFDA and other regulatory agencies in the APEC region
- Learned inspector's view of clinical trial and responsibilities of involving parties in clinical trials
- Review the principle of Good Clinical Practice and key responsibilities
- Other economies' strategies and challenges
- Qualification of an inspector

Question (c): What, if any, changes do you plan to pursue in your home economy as a result of the project?

- Set up IND-like process
- Set up and improve GCP inspection system for both clinical trial and BE study
- Develop a plan for reviewing all documents and procedures of clinical trials and GCP in order to improve the system
- Establish guidelines and SOPs with regard to GCP Inspection
- Assist in the formulation of policies to adopt the internationally recognized ICH GCP guideline
- Strengthen my economy's current inspection team for BABE center by giving feedback in the proceedings of this 4 day workshop
- Move all activities of GCP and clinical trial to our drug regulatory agency of Ministry of Health (Currently, belongs to the Department of Training and Sciences)
- Regulate clinical trials conducted by different organization.
- Draft an administrative order to regulate clinical trial sites and studies
- Share the knowledge gained from the workshop with members of the regulatory authorities
- Build GCP model and start training and education for all parties involve.
- Reconsider current GCP inspection procedure and how to make the inspection become more efficient

Question (d):What needs to be done next? How should the project be built upon?

- Next steps
    - Cooperation of GCP inspection among APEC economies
    - Need to continue the project with advanced workshop in GCP inspection
    - Improve the regulation for GCP inspection
    - Improve SOP's for GCP Inspection
    - Increase our capacity building
    - Draft an Administrative Order(guideline) in continuous training
    - Should include the authority of inspection and penalty for non-compliance to GCP
    - More capacity building type projects
- The next project should provide
    - How to evaluate the report
    - Hands-on training and more focus on inspection process
    - How to form training in each economy
    - Provision of examples of more technical documents involved in GCP e.g. evaluation of forms would be more informative
    - More exercises on evaluation of a case study with respect to GCP inspection
    - Mock inspection
    - Inspection report writing
    - Evaluation of Lab results
    - Appropriate objective of protocol, end point, and data management
    - More details, case studies, and discussions
    - Practice the inspection skill

Question (e): Is there any plan to link the project s outcomes to subsequent collective actions by fora or individual actions by economies?

- To harmonize among APEC region
- To formulate policies
- To strengthen staff
- Each economy's government need to support the GCP and clinical trial regulatory system
- To share information and experience in the region and among my colleagues
- To establish clinical trial inspection system my economy

Question (f): Please use the same scale to rate the project on an overall basis.

- [5] (good) : 15 (88%)
- [4] : 2 (12%)
- [3] : 0
- [2] : 0
- [1] (poor) : 0

Question (g):What is your assessment of the overall effectiveness of the project?

- It's very useful for all participant especially for beginners on GCP inspection area
- Very good and well found workshop with regards to GCP inspection
- For people who attended this workshop, especially to those, who are relatively new in the area of GCP inspection and clinical trial monitoring, the project help to strengthen the current knowledge, techniques, and skills in clinical research inspection
- Very effective since the project in basic workshop on Good Clinical Practice (GCP)/ Clinical Research Inspection and almost all of the participating economies do not regulate and do not have any regulations regarding the project
- Sharing information among participants from other economies/regulators
- The presentations provide very useful knowledge
- For the overall, this project is very good to improve my skill in GCP inspection
- Very efficient and friendly
- It is beneficial to all participants, especially for economies, which are on the way of building up GCP

Question (h):Was the project content: (Check One):

- Just Right (14)
- Too Detailed (1)
- Not Detailed Enough (2)
- N/A(0)

Question (i): Please provide any additional comments. How to improve the project, if any?

- Need more exercises and examples
- More time per topic
- Excellent lectures, topics and presentations
- Support the advanced course to improve the effectiveness of this project
- Support more consultants

- Need more open discussion based on case study in order to learn in practice
- This workshop should be conducted every year
- More in-depth theoretical exercise on case examples as well as mock inspection at the clinical trial site and ethical committees
- Provide evaluation forms that are related to the inspection e.g. checklists, etc.
- More examples and discussions on common issues encountered during GCP Inspection
- I would like to learn how to prepare draft plan for an inspection with examples produced
- The role of technology in improving investigational system

Part B for Speakers

Number of respondents was 2 among 2 speakers.

(a): Do you think the project achieved its objectives? What were the project's results/achievements?

- The project achieved its objectives
- Interactive, instruction in conducting clinical research (GCP) inspections to improve the quality of research in APEC underlying the development and marketing of medicine (pharmaceutical) products
- Good discussions among participants about what is necessary for quality GCP inspections—Many only thinking of initiating, so learning from experiences of others

(b): Were the attendees the most appropriate target group?

- The attendees were the most appropriate target group
- Regulators involved in the review of clinical trials and applications for product marketing based on clinical trials

(c): What is your assessment of the overall effectiveness of the project?

- Highly effective juding by the :
    - Number of economies represented
    - Level of participant discussion
    - Nature and breadth of questions asked / issues discussed
    - Commitment to move forward with systems for GCP inspection by economies that currently lack such systems

- From active discussion and cross discussion during workshop appears all participating considering what are the essential elements of a quality GCP inspection program – Just what wanted to promote

(d): Was there any room for improving the project? If so, how?

- Always room to tweak details but general content seems appropriate as presented
- English Language comprehension in some technical areas
- Therefore the possible advantage of translation/ translators for some participants

(e): Any other suggestions?

- Make advanced course truly hands-on and ensure most, if not all of participants from this course are the attendees