APEC LSIF Project "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)"

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

Court yard by Marriott Hotel, Bangkok, 2-6 March 2009

REPORT

by thitiphoto.multiply.com

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APEC Asia-Pacific Economic Cooperation

Thai Food and Drug Administration

Part I.

GENERAL INFORMATION

Project Background

Thailand by Thai Food and Drug Administration, Ministry of Public Health, proposed the APEC Project CTI36/2008T or "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)" for the year 2008-2009. This project is the second project providing continuing training activities after the first project or CTI24/2007T (2007-2008)

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 It means that if the product has shown life threatening adverse effects, it would be withdrawn from the market regardless of how much the company invested in research, development or even marketing of the product.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.

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

Workshop Information

The Advanced Workshop on GCP/ Clinical Research Inspection is the second workshop conducted under the APEC Project CTI36/2008T. Its curriculum was designed to cover advanced topics after the "Basic Workshop" that was conducted on 27-30 May 2008 under the prior APEC Project CTI24/2007T.

It has been more than a year for the planning stage. US FDA and Thai FDA designed the first draft agenda by information taken from the basic workshop. The agenda have been adjusted and finalized later accordingly via lots of email exchanges and a teleconference call. Because the workshop format was planned to include on-site mock inspection exercises, Thai FDA approached many research hospitals and leading pharmaceutical companies in Bangkok. We had received favorable responses from Chulalongkorn Hospital, Ramathibodi Hospital, HIV Natherlands Australia Thailand Research Collaboration, Siriraj Hospital, Tropical Meidcine Hospital, Roche (Thailand) Co, Ltd., GlaxoSmithKline (Thailand) Co, Ltd., and MSD (Thailand) Co, Ltd. Therefore, we were finally able to identify 5 different clinical research studies and 1 bioequivalence study for the mock inspection exercises. In term of facilitators, beyond the lead facilitators from US FDA, additional facilitators were from public sector i.e. Health Canada and US FDA, and from private sector i.e. Roche Products Limited, GlaxoSmithKline R&D, Merck and Co. ,inc. Our 7 facilitators played important roles as lecturers for classes and mentors for the small group inspection exercises.

Thai Food and Drug Administration hosted the advanced workshop in Bangkok on 2-6 March 2009. 7 facilitators, 27 participants, and 3 observers are from 15 different APEC economies and countries i.e. Brunei, Canada, Chile, Indonesia, Korea, Malaysia, Peru, Philippines, Singapore, Chinese Taipei, Thailand, United States, Viet Nam, Saudi Arabia, and United Kingdom. The facilitators are from both public and private sectors i.e. US Food and Drug Administration, Health Canada, GlaxoSmithKline R&D, Merck and Co, inc. and Roche Products Limited. The participants are all drug regulatory agencies' officials.

The workshop provided training presentations, case studies, exercises, experience sharing and discussion opportunities according to clinical research and bioequivalence study inspection. The main topics were "Review of Basic GCP and the Elements of a GCP

Inspection", "Basic Concepts in Bioequivalence (BE)", "Clinical and Analytical Components of a BE Inspection", and "On-Site Mock Clinical Investigator Inspection".

The participants of this workshop also had opportunities to present and exchange updates on clinical trial regulations of their economies and country, and discuss the gaps and challenges for implementation as well as suggestion for future cooperation.

Opening and Welcome Speech

Mrs Werawan Tangkeo

The Deputy Secretary General of Thai Food and Drug Administration

@ The Courtyard by Marriot Hotel, Bangkok

2-6 March 2009

Dr David Lepay, US FDA Senior Advisor for Clinical Science

Dr Martin Yau , Pharmacologist, Office of Compliance, CDER, US FDA

Dr Gerald McGirl, National Expert, Bioresearch Monitoring, Division of Field Investigations, USFDA

Ms Alicja Kasina, Drug Specialist, Inspectorate, Health Canada

Dr Beat Widler, Global Head of PDQ, Roche Products Limited

Ms Joanne North, Director, Clinical Quality Assurance Asia Pacific, Japan and Emerging Markets, GlaxoSmithKline R&D

Ms Larvan Amornwichet, Associate Director, Worldwide Clinical Quality Assurance Resource, Merck and Co., Inc

Distinguished participants,

Ladies and Gentlemen:

It is my great pleasure, as a representative of Thai FDA, to welcome all of you for the "Advanced 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.

First of all, I would like to draw your attention to APEC, who has foreseen the important of this training course and granted the approval of the project "Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)" for the year 2008-2009. It is because APEC realizes that the difference in regulatory practices exists across APEC member economies, even though we have adopted the same ICH GCP standard. APEC hopes that this project could somehow narrow down the gap and lead the way to harmonization of standards in the future.

I would like to recall you the last year workshop or the “Basic Workshop on Clinical Research Inspection” from 27-30 May 2008. That workshop had already trained 24 regulators from 10 difference economies and country to learn the principles of clinical research inspection from 2 US FDA experts. It had been an effective kick-off training course, which provided both theoretical and practical knowledge from lecture series, mock inspection exercise and clinical trial site visit. Furthermore, at the end of the workshop, participants had opportunities to brainstorm for the new topics to be included in the advanced workshop.

The second or advanced workshop has been planned by our lead facilitators from US FDA and suggested by our colleagues. It includes the Review of the basic workshop and GCP Inspection, the Basic Concepts in Bioequivalence, the Clinical and Analytical Components of a BE Inspection, and, the last but not least, the “On-Site Mock Clinical Investigator Inspection”. This workshop starting from today to 6 March is attended by 7 facilitators from leading regulatory agencies and industries, and 27 participants from 12 different economies and country, those are Brunei, Chile, Indonesia, Korea, Malaysia, Peru, Philippines, Singapore, Chinese Taipei, Thailand, Viet Nam, and Saudi Arabia.

This workshop has been warmly supported by numbers of parties; those are APEC Life Sciences Innovation Forum, ICH Global Cooperation Group, ASEAN Working Group in Pharmaceutical Development, United States Food and Drug Administration, Health Canada, the HIV Natherlands Australia Thailand Research Collaboration, Chulalongkorn Hospital, Ramathibodi Hospital, Siriraj Hospital, Tropical Meidcine Hospital, Roche Products Limited, GlaxoSmithKline R&D, Merck and Co.,inc and Thai FDA. Therefore, on behalf of Thai FDA and organizing committees, I would like to take this opportunity to express my sincere thanks to them all and in particular to our facilitators. I truly appreciate your contribution. 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.

Finally, this is an opportune time to declare the official opening of the “Advanced Workshop on Good Clinical Practice (GCP)/Clinical Research Inspection” and I wish all 5 fruitful days of interesting and stimulating discussions and sharing of experiences. Also I wish you have a pleasant stay in Bangkok. I warmly welcome you all again.

Facilitators' Biographical Sketches

(1) David A. Lepay, MD, PhD

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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) Martin K. Yau, Ph.D.

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Dr, Martin K. Yau earned his Doctorate in Biopharmaceutics and Pharmacokinetics at the University of Tennessee Center for the Health Sciences under Dr. Marvin C. Meyer. He has over 25 years of professional experience in the areas of drug development, drug regulatory review, and compliance. Dr. Yau began his career at US FDA in the Division of Biopharmaceutics (currently Office of Clinical Pharmacology). As a reviewer for New Drug Applications (NDAs), his responsibilities included evaluating the results of all phase 1 clinical studies and protocol designs. After five years at US FDA, he moved to industry and joined the Burroughs Welcome Co. in Research Triangle Park, North Carolina, USA for eight years. At Burroughs Welcome Co., Dr. Yau was a senior level pharmacokineticist involved with the designs and development of phase I clinical studies. He returned to US FDA as a pharmacologist in the Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research (CDER). Dr. Yau has been involved with bioavailability, bioequivalence, and all phase I clinical study inspections from 1995 to present, and has participated in many FDA inspections in the US and internationally.

(3) Gerald N. McGirl, D.D.S.

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Dr. McGirl is the Bioresearch Monitoring National Expert for the Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, U.S. Food and Drug Administration. Prior to joining FDA in 1990, he practiced the dental specialty of periodontics in San Francisco. He specializes in inspections covering both GCPs (Clinical Investigator, Institutional Review Board, and Sponsor/Contract Research Organization/Monitor programs) and GLPs (Good Laboratory Practices program). He is a member of the international inspections group. He is also a member of the course advisory groups and faculties for FDA Clinical Bioresearch Monitoring (GCPs) and FDA Nonclinical Bioresearch Monitoring (GLPs) courses. He has given numerous GCP and GLP presentations to local, national, international, and university groups.

(4) Alicja Kasina, PhC , MSc

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Alicja received her education in Poland (MSc in Molecular Biology, Jagiellonian University) and Canada (BPharm, Dalhousie University). She has worked over 15 years in medical research in the areas of endocrinology, immunology and microbiology and is a licenced pharmacist. She joined the Public Service in 1996 where she has been active in several roles including Drug Inspector and Medical Devices Specialist for Health Canada. Currently, Alicja is a Drug Specialist with the Health Products and Food Branch Inspectorate. She has performed many inspections of clinical trials in Canada and is an active member of the Pharmaceutical Inspection Co-operation Scheme Joint Visits Programme in Europe. She is a co-author of several research papers and has given several presentations on subjects related to regulatory matters concerning health products.

(5) Beat Widler, Ph.D.

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Dr. Widler who is a Ph.D. in Microbiology has been in the Pharma industry since 1983, his experience covers Drug Regulatory Affairs and Clinical Science. In 1993 he joined the QA department of Hoffmann-La Roche and in September 1997 was appointed International Head of QA

Dr. Widler is a member in a variety of GCP working parties eg: EFPIA, DIA, EFGCP

(6) Joanne North

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Joanne North has worked in the clinical quality assurance field for GlaxoSmithKline (GSK) for approximately 12 years, having worked in both the pharmaceutical and Consumer Healthcare parts of the organisation.

She graduated in Biological Sciences and began her career in academic clinical research. She then progressed to data management, working at the contract research organisation, Parexel before joining the Glaxo company.

(7) Larvan Amornwichet, MSc, MBA

Associate Director, Worldwide Clinical Quality Assurance Resource
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Email: larvan_amornwichet@merck.com

Manage and direct the overall collaborative partners audit and assessment programs in support of Merck Research Laboratories (MRL) outsourcing activities. The collaborative partners include but not limited to: Laboratories (internal and external); Contract Research Organizations (CROs); Academic Research Organizations (AROs); Central Facilities, Research Partners, and Investigator Sites. Ensure compliance to applicable regulations (ICH-GCP, and local requirements).

Extensively involved in the drug development processes, as well as GXP regulation requirements. Provided support to many FDA regulatory inspection programs which include: Sponsor Monitored inspections for NCE applications, Pharmacovigilance inspections, and pre-approval investigator site inspections. Worked at Merck and Co., Inc. for 21 years with various responsibilities in basic research, manufacturing and clinical research areas. For 7 years prior to joining Merck, worked at Smith Kline Beecham and University of Chicago in the Epstein - Barr virus research laboratory.

Hold M.S. Microbiology, B.S. Biology, and M.B.A., Pharmaceutical Marketing. Affiliate with Drug Information Associate.

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

ADVANCED WORKSHOP ON GCP/CLINICAL RESEARCH INSPECTION
BANGKOK, THAILAND
2-6 MARCH 2009

Brunei Country Report

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Website: www.moh.gov.bn
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By:
Zanatul 'Aini H.Zainin
Pharmacist
Drug Registration Unit
Drug Administration Section
Dept. of Pharmaceutical Services

4/7/2009 1

OVERVIEW

- Background
- Regulatory Infrastructure
- Current GCP Laws and Practices
- Requirements for Ethics – IEC/IRB
- Update on Status of GCP Inspection
- Future Plans

4/7/2009 2

BACKGROUND

- DEPARTMENT OF PHARMACEUTICAL SERVICES (DPS), **MINISTRY OF HEALTH**

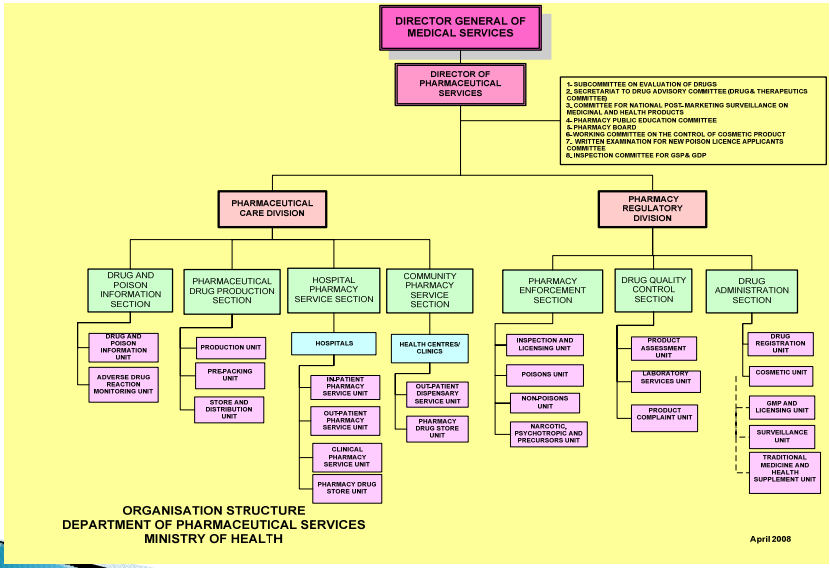
is reponsible for….

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

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

4/7/2009 3

REGULATORY INFRASTRUCTURE – *Organisation Chart*



4/7/2009 4

CURRENT GCP LAWS & PRACTICES

- The regulatory arm that is mainly involved and is responsible for executing the regulation of clinical trials and GCP inspection – *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'*

4/7/2009 5

GUIDELINES

- *Guideline for Good Clinical Practice* officially launched by Ministry of Health Brunei Darussalam (2008)
- Guideline was formulated in accordance with WHO and ICH

4/7/2009 6

REQUIREMENT FOR ETHICS – COMMITTEES (IEC/IRB)

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

4/7/2009 7

UPDATE ON STATUS OF CT/GCP INSPECTION

- No clinical trial has yet been conducted in Brunei Darussalam so far
- Thus no GCP Inspection ever conducted
- The Brunei Darussalam Medical & Health Research & Ethics Committee have the intention for the conduct of CT activities to be executed by a mix of resources

4/7/2009 8

FUTURE PLANS

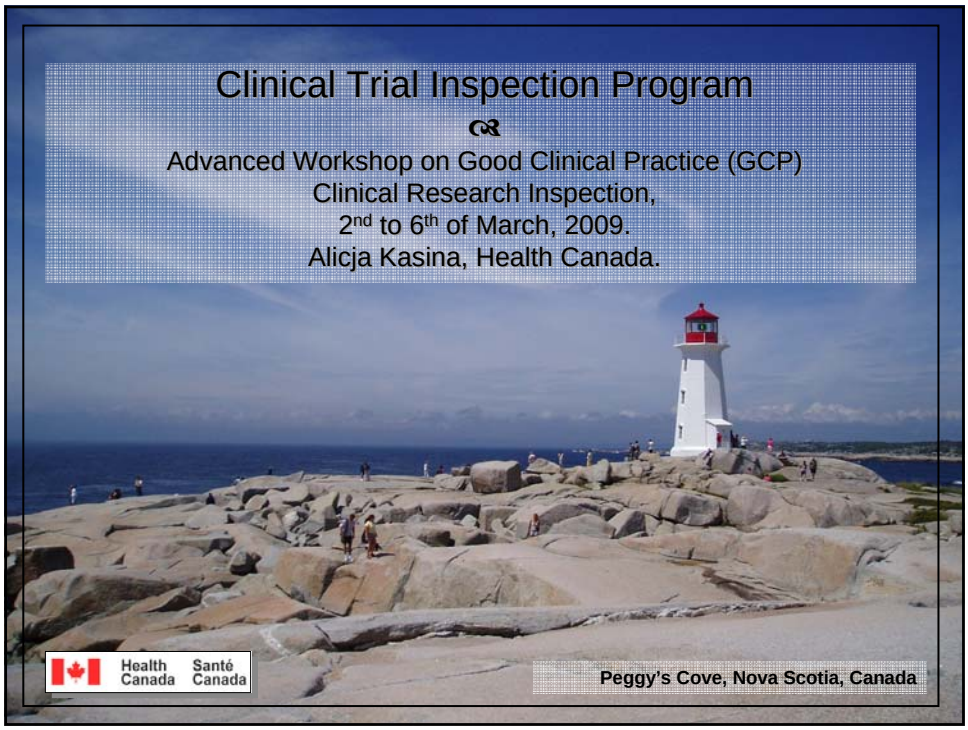
LEGISLATION

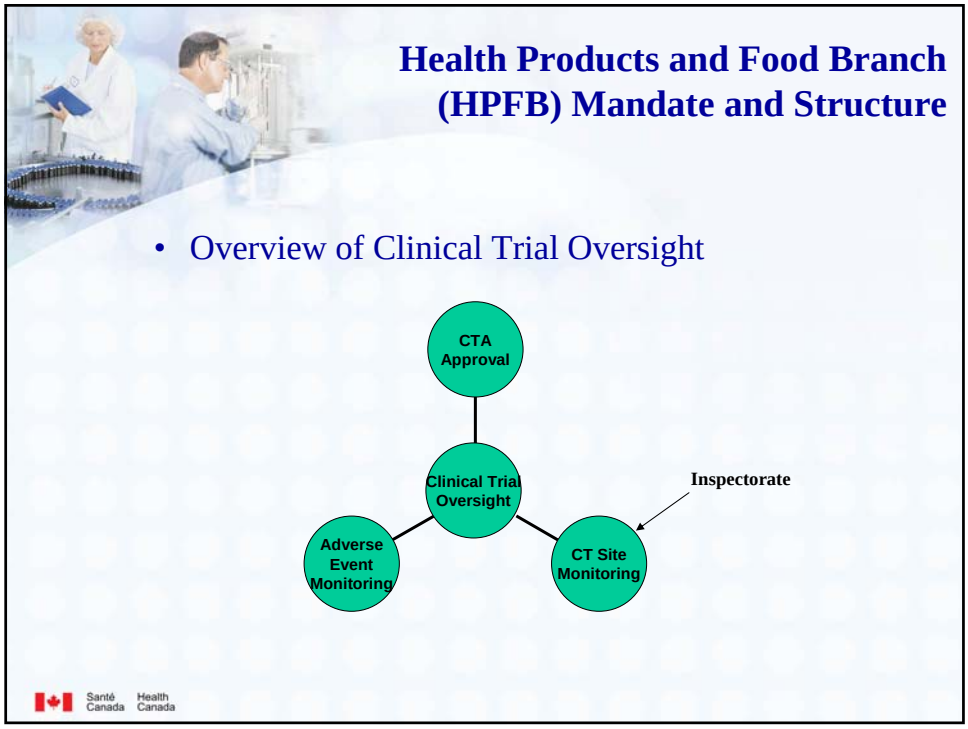
- To draft the relevant rules for GCP/Clinical Research inspection under the provisions of the Medicines Order 2007
- Reference to ICH, WHO, other relevant guides
- To regulate the conduct of clinical trials and GCP Inspection, in collaboration with the Attorney Generals Chambers.

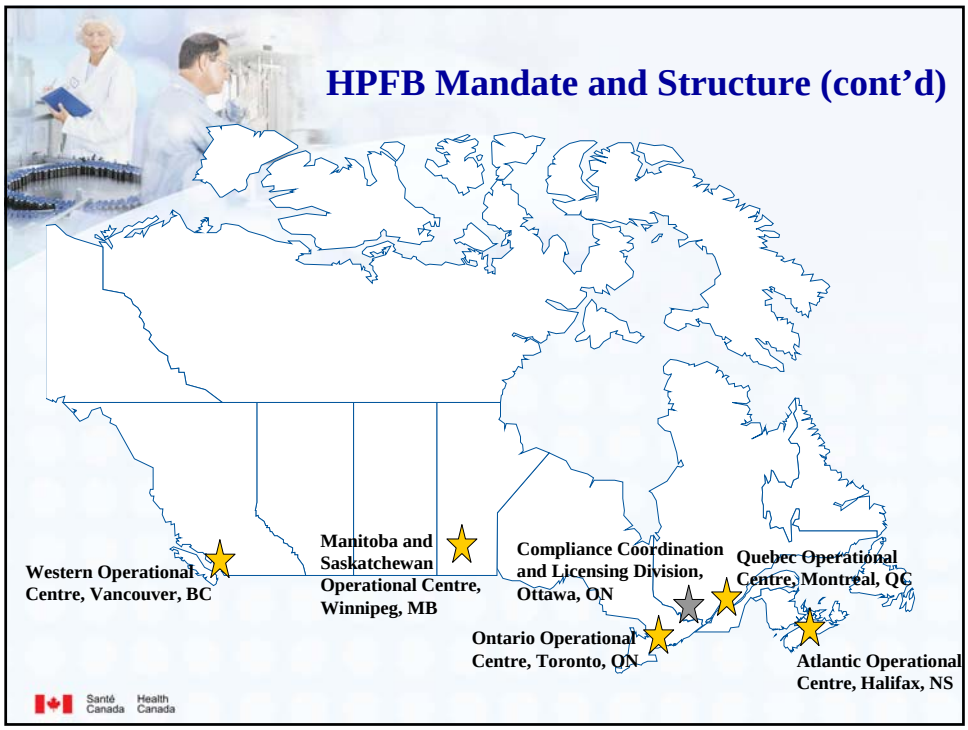
4/7/2009 9

THANK YOU

4/7/2009 10


Clinical Trial Inspection Program
Advanced Workshop on Good Clinical Practice (GCP)
Clinical Research Inspection,
2nd to 6th of March, 2009.
Alicja Kasina, Health Canada.
Health Canada Santé Canada
Peggy's Cove, Nova Scotia, Canada


Health Products and Food Branch (HPFB) Mandate and Structure
• Overview of Clinical Trial Oversight
CTA Approval
Clinical Trial Oversight
Adverse Event Monitoring
CT Site Monitoring
Inspectorate
Santé Canada Health Canada


HPFB Mandate and Structure (cont'd)
Western Operational Centre, Vancouver, BC
Manitoba and Saskatchewan Operational Centre, Winnipeg, MB
Compliance Coordination and Licensing Division, Ottawa, ON
Quebec Operational Centre, Montreal, QC
Ontario Operational Centre, Toronto, ON
Atlantic Operational Centre, Halifax, NS
Santé Canada Health Canada


Clinical Trials Regulatory Framework
• Food and Drugs Act (FDA)
• Food and Drug Regulations (FDR), Division 5 "Drugs for Clinical Trials Involving Human Subjects"
– Came into force on September 1, 2001.
– These regulations are not applicable to Medical Devices or Natural Health Products (NHPs) (other requirements apply).
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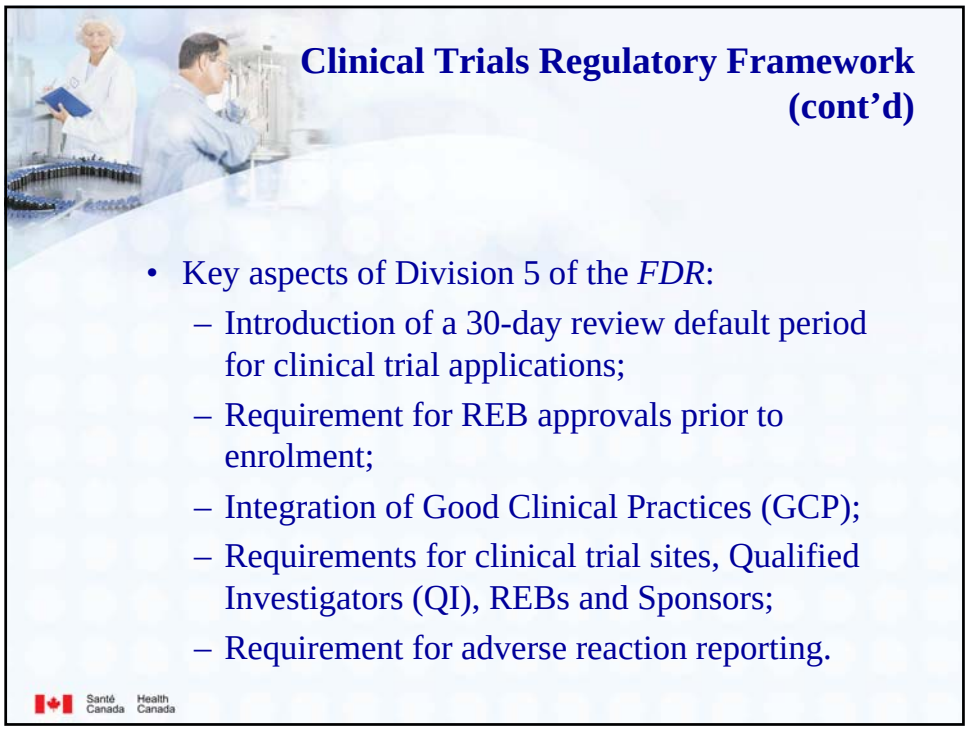
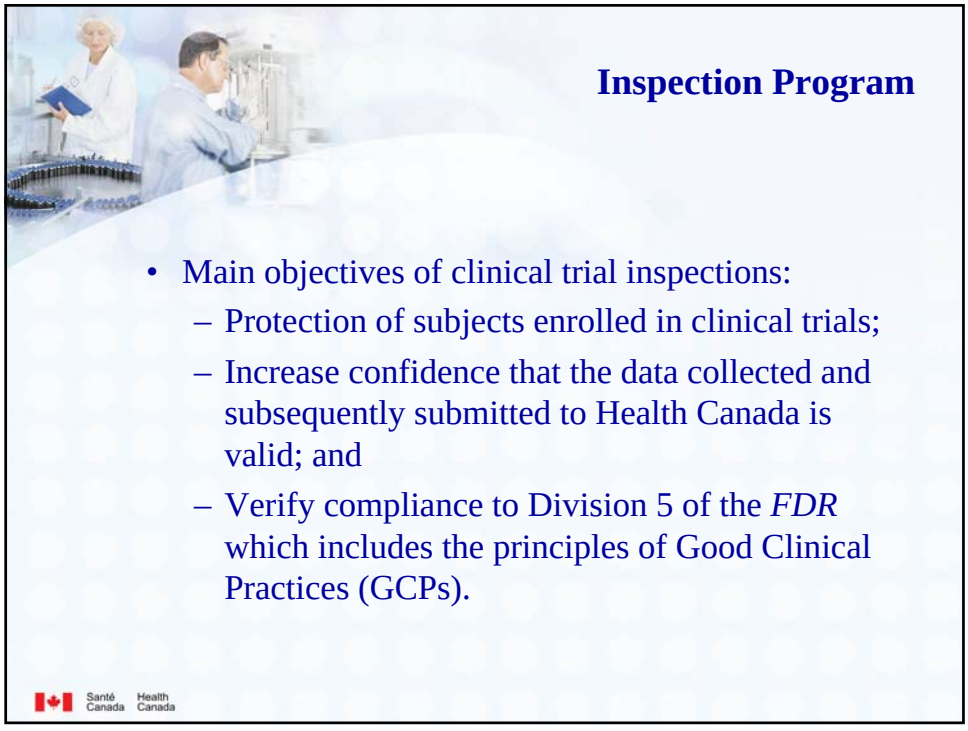
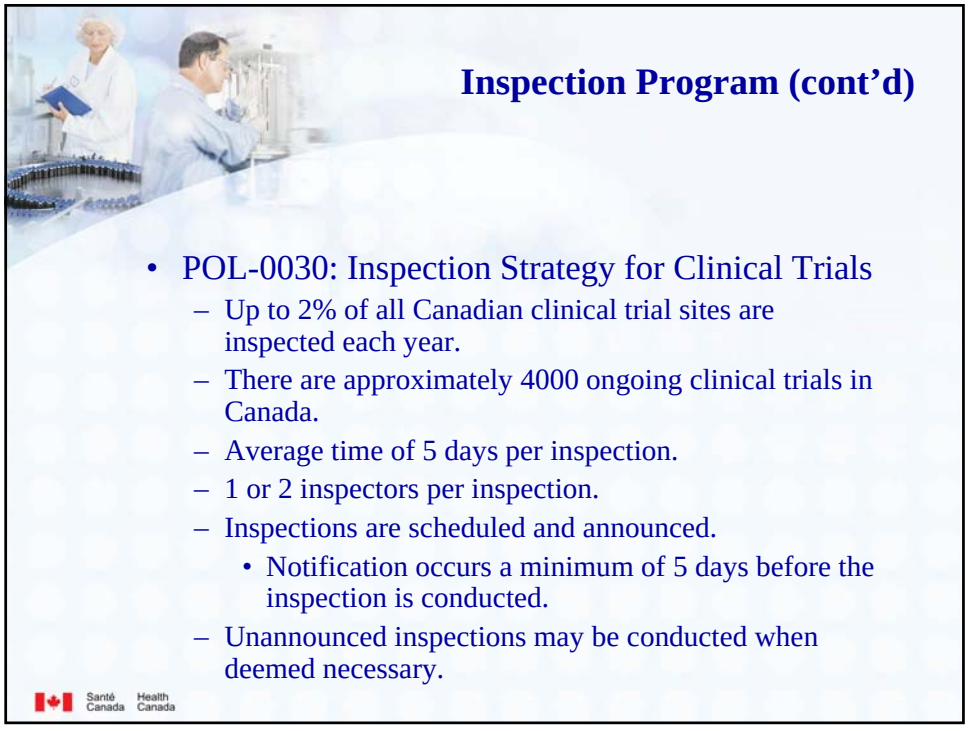
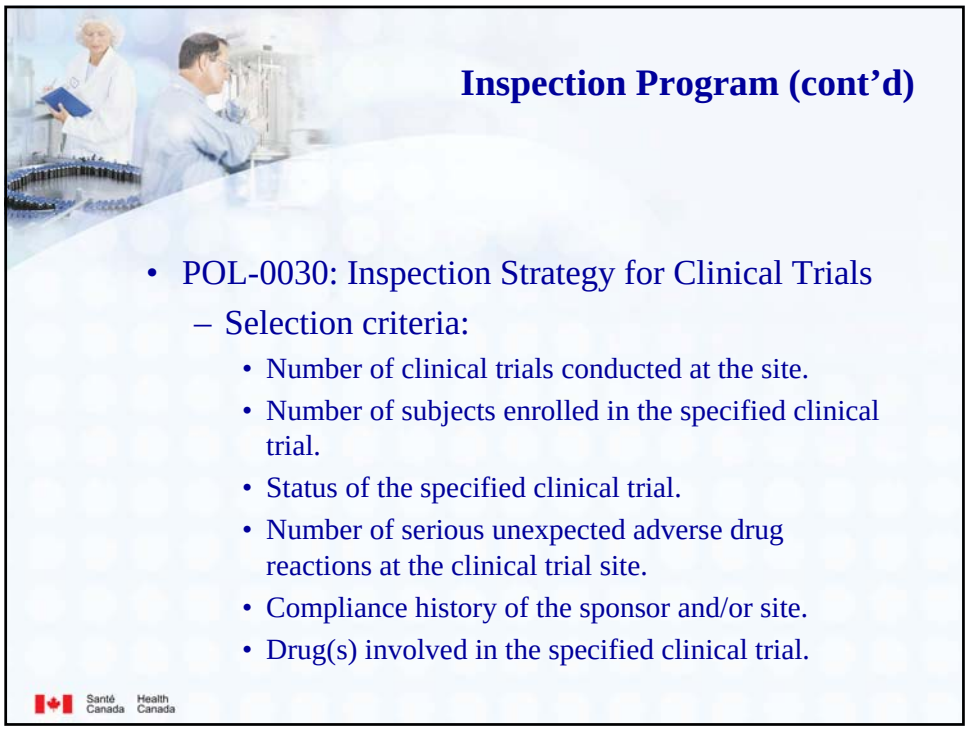

Clinical Trials Regulatory Framework (cont'd)
• Key aspects of Division 5 of the *FDR*:
– Introduction of a 30-day review default period for clinical trial applications;
– Requirement for REB approvals prior to enrolment;
– Integration of Good Clinical Practices (GCP);
– Requirements for clinical trial sites, Qualified Investigators (QI), REBs and Sponsors;
– Requirement for adverse reaction reporting.
Santé Canada Health Canada


Inspection Program
• Main objectives of clinical trial inspections:
– Protection of subjects enrolled in clinical trials;
– Increase confidence that the data collected and subsequently submitted to Health Canada is valid; and
– Verify compliance to Division 5 of the *FDR* which includes the principles of Good Clinical Practices (GCPs).
Santé Canada Health Canada


Inspection Program (cont'd)
• POL-0030: Inspection Strategy for Clinical Trials
– Conducted under the authority of section 23 of the *Food and Drugs Act*.
– Conducted at the following sites:
• Qualified Investigator (QI) site
• Sponsor
• Contract Research Organization (CRO)
• Site Management Organization (SMO)
• Research Ethics Board (REB)
Santé Canada Health Canada


Inspection Program (cont'd)
• POL-0030: Inspection Strategy for Clinical Trials
– Up to 2% of all Canadian clinical trial sites are inspected each year.
– There are approximately 4000 ongoing clinical trials in Canada.
– Average time of 5 days per inspection.
– 1 or 2 inspectors per inspection.
– Inspections are scheduled and announced.
• Notification occurs a minimum of 5 days before the inspection is conducted.
– Unannounced inspections may be conducted when deemed necessary.
Santé Canada Health Canada


Inspection Program (cont'd)
• POL-0030: Inspection Strategy for Clinical Trials
– Selection criteria:
• Number of clinical trials conducted at the site.
• Number of subjects enrolled in the specified clinical trial.
• Status of the specified clinical trial.
• Number of serious unexpected adverse drug reactions at the clinical trial site.
• Compliance history of the sponsor and/or site.
• Drug(s) involved in the specified clinical trial.
Santé Canada Health Canada


THANK YOU.
http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index-eng.php
Health Canada Santé Canada
Halifax, Nova Scotia, Canada


INSTITUTO DE SALUD PÚBLICA DE CHILE
CLINICAL RESEARCH INSPECTION
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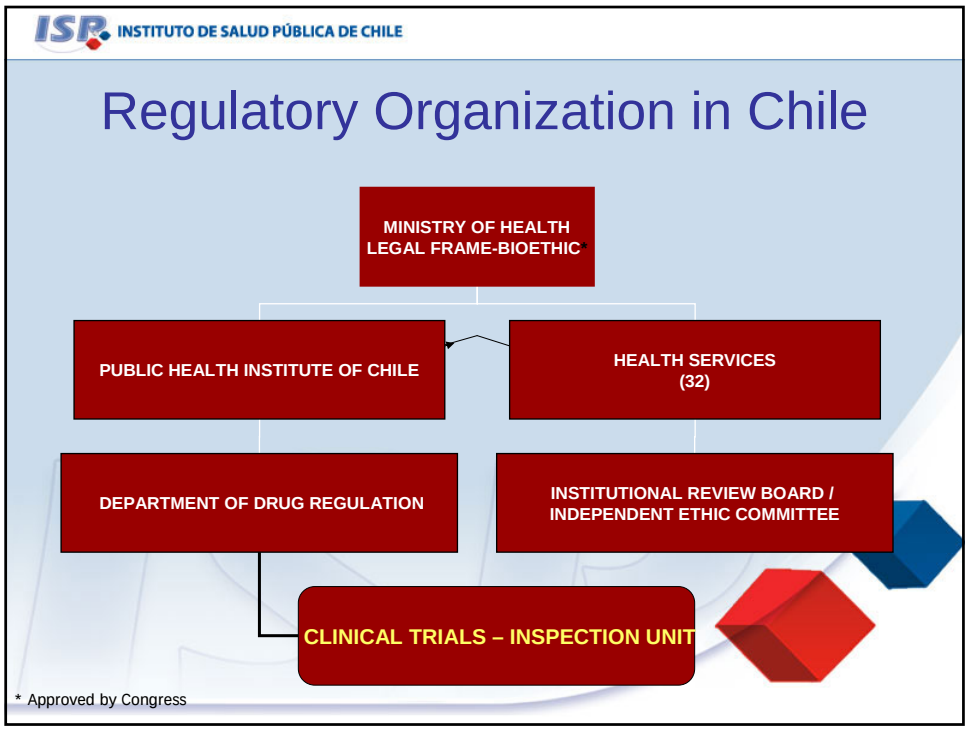
Miguel Gonzalez G . (PS)
CLINICAL TRIALS - INSPECTION


INSTITUTO DE SALUD PÚBLICA DE CHILE
Regulatory Organization in Chile
MINISTRY OF HEALTH
LEGAL FRAME-BIOETHIC *
PUBLIC HEALTH INSTITUTE OF CHILE
HEALTH SERVICES
(32)
DEPARTMENT OF DRUG REGULATION
INSTITUTIONAL REVIEW BOARD /
INDEPENDENT ETHIC COMMITTEE
CLINICAL TRIALS – INSPECTION UNIT
* Approved by Congress

INSTITUTO DE SALUD PÚBLICA DE CHILE

CHILE

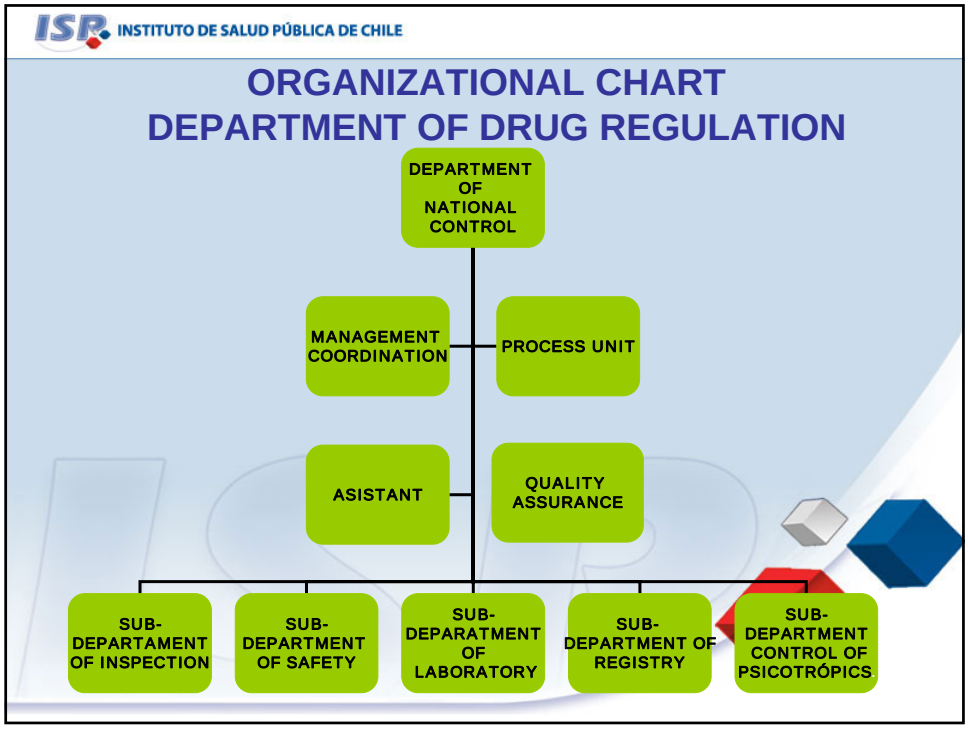
CLINICAL TRIALS -INSPECTION

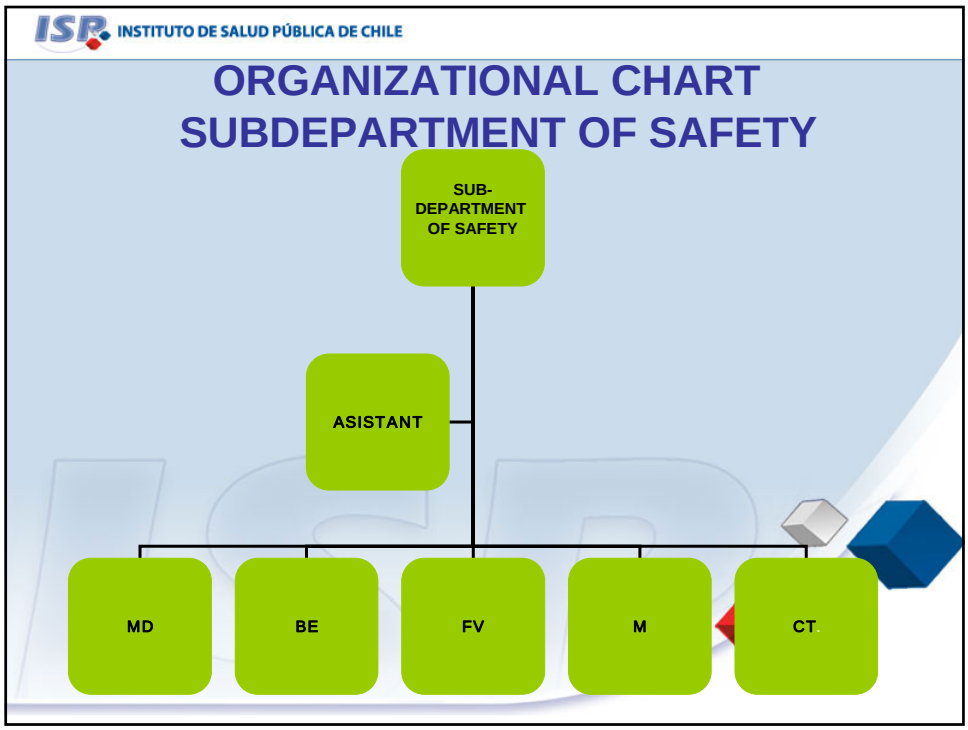
INSTITUTO DE SALUD PÚBLICA DE CHILE

MISSION

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

CLINICAL TRIALS -INSPECTION


INSTITUTO DE SALUD PÚBLICA DE CHILE
ORGANIZATIONAL CHART
DEPARTMENT OF DRUG REGULATION
DEPARTMENT OF NATIONAL CONTROL
MANAGEMENT COORDINATION
PROCESS UNIT
ASISTANT
QUALITY ASSURANCE
SUB-DEPARTAMENT OF INSPECTION
SUB-DEPARTMENT OF SAFETY
SUB-DEPARATMENT OF LABORATORY
SUB-DEPARTMENT OF REGISTRY
SUB-DEPARTMENT CONTROL OF PSICOTRÓPICS


INSTITUTO DE SALUD PÚBLICA DE CHILE
ORGANIZATIONAL CHART
SUBDEPARTMENT OF SAFETY
SUB-DEPARTMENT OF SAFETY
ASISTANT
MD
BE
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M
CT

INSTITUTO DE SALUD PÚBLICA DE CHILE

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 -2006)

CLINICAL TRIALS -INSPECTION

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 by the ISP in order to comply with the 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.

CLINICAL TRIALS -INSPECTION

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

Authority 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)

CLINICAL TRIALS -INSPECTION

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 source documents.

CLINICAL TRIALS - INSPECTION

INSTITUTO DE SALUD PÚBLICA DE CHILE

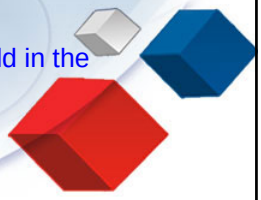
Inspections 2008

- Goals for 2008
  - 10 % of the universe of approved clinical trials 2007.
  - 15 protocol and 42 site (realized)
- Goals for 2009
  - 20 % of the universe of approved clinical trials 2008.
  - 34 protocol and 76 site (proyected)

INSTITUTO DE SALUD PÚBLICA DE CHILE

Finds in inspections

- They do not present express authorization of the director of the center, since it the Law demands 20.120, Art. 10.
- The centers declared in the request and authorized in the resolution do not agree with the sites..
- Product of investigation stored in refrigerator that is not designed for such a use and shared with other products.
- Without program of maintenance not even procedures opposite to cuts of electric power.
- Not have SOPs the maintenance of the chain of cold in the movement of the product of investigation.



INSTITUTO DE SALUD PÚBLICA DE CHILE

Finds in inspections

- **Not suitable personnel for the managing, administration and dispensation of the product of investigation.**
- **Form designed for the accounting of the product of investigation does not allow to determine the quantity used in every site.**
- **Laboratory examinations and others needed by protocol without record of having being evaluated by principal or representative investigator.**
- **There are no procedures written on medical emergencies.**
- **Implementation for medical emergencies deficient and in some cases with losing medication.**
- **There is no formal training in Good Clinical Practices of the investigator and your team.**

INSTITUTO DE SALUD PÚBLICA DE CHILE

Finds in inspections

- Does not exist document that credits the identity and age of the subjects.
- Incomplete Curricula of investigators and team: without certificate of title, without certificate of speciality, in addition without signature and differing dates.
- There is no record on the procedure of enrolamiento of the subjects: from where they are derived, for medical consultation or only to take part in the study.
- In the review of the medical evolution of the subject the differentiation is impeded between(among) records of welfare practice by the procedures of the study.

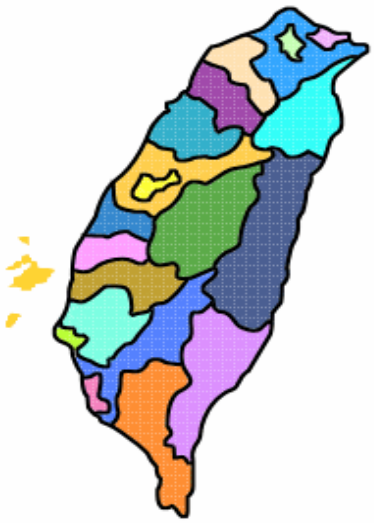

ISP
INSTITUTO DE SALUD PÚBLICA DE CHILE

Updates on Status of GCP Inspection in Chinese Taipei

Chao-Yi Wang
Bureau of Pharmaceutical Affairs,
Department of Health, Chinese Taipei
March 2, 2009

Chinese Taipei - Geographic features

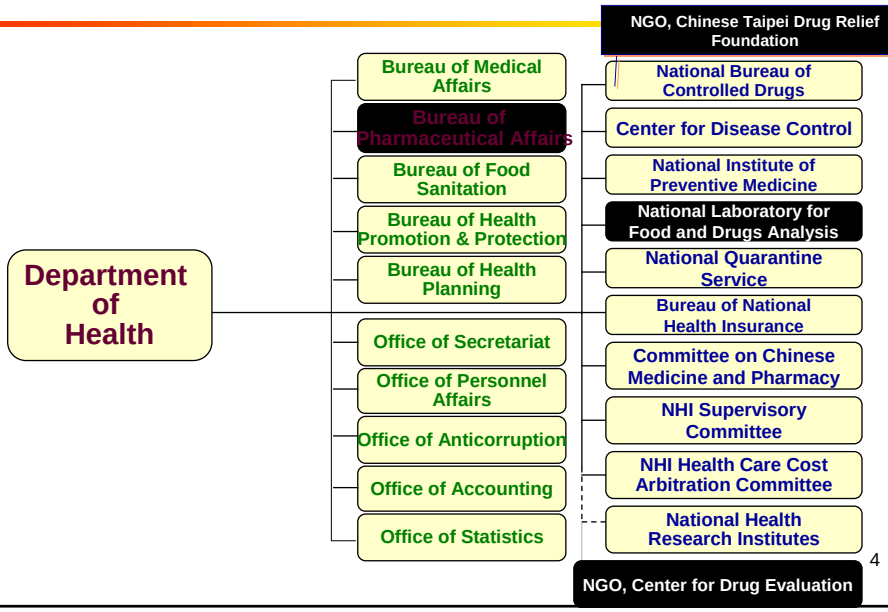
- **Geographic features**
  - **South-eastern coast of Asia**
  - **Total area of 36,179 sq. km**
  - **Population of 23 millions**



DOH's Core Missions

- ✓Advocator of Health for All
- ✓Educator of Healthy Lifestyle
- ✓Promoter of Healthcare Industries
- ✓Participant of International Health Activities

Current Organization of the Department of Health (DOH)



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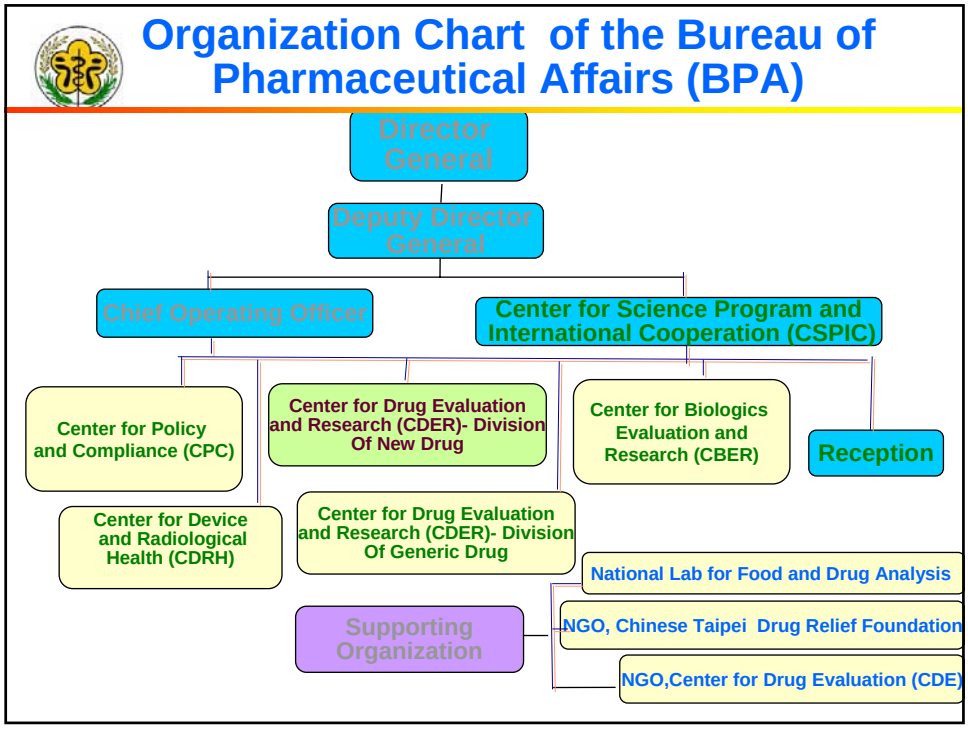
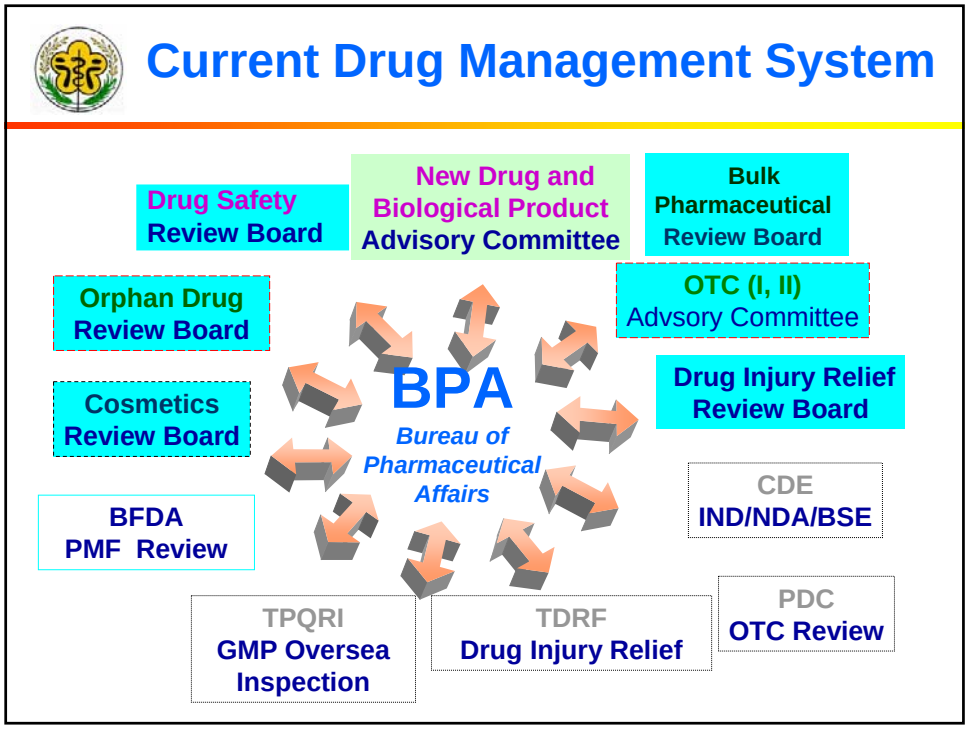
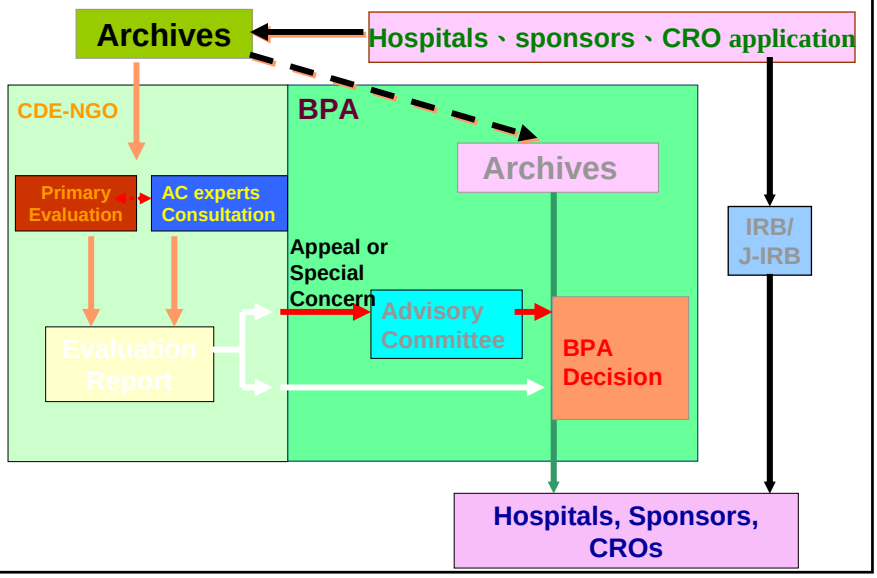

Organization Chart of the Bureau of Pharmaceutical Affairs (BPA)
Director General
Deputy Director General
Chief Operating Officer
Center for Science Program and International Cooperation (CSPIC)
Center for Policy and Compliance (CPC)
Center for Drug Evaluation and Research (CDER)- Division Of New Drug
Center for Biologics Evaluation and Research (CBER)
Reception
Center for Device and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)- Division Of Generic Drug
National Lab for Food and Drug Analysis
Supporting Organization
NGO, Chinese Taipei Drug Relief Foundation
NGO,Center for Drug Evaluation (CDE)


Current Drug Management System
Drug Safety Review Board
New Drug and Biological Product Advisory Committee
Bulk Pharmaceutical Review Board
Orphan Drug Review Board
OTC (I, II) Advsory Committee
Cosmetics Review Board
BPA
Bureau of Pharmaceutical Affairs
Drug Injury Relief Review Board
BFDA PMF Review
CDE IND/NDA/BSE
TPQRI GMP Oversea Inspection
TDRF Drug Injury Relief
PDC OTC Review

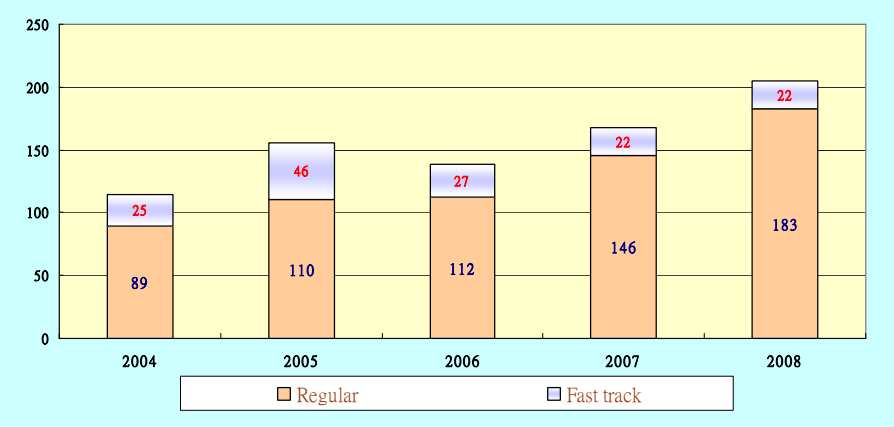
GCP Laws/Regulations

- 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



IND Application (2004-2008)



Distribution of CT Phases (2004-2008)

	2004		2005		2006		2007		2008	
	P	S	P	S	P	S	P	S	P	S
Phase I	8	12	14	26	12	20	10	18	11	14
Phase II	22	57	33	78	32	98	46	158	46	120
Phase III	85	237	69	242	86	300	106	391	132	527
Phase IV	4	10	4	5	3	4	6	14	16	21
Total	119	316	120	351	133	422	168	581	205	682

P: protocol S: site

IND type analysis (2004 - 2008)

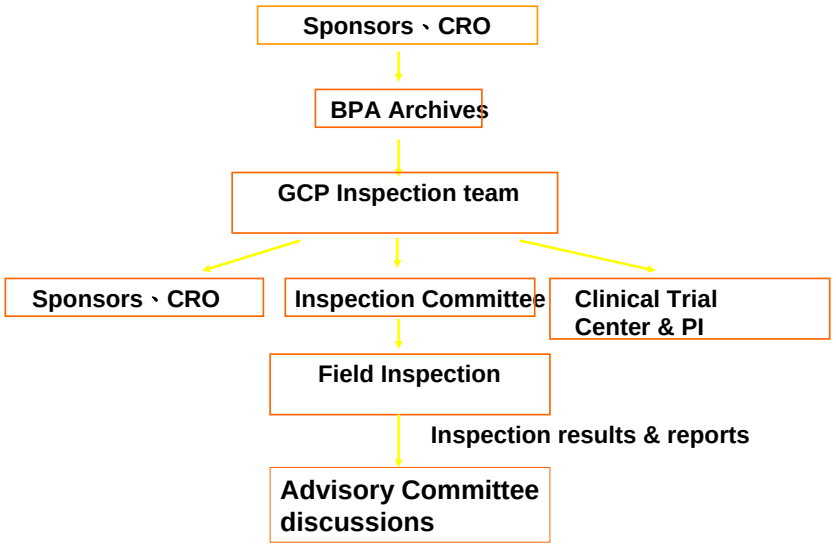
	2004		2005		2006		2007		2008	
	P	S	P	S	P	S	P	S	P	S
TW single site	32	32	24	24	11	11	21	21	34	34
TW multiple sites	25	88	10	43	22	74	20	81	16	49
MN trials	62	196	86	284	100	337	127	479	155	599
% of MN trials, P	52.1%		71.7%		75%		75.6%		75.6%	
Total	119	316	120	351	133	422	168	581	205	682

P: Protocol, S: Sites

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
- Serious Adverse Event Reporting during Clinical Trial
- GCP Inspection

Review process for Clinical Trial Report



Statistics for Clinical Trial Reports (2002-2008)

Year	2002	2003	2004	2005	2006	2007	2008
Inspection cases	37	47	36	34	38	23	23
Disapproval Reports	4	4	5	2	2	0	4
Disapproval rate	11%	9%	14%	6%	5.2%	0%	17.4%

Clinical Trials Network in Chinese Taipei

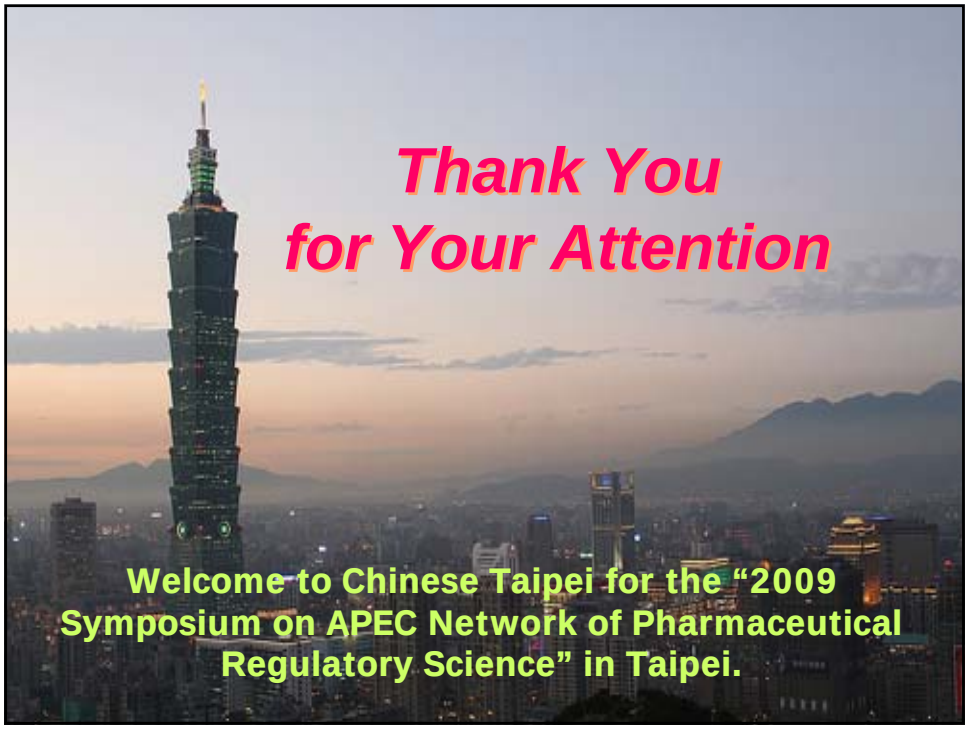
http://www.cde.org.tw/ct_taiwan/index.htm

BA/BE Inspection

- Routine Inspection
  - Every Two Year
  - Observational Report
- For Cause Inspection

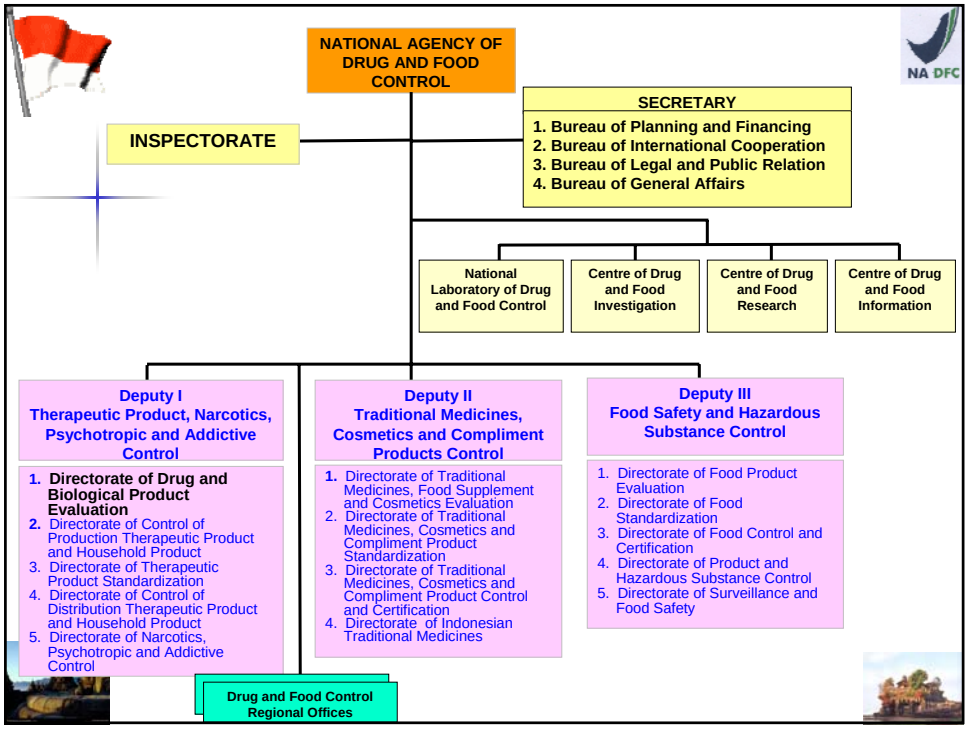
FutureA Plan

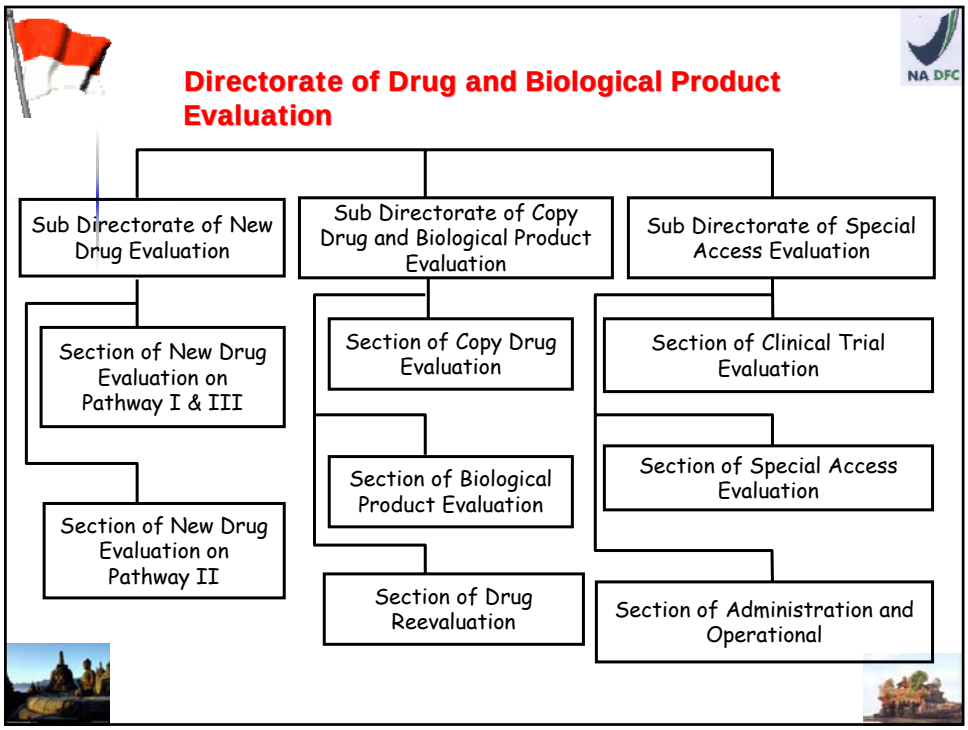
- Foreign Country Inspection
- Put more efforts on for Cause Inspection
- Training Workshop
  - Clinical Trial
  - GCP Inspection
  - BA/BE
- Strengthen the SAE Reporting

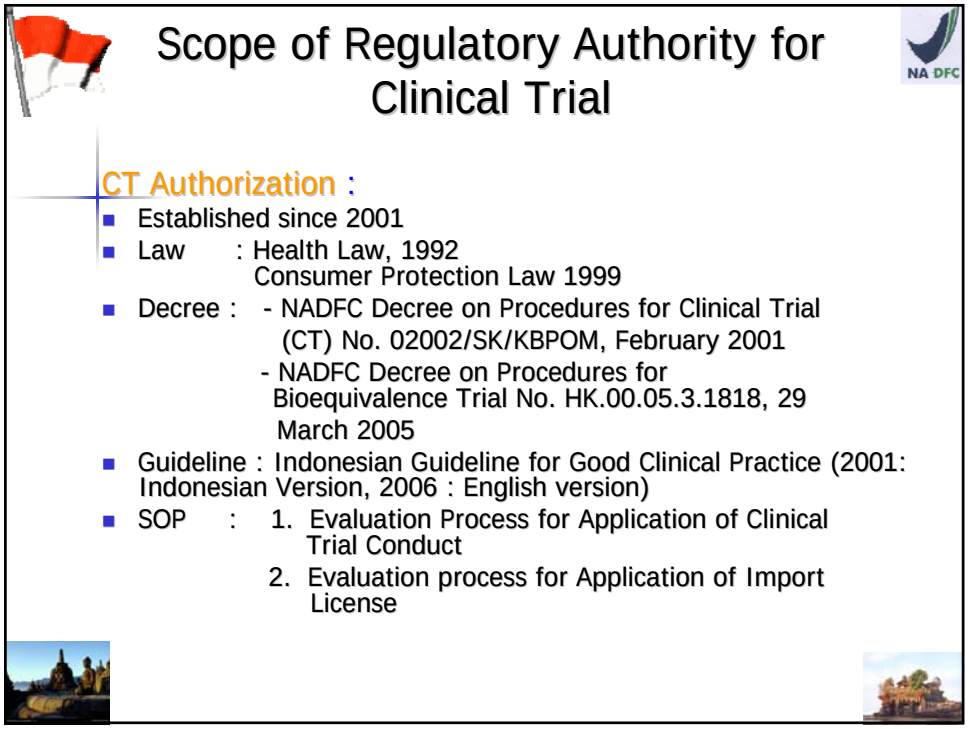


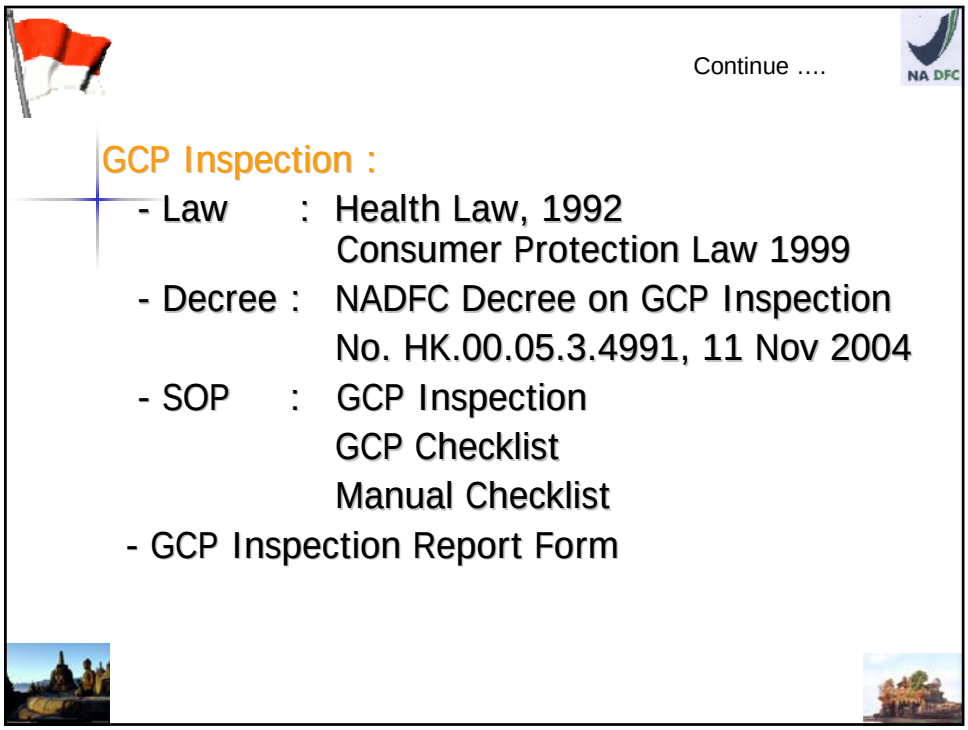
Current GCP in Indonesia

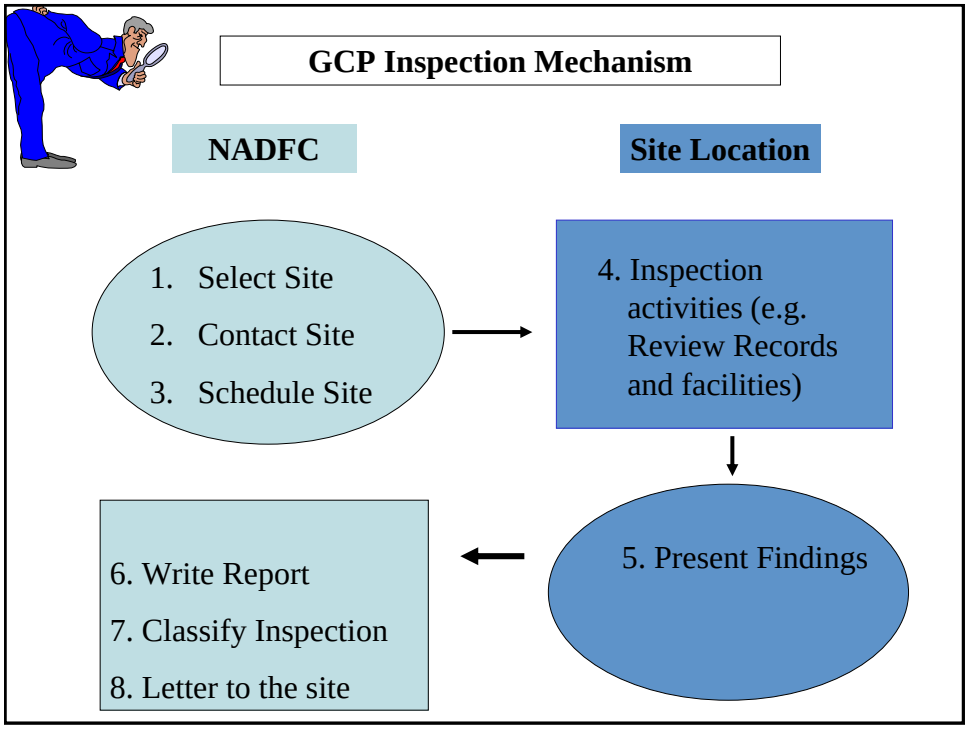
Bangkok, 2 – 6 March 2009

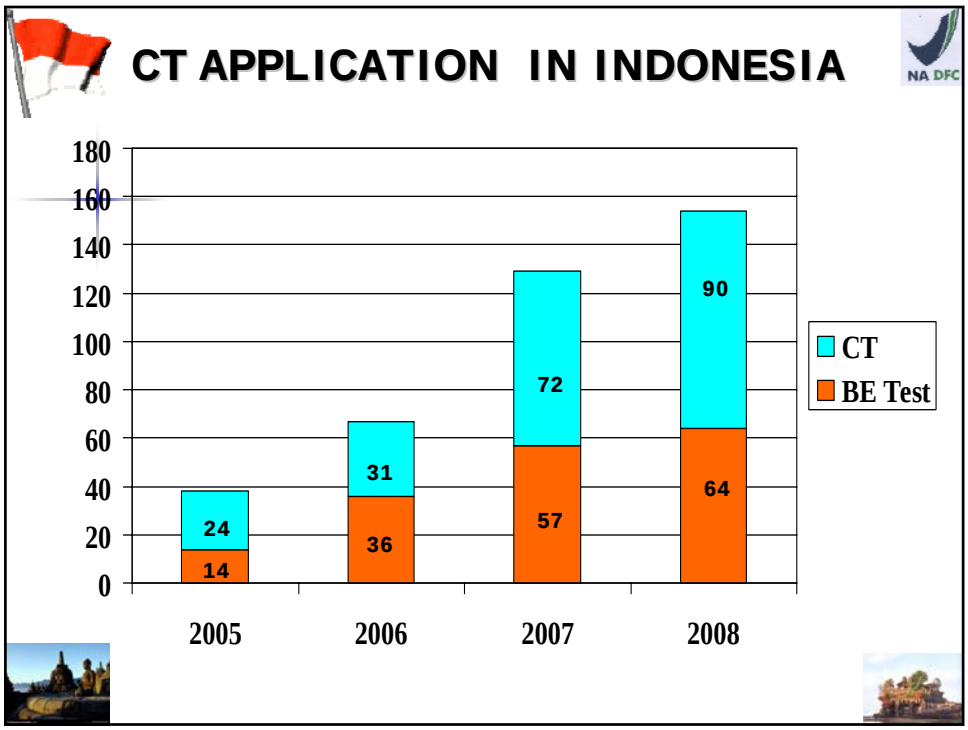


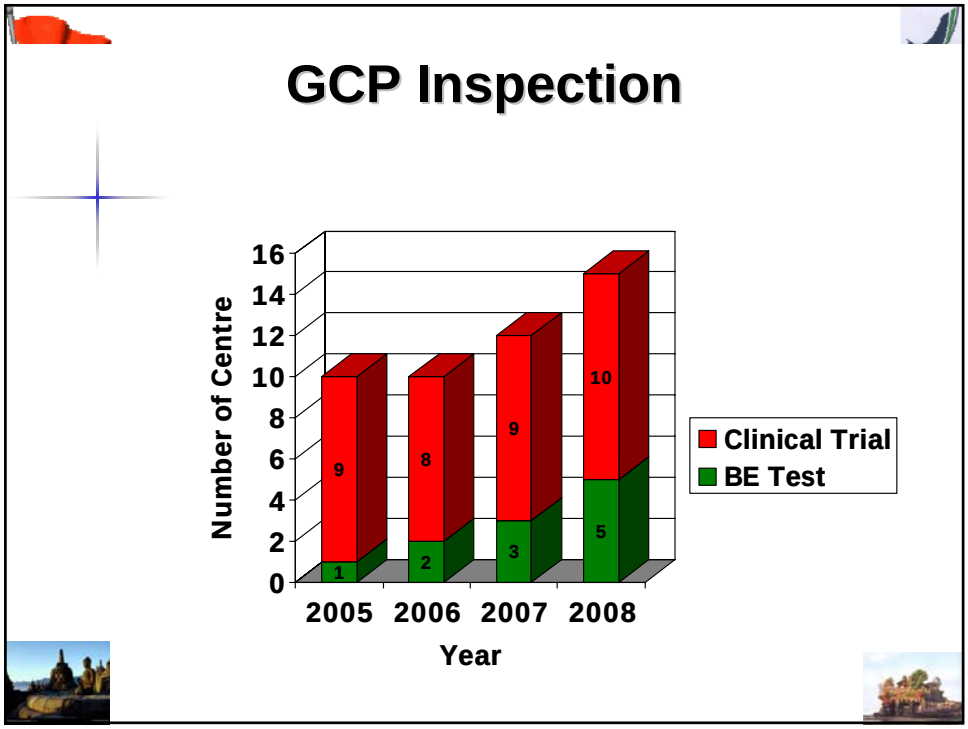

Directorate of Drug and Biological Product Evaluation
NA DFC
Sub Directorate of New Drug Evaluation
Sub Directorate of Copy Drug and Biological Product Evaluation
Sub Directorate of Special Access Evaluation
Section of New Drug Evaluation on Pathway I & III
Section of New Drug Evaluation on Pathway II
Section of Copy Drug Evaluation
Section of Biological Product Evaluation
Section of Drug Reevaluation
Section of Clinical Trial Evaluation
Section of Special Access Evaluation
Section of Administration and Operational


Scope of Regulatory Authority for Clinical Trial
NA DFC
CT Authorization :
Established since 2001
Law : Health Law, 1992
Consumer Protection Law 1999
Decree : - NADFC Decree on Procedures for Clinical Trial (CT) No. 02002/SK/KBPOM, February 2001
- NADFC Decree on Procedures for Bioequivalence Trial No. HK.00.05.3.1818, 29 March 2005
Guideline : Indonesian Guideline for Good Clinical Practice (2001: Indonesian Version, 2006 : English version)
SOP : 1. Evaluation Process for Application of Clinical Trial Conduct
2. Evaluation process for Application of Import License


Continue ….
NA DFC
GCP Inspection :
- Law : Health Law, 1992
Consumer Protection Law 1999
- Decree : NADFC Decree on GCP Inspection
No. HK.00.05.3.4991, 11 Nov 2004
- SOP : GCP Inspection
GCP Checklist
Manual Checklist
- GCP Inspection Report Form


GCP Inspection Mechanism
NADFC
Site Location
1. Select Site
2. Contact Site
3. Schedule Site
4. Inspection activities (e.g. Review Records and facilities)
5. Present Findings
6. Write Report
7. Classify Inspection
8. Letter to the site


CT APPLICATION IN INDONESIA
NA DFC
180
160
140
120
100
80
60
40
20
0
24
14
31
36
72
57
90
64
2005
2006
2007
2008
CT
BE Test


GCP Inspection
Number of Centre
16
14
12
10
8
6
4
2
0
9
1
8
2
9
3
10
5
2005
2006
2007
2008
Year
Clinical Trial
BE Test

Future Challenges

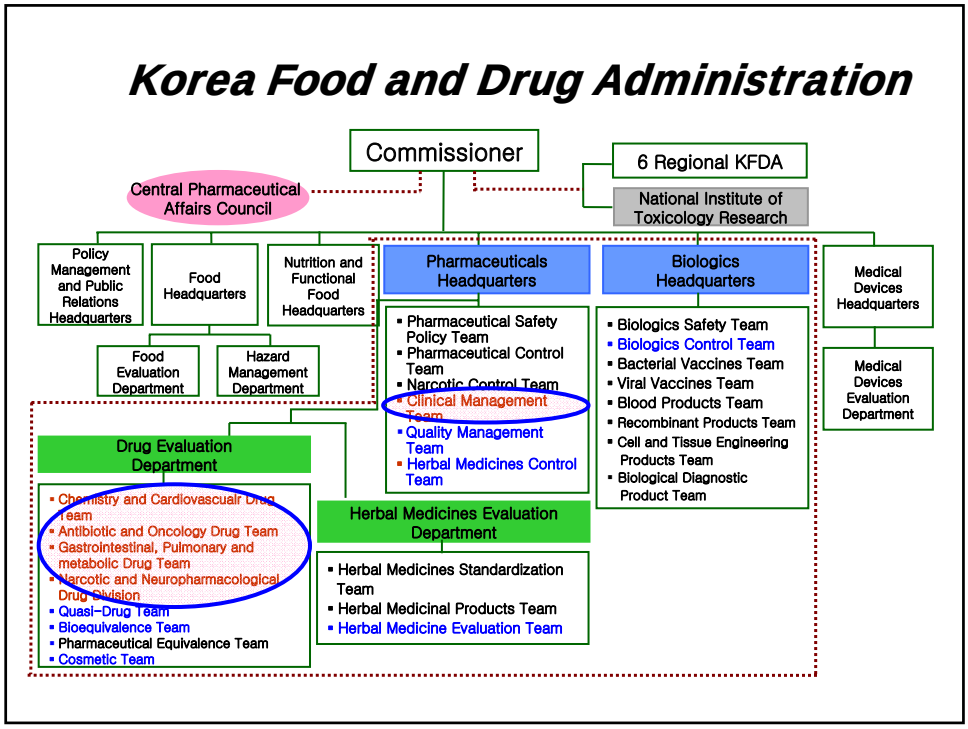
- To increase GCP compliance among parties involved in CT conduct
- To be one of the CT centers for global studies
- To participate in the joint GCP Inspection
- International Collaborations i.e. WHO (Indonesia as GTN/WHO centre for CTA and Clinical Data Evaluation for Vaccine)

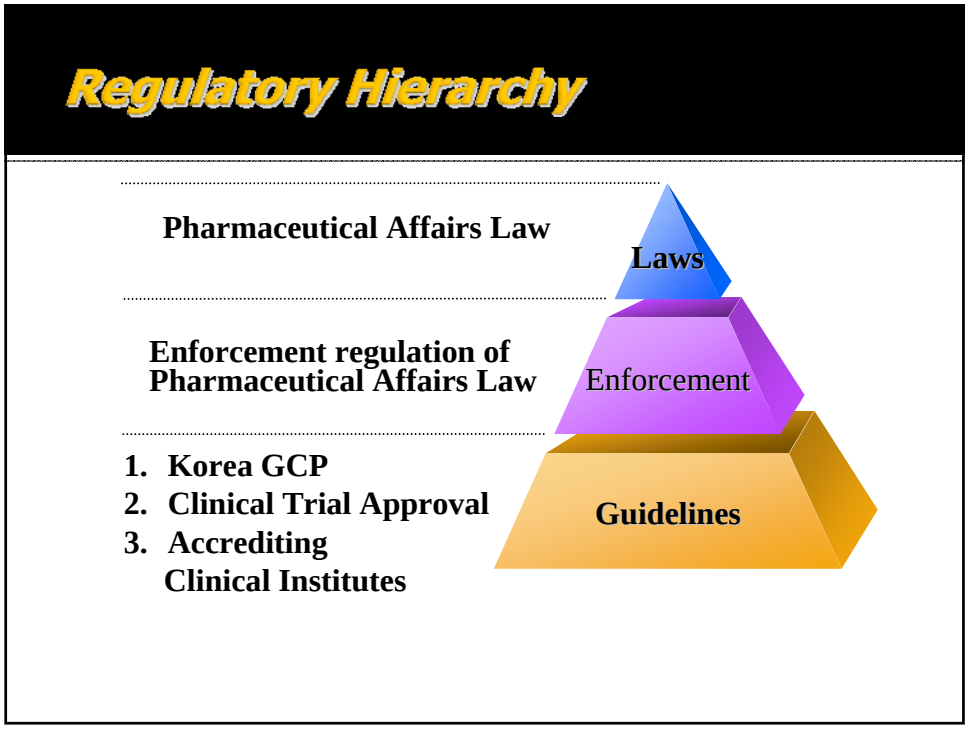
Thank you

IND Process and Global Clinical Trials in Korea

Myung-Ah Chung
Drug Evaluation Department
Korea Food and Drug Administration

Contents

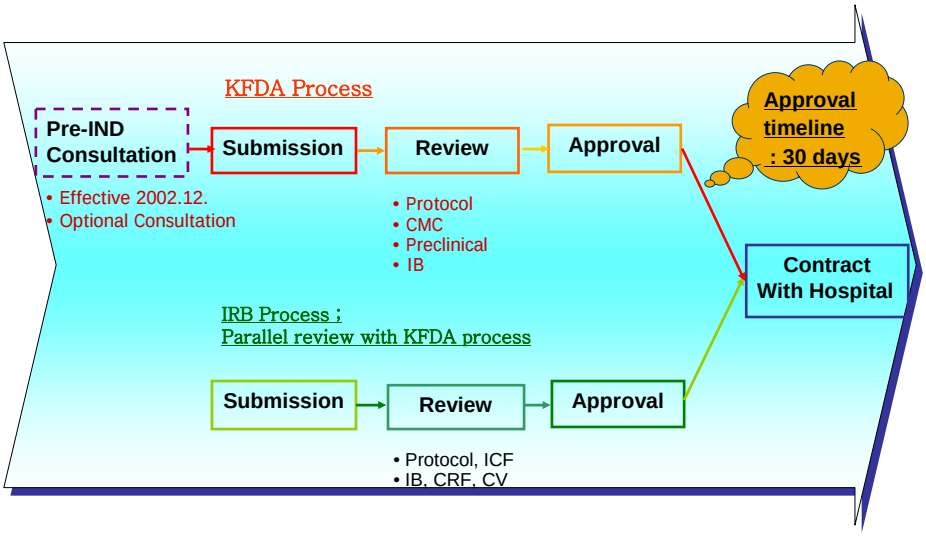

Korea Food and Drug Administration
Commissioner
6 Regional KFDA
Central Pharmaceutical Affairs Council
National Institute of Toxicology Research
Policy Management and Public Relations Headquarters
Food Headquarters
Nutrition and Functional Food Headquarters
Pharmaceuticals Headquarters
Biologics Headquarters
Medical Devices Headquarters
Food Evaluation Department
Hazard Management Department
Medical Devices Evaluation Department
Pharmaceutical Safety Policy Team
Pharmaceutical Control Team
Narcotic Control Team
Clinical Management Team
Quality Management Team
Herbal Medicines Control Team
Biologics Safety Team
Biologics Control Team
Bacterial Vaccines Team
Viral Vaccines Team
Blood Products Team
Recombinant Products Team
Cell and Tissue Engineering Products Team
Biological Diagnostic Product Team
Drug Evaluation Department
Chemistry and Cardiovascular Drug Team
Antibiotic and Oncology Drug Team
Gastrointestinal, Pulmonary and metabolic Drug Team
Narcotic and Neuropharmacological Drug Division
Quasi-Drug Team
Bioequivalence Team
Pharmaceutical Equivalence Team
Cosmetic Team
Herbal Medicines Evaluation Department
Herbal Medicines Standardization Team
Herbal Medicinal Products Team
Herbal Medicine Evaluation Team


Regulatory Hierarchy
Pharmaceutical Affairs Law
Laws
Enforcement regulation of Pharmaceutical Affairs Law
Enforcement
1. Korea GCP
2. Clinical Trial Approval
3. Accrediting Clinical Institutes
Guidelines

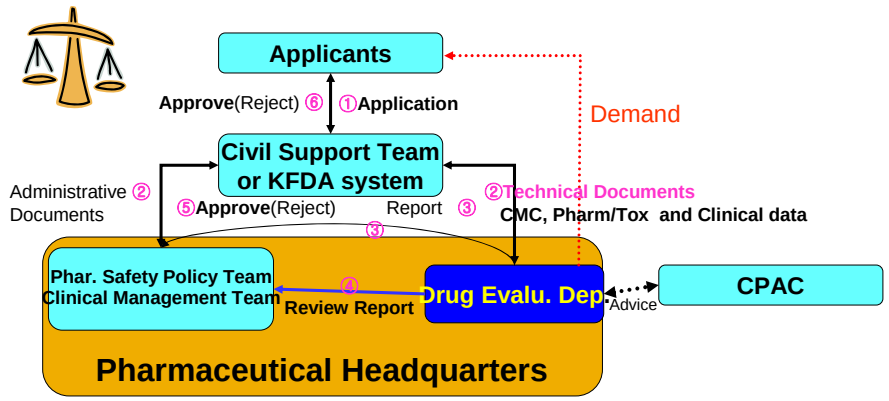
Major Regulatory Changes

1. Dec. 28, 1987	• Establishment of KGCP (recommendation)
2. Oct. 1, 1995	• Requirement for compliance of KGCP
3. Dec. 12, 1999 (enforced .Jul. 1, '00)	• Adoption of the Bridging Concept - Harmonized to ICH guideline E5 - Diverse bridging strategies were required
4. Jan. 4, 2000 (enforced Jan. 1, '01)	• KGCP Amendment for Harmonizing with ICH GCP - Harmonized with ICH guideline E6 - Protect the rights and safety of subjects - Responsibility of investigator
6. Dec. 3. 2002	• Introduction of IND System - Separation between developmental clinical stage and commercial product approval, such as IND and NDA - Participation in international study enabled
7. Jun. 30. 2006	• Organization of Clinical management Team
8. Jan. 4. 2007	• Introduction of Joint-IRB

Clinical Trial Approval Process



Review Process in KFDA



All application documents should be requisitioned by KFDA online system by electronic documents from Oct. 2nd, 2006

Essential Elements in Clinical Trials

defined in the Enforcement regulation of Pharmaceutical Affairs Law

- Protocol approved by KFDA
- Only at the accredited clinical sites
- Qualified investigator
- Protect the right and safety of subjects
- Informed consent before enrollment of subjects
- Investigational drugs

Accredited Clinical Institutes

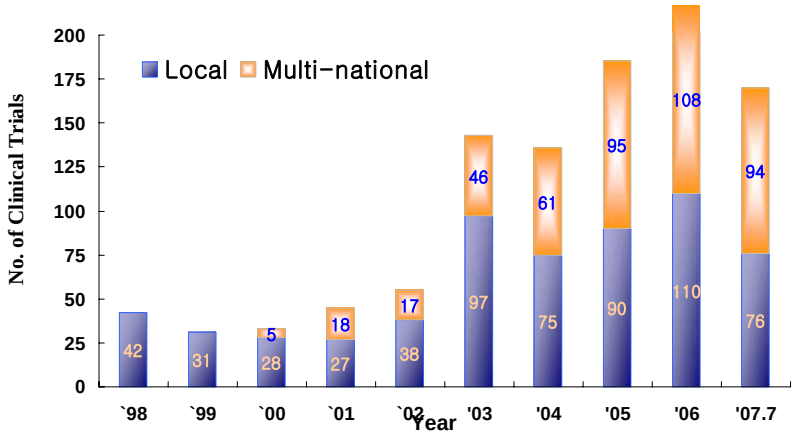
defined in the Enforcement regulation of Pharmaceutical Affairs Law

- Purpose
  - To assure the quality of clinical study and institutes
- What are essential to accredit?
  - Appropriate facilities and equipments
  - Pool of personnel to support the clinical study
  - Activities of IRB
  - Education program of GCP
  - Structures and activities to manage the clinical study

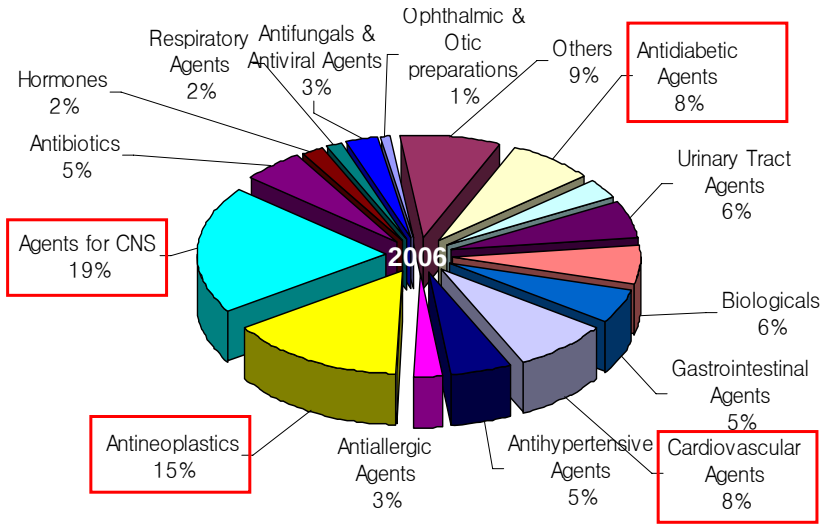
Challenges for implementation

- Qualification of Investigator
- Importance of IRB review
- Importance of SOP
- Need for Clinical Research Resources
- Need for Regulatory Service from Authorities
- Need for communication and harmonization with
- Foreign Authorities

Number of Clinical Trials approved by KFDA



Clinical Trials by Product Category



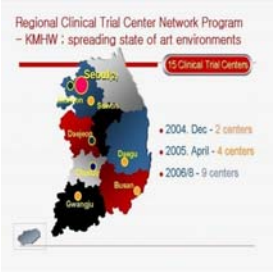
Market Share in the World

Number of Clinical Trials (www.clinicaltrials.gov) (Jun,'07)

No	Economies /Countries	Number of Clinical Trials	Share
1	USA	11,044	58.1%
2	Canada	1,771	9.3%
3	Australia	630	3.3%
4	Chinese Taipei	538	2.8%
5	Mexico	531	2.8%
6	Japan	335	1.8%
7	China	286	1.5%
8	Brazil	271	1.4%
9	**Korea**	**269**	**1.4%(about 100billion Won)**
10	India	264	1.4%
11	Hong Kong	173	0.9%
12	Singapore	150	0.7%
13	Thailand	133	0.7%
14	Philippines	71	0.4%
Total Number (estimated)		19,000 (about 40 thousand billion won)	

Strong Supporting Plan

- **Supported plan for Clinical Center by MOHW**
  - 9 Regional centers designated in 2004-2006
  - Support for Facilities, Operation systems, R&D etc.
  - $ 0.5 ~ 1 million/center/yr for 5 years



- **Ko-NECT**
  (Korea National Enterprise of Clinical Trials)
  - Clinical Hub of North-East Asia
  - Regional centers will be increased by 15 centers until 2010
  - Regional centers will be network
  - Training center and Development center to support clinical trials

➢ MOHW : Ministry of Health and welfare

Korean Investigator's Contribution to Global Trials

More than these…..

- **Prof. Byung-Hee Oh: Cardiology, SNUH**
  Global PI of Aliskiren, Norvatis
- **Prof. Yoon-Ku Kang: Oncology, AMC**
  Global PI of Xeloda Phase III study in GC, Roche
- **Prof. Young-Joo Bang: Oncology, SNUH**
  Global PI of Sunitinib Phase II study in GC, Pfizer
- **Prof. Sun-Young Ra: Oncology, YUMC**
  AP PI of Sunitinib Phase II study in RCC, Pfizer
- **Prof. Sun-Woo Kim: Endocrinology, SMC**
  Global PI of Vildagliptin, Phase III study in T2DM, Norvatis
- **Dr. Jin Soo Lee: Oncology, NCC**
  Global PI of ZD6474 Phase III study for LC, AZ
- **Prof. Joon Soo Kwon: Psychiatry, SNUH**
  Global PI of 11286 Sertindole, Phase III study for schizophrenia, Lundbeck

What's attractiveness?

- **Attractive Pharmaceutical Market**
  - **10th largest in the world & 2nd largest in AP (excluding Japan)**
  - **Two digit growth every year: 16.8%, 2005**
  - **Increasing healthcare expenditure**
- **Fastest aging country**
- **Life expectation: 75.1yr (M) vs. 80yr (F)**

- **Efficient Regulatory Agency**
  - **Open communication with KFDA officer**
  - **Clear review timeline from 1 month up to 4.2 month**
  - **Clear requirement for review & approval**

- **Qualified Investigator and Institution**
  - **Global PI in global trials**
  - **Good Clinical Trial Centers**
  - **Experienced staff by training**
  - **Facility: clinic, lab, pharmacy, archiving**
  - **Efficient IRB process**

- **Strong Support from Government**
  - **60M USD government investment by 2010 for 15 regional CTC**
  - **Korea National Enterprising of Clinical Trial (KoNECT)**
  - **MOU between KoNECT & J-CLIPNET**


Thank you !

GCP INSPECTION IN MALAYSIA

Kamaruzaman Saleh,

Section for Clinical Research and Compliance,
National Pharmaceutical Control Bureau,
Ministry of Health Malaysia

Outline

- Current Progress
- Future Plan of Action

CURRENT PROGRESS

- GCP Inspection is still a voluntary basis
- Joint-Inspection with Foreign Regulatory Authorities to local Research Centres
  - French Health Product Safety Agency (AFSSAPS) (GCP)
  - German GLP Federal Bureau (OECD GLP)
- Joint-Audit with Sponsors to their local Research Centres
  - MSD
  - AstraZeneca

FUTURE PLAN OF ACTION

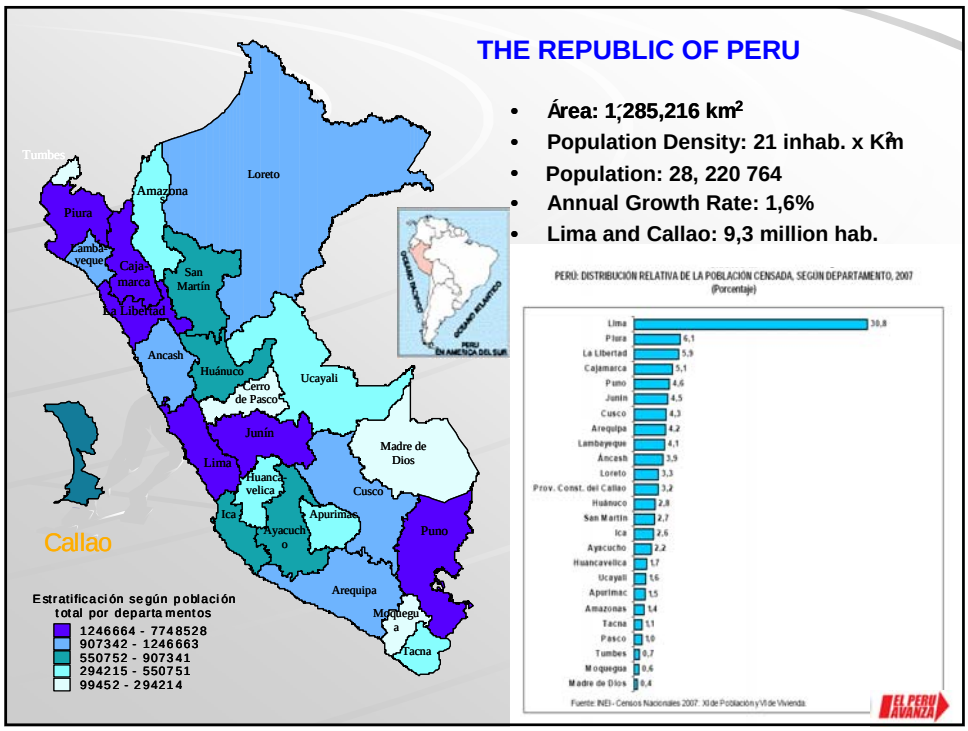
- Effective monitoring on the implementation of GCP
- Plan to launch GCP Inspection Programme in 3Q 2009
  - Preparation of SOPs for the following docements :
    - Directive for GCP Inspection
    - Procedure For Coordinating GCP Inspection
    - Procedure For Conducting An Inspection
    - Procedure For Preparing A GCP Inspection Report

- Qualification Of Lead Inspector And Inspector
- Training For Personnel
- Evaluation Assessment Of Inspectors
- Annex I Procedure For Conducting An Inspection - Bioequivalence Centres
- Annex II Procedure For Conducting An Inspection - Ethics Committee

- Annex III Procedure For Conducting An Inspection - Investigator Site
- Annex IV Procedure For Conducting An Inspection - Sponsor And CRO Site
- Annex V Procedure For Conducting An Inspection - Clinical Laboratories

THANK YOU


Ministerio de Salud
Personas que atendemos Personas
Clinical Trials
Regulations in Peru
Hans Vásquez, MD
National Direction of Drugs and Medical Device (DIGEMID)
Ministry of Health. Peru
Thailand, March 2009
Advanced Workshop - APEC


THE REPUBLIC OF PERU
Área: 1,285,216 km²
Population Density: 21 inhab. x Km²
Population: 28, 220 764
Annual Growth Rate: 1,6%
Lima and Callao: 9,3 million hab.
Tumbes
Loreto
Amazonas
Piura
Lambayeque
Cajamarca
San Martín
La Libertad
Ancash
Huánuco
Cerro de Pasco
Ucayali
Junín
Lima
Huancavelica
Madre de Dios
Cusco
Ica
Apurímac
Ayacucho
Puno
Arequipa
Moquegua
Tacna
Callao
Estratificación según población total por departamentos
1246664 - 7748528
907342 - 1246663
550752 - 907341
294215 - 550751
99452 - 294214
PERÚ: DISTRIBUCIÓN RELATIVA DE LA POBLACIÓN CENSADA, SEGÚN DEPARTAMENTO, 2007
(Porcentaje)
Lima 30,8
Piura 6,1
La Libertad 5,9
Cajamarca 5,1
Puno 4,6
Junín 4,5
Cusco 4,3
Arequipa 4,2
Lambayeque 4,1
Áncash 3,9
Loreto 3,3
Prov. Const. del Callao 3,2
Huánuco 2,8
San Martín 2,7
Ica 2,6
Ayacucho 2,2
Huancavelica 1,7
Ucayali 1,6
Apurímac 1,5
Amazonas 1,4
Tacna 1,1
Pasco 1,0
Tumbes 0,7
Moquegua 0,6
Madre de Dios 0,4
Fuente: INEI - Censos Nacionales 2007: XI de Población y VI de Vivienda.
EL PERU AVANZA

Regulation

- Decreto Supremo No 017-2006-SA. Regulation of Clinical Trials in Peru.
- Decreto Supremo No 006-2007-SA. Modify some requirements of the first regulation.

Regulations of phase I, II, III and IV

General aspects

- There are 2 Regulatory Authorities in Clinical Trials:
  1. National Institute of Health (Peru-NIH)
  2. National Direction of Drugs and Medical Device (Regulatory Authority of Medicines).DIGEMID
- Total time for to approve a CT: 40 days (working/business days).
- We approve each Clinical Trial (CT). Not exist IND system or other similar.
- Sponsor (ussually CRO) only can start a CT if have:
  1. Document of approval of CT.
  2. Document of approval the importation of investigational products (drugs).

Requirements.

DS 006-2007. Artículo No 66

- Sponsor Form. Application.
- Approval of "Institution".
- Approval of Institutional Ethics Comitee.
- Protocol (original language and spanish).Last version
- Investigator´s Brochure (original language and spanish). Last version (actualization each year).
- Budget
- Sworn declaration of compensation.
- Insurance.
- Supplies List
- Curriculum Vitae of Principal Investigator.
- Other information: requirements of the Authorities

Peru-NIH/DIGEMID

Perú-NIH

- Reception of requirements.
- Oficial document of approval CT. In charge of review, ammendments or extension.
- Review protocol (and ethics aspects) of each CT.
- Inspections.

DIGEMID

- Technical Opinion of safety of investigational product binding to approve a CT (Review of investigational product).
- Inspections (about use and storage of investigational product).
- Importation of investigational product.
- Compasive use.

Coordination PERU-NIH and DIGEMID

Work-Meeting each month
There is more meeeting if is neccesary: inusual or difficult trials
Frecuently coordination with email and telephone

Clinical Trials submitted

Year	Number of CT submitted
2006	84
2007	123
2008	176

Source: www.ins.gob.pe

Clinical Trials approved (until Jan 2009)

Phases	2006	2007	2008
I	3	4	4
II	18	25	33
III	58	82	86
IV	5	7	9
Total:	**84**	**118**	**132**

Source: www.ins.gob.pe

Inspections

- 2007: ~ 36 GCP inspections.
- 2008: ~ 17 GCP inspections.

Perú-NIH coordinate the GCP inspections.

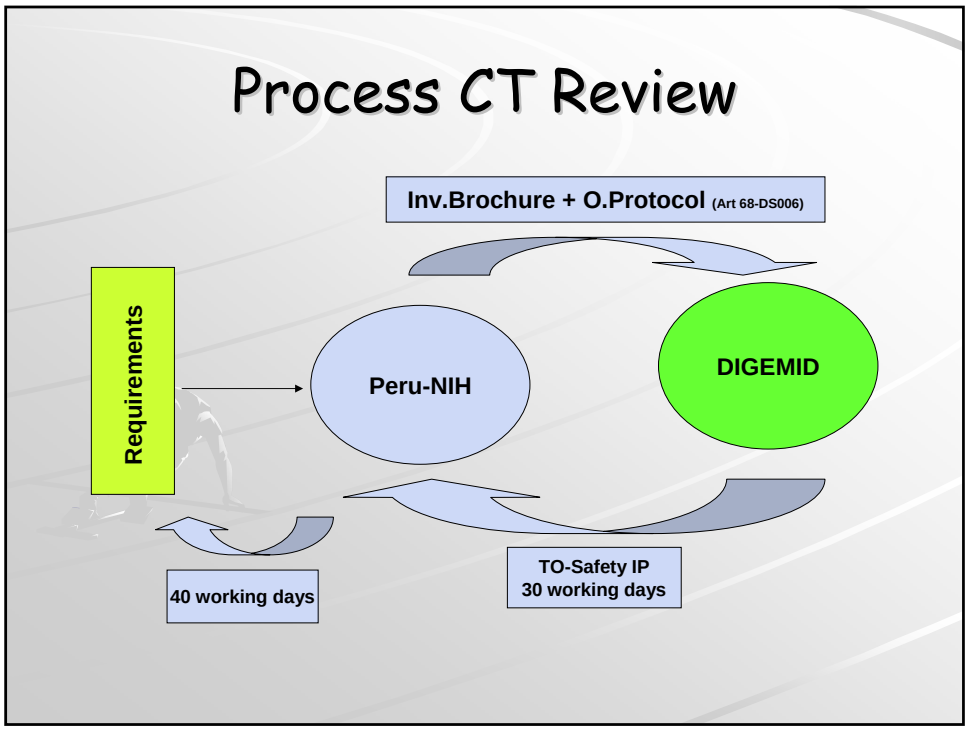
DIGEMID participate in GCP inspections in aspects regarding use of Investigational pruduct (storage, manufacture, use and adverse events).

At date, we don´t have approved procedure to conduct GCP inspections.

Peru-NIH and DIGEMID reviewers conduct the GCP inspections. Also, DIGEMID Inspectors (GMP and GSP) participate in GCP inspections.

Some observations in inspections

- Storage inadecuate
- Without temperature control
- Expired Investigational Products with inadecuates storage
- Sites without essentials documents
- Don´t reporting of Adverse events



Perspectives

- Improve the GCP inspections (number and quality). Procedure approved.
- Strengthen the Regulatory Authorities.
- Improve the coordination between Peru-NIH and DIGEMID.
- More contact between regulation of CT and new drug office (recently Peru/DIGEMID was significative change in regulation of new drugs and biologics).
- Understanding Memorandum with others Regulatory Authorities


Ministerio de Salud
Personas que atendemos Personas
GRACIAS!
Thank you!
HUASCARAN
PUYA RAYMONDI

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

Dr. Tito King – Medical Specialist III
Ms. Marle B. Koffa – Food-Drug Regulation Officer III

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

March 2009
Bangkok, THAILAND

Bureau of Food and Drugs

Filinvest Corporate City, Alabang, Muntinlupa City

2

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

3

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.

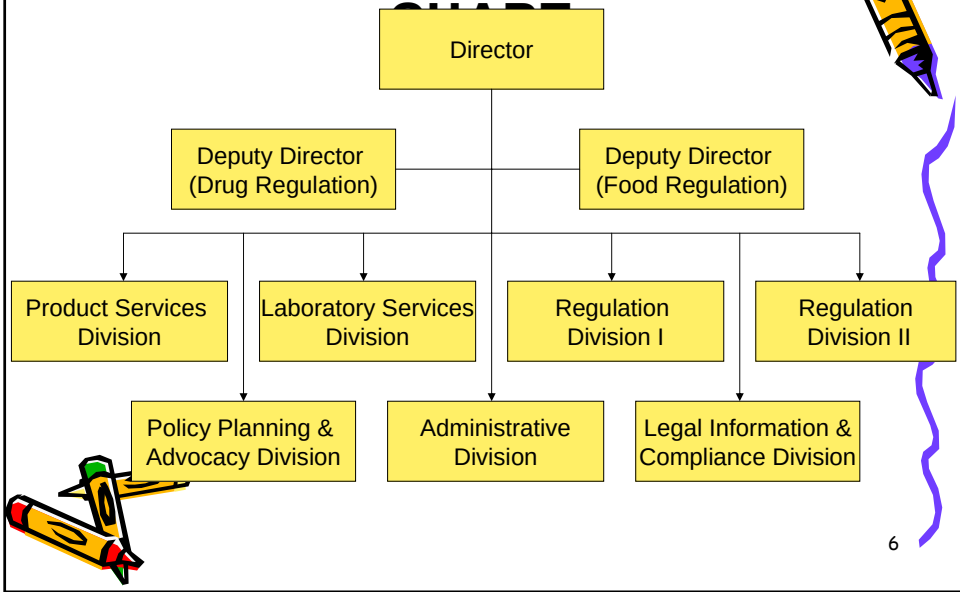
4

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.

5

ORGANIZATIONAL



6

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

7

Quality Control System

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

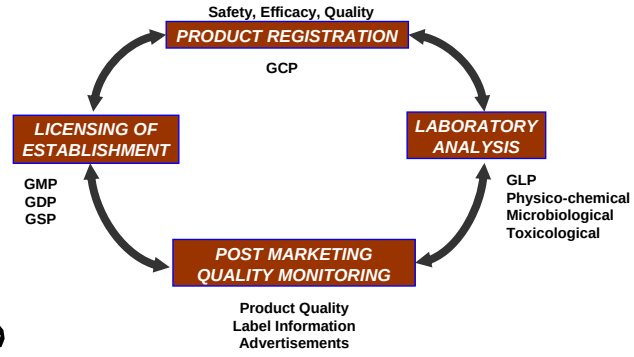
2) The **Product Services Division** assures that a product meets the criteria for safety, efficacy and quality (GCP).

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.

8

Quality Control Loop



9

HISTORICAL BACKGROUND

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.

10

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.

11

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).

12

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*

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

13

So what has been going on?

GCP Compliance Monitoring

14

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.

15

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

16

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.

17

Stumbling Blocks

Current Problems

18

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.

19

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.

20

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.

21

Current Problems (4)

- There is selective reporting of trials, including Adverse Drug Reactions (ADRs) by sponsors, investigators and researchers.
- Concerted efforts involving several government agencies to come-up with a solid Philippine Health Research Framework have not yet really taken off.

22

What Lies Ahead?

Future Plans

23

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.

24

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.**

* [illegible] development stage ** In planning stage

25

At the end of this Workshop…

GOALS

26

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.

27

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.***

28

Recent Developments

29

Recent Developments (1)

- A Department of Health (DOH) Administrative Order had been drafted adopting the ICH Harmonized Tripartite Guideline for Good Clinical Practice.
- The draft document is currently being circulated in the different offices of the DOH for further inputs and comments. It is targeted to be implemented within 2009.

30

Recent Developments (2)

- The Bureau of Food and Drugs is planning to transfer the activities of the BA/BE testing center audit team (involved in monitoring GCP and GLP compliance) to the GMP Inspection Division of BFAD. This is to consolidate all audit/inspection activities under one division.
- Since the Bureau's GMP Inspection Division is relatively new to GCP and GLP principles, appropriate in-house trainings will be conducted.

31

Maraming salamat po

Thank you

ขอบคุณ

32

Updates on Status of GCP Inspection: SINGAPORE

2 March 2009, Bangkok

Foo Yang Tong
Deputy Director, Clinical Trials Branch
Health Products Regulation Group
HEALTH SCIENCES AUTHORITY
SINGAPORE

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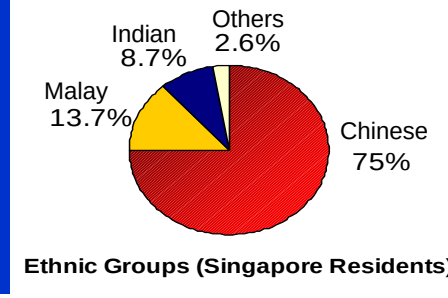
PRESENTATION OUTLINE

- Overview of the Health Sciences Authority
- Drug Development Environment – Regulatory Perspective
- Legislation Changes & GCP Inspection Updates

Singapore

- Total land area: 707.1 sq km
- Population *(Jun 08)*
  - 4.84 mil (Total)
  - 3.64 mil (Singapore Residents)



Ethnic Groups (Singapore Residents)

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Overview of HSA

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HSA
HSA
Health Sciences Authority
A Statutory Board of the Ministry of Health
The Singapore Public Service
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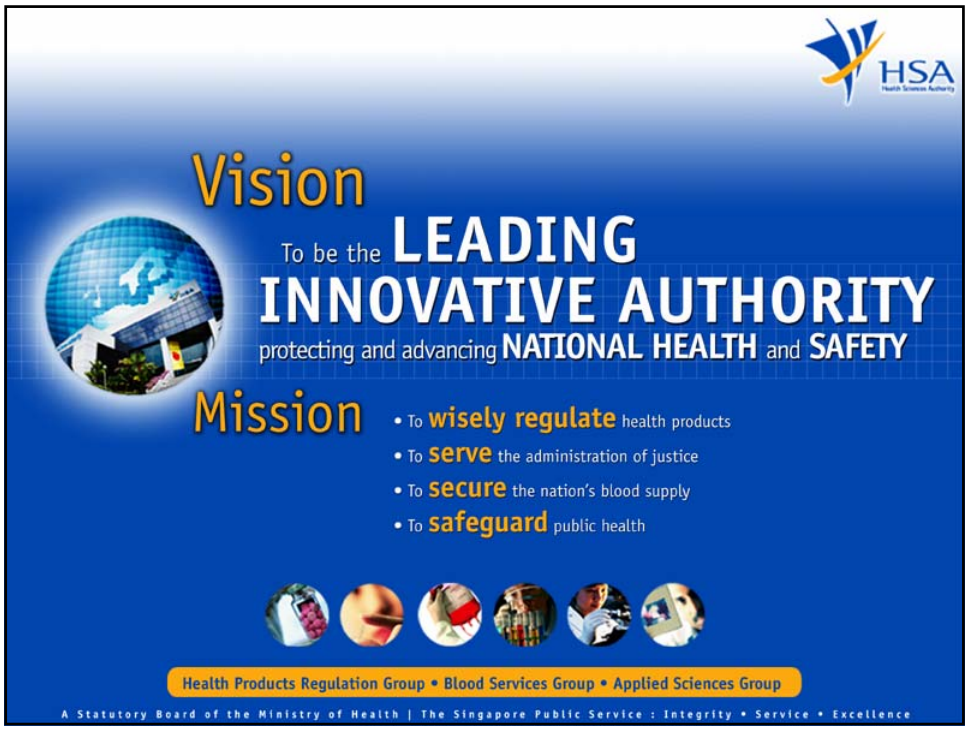
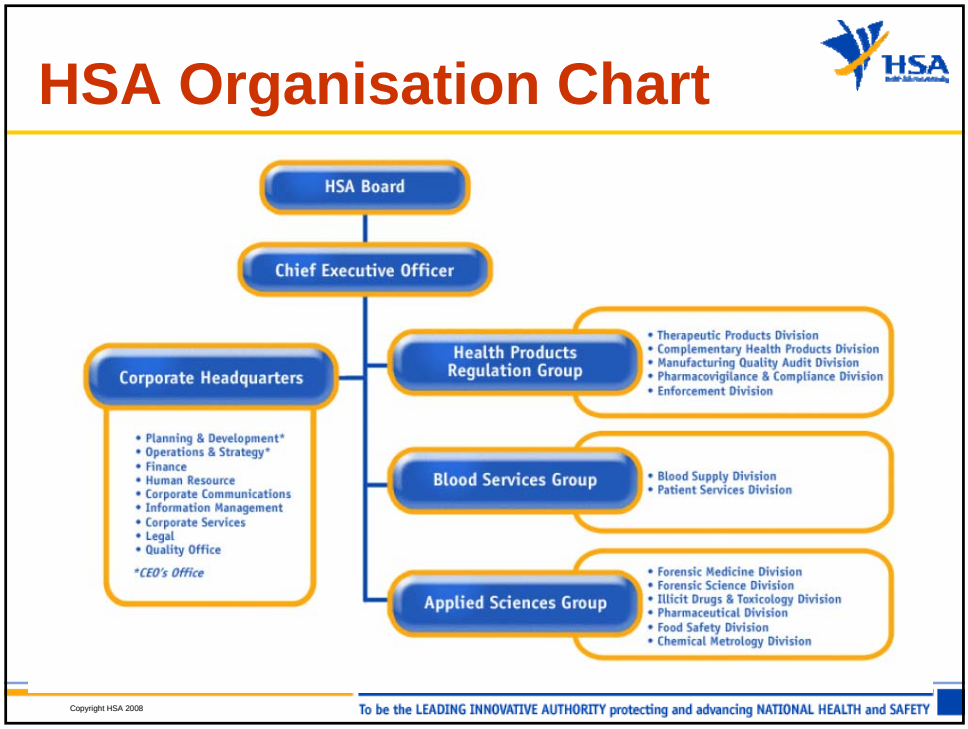

HSA
Vision
To be the LEADING
INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY
Mission
• To wisely regulate health products
• To serve the administration of justice
• To secure the nation's blood supply
• To safeguard public health
Health Products Regulation Group • Blood Services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


HSA Organisation Chart
HSA Board
Chief Executive Officer
Corporate Headquarters
• Planning & Development*
• Operations & Strategy*
• Finance
• Human Resource
• Corporate Communications
• Information Management
• Corporate Services
• Legal
• Quality Office
*CEO's Office
Health Products Regulation Group
• Therapeutic Products Division
• Complementary Health Products Division
• Manufacturing Quality Audit Division
• Pharmacovigilance & Compliance Division
• Enforcement Division
Blood Services Group
• Blood Supply Division
• Patient Services Division
Applied Sciences Group
• Forensic Medicine Division
• Forensic Science Division
• Illicit Drugs & Toxicology Division
• Pharmaceutical Division
• Food Safety Division
• Chemical Metrology Division
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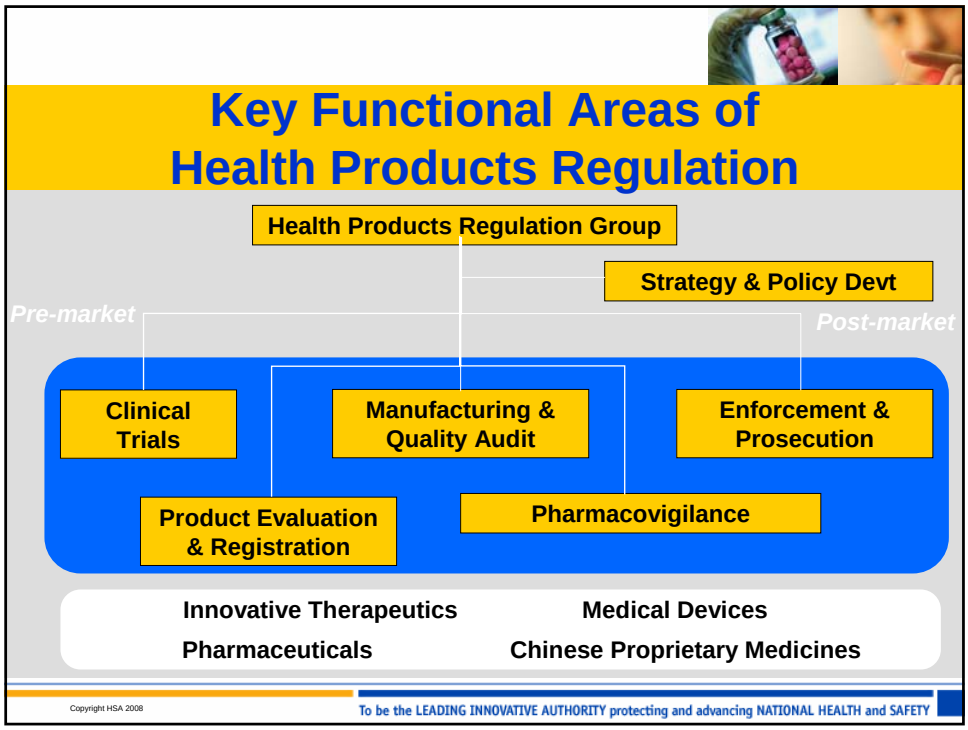
Key Functional Areas of
Health Products Regulation
Health Products Regulation Group
Strategy & Policy Devt
Pre-market
Post-market
Clinical Trials
Manufacturing & Quality Audit
Enforcement & Prosecution
Product Evaluation & Registration
Pharmacovigilance
Innovative Therapeutics
Medical Devices
Pharmaceuticals
Chinese Proprietary Medicines
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Drug Development Environment
Regulatory Perspective

Clinical Trials Regulatory Framework

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

Clinical Trials Regulatory Framework

- Parallel Submission to both HSA and IRB(s)
- Electronic submission to HSA
- Target Review timeline ~ 4-6 weeks
- Regulatory approval - Clinical Trial Certificate (CTC) - specific for each protocol, PI and site

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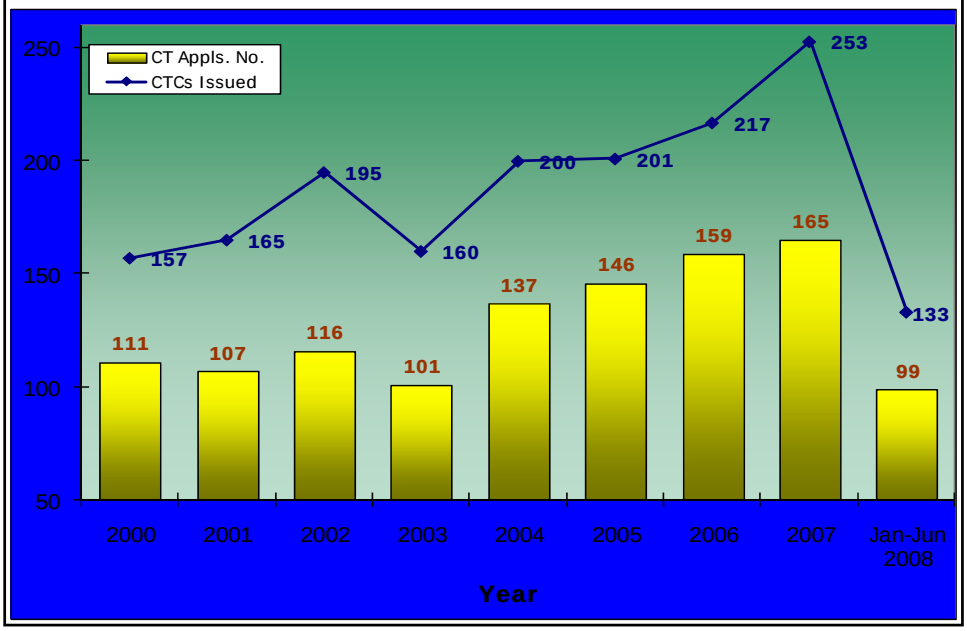
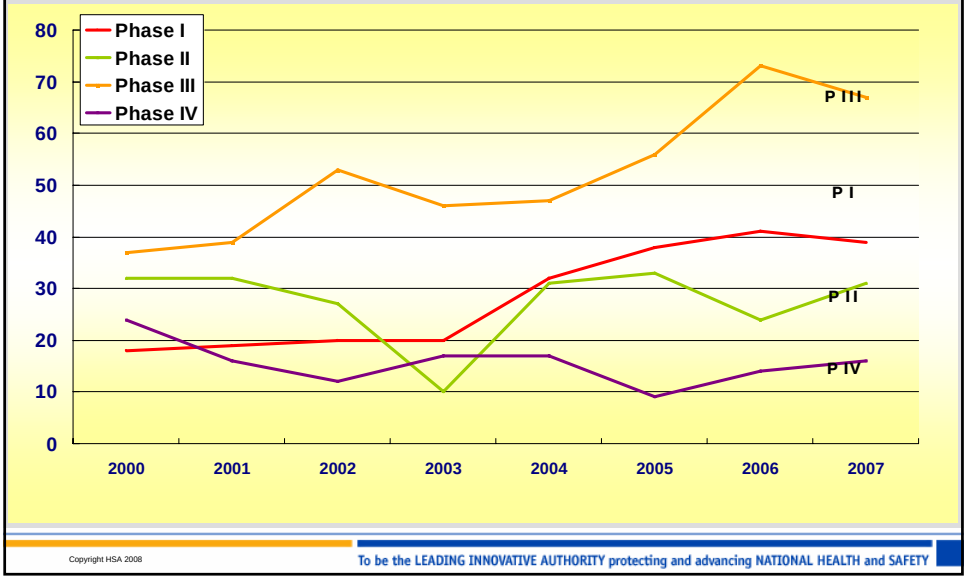
No. of CT Applications & CTCs issued



No. of Approved CT Applications



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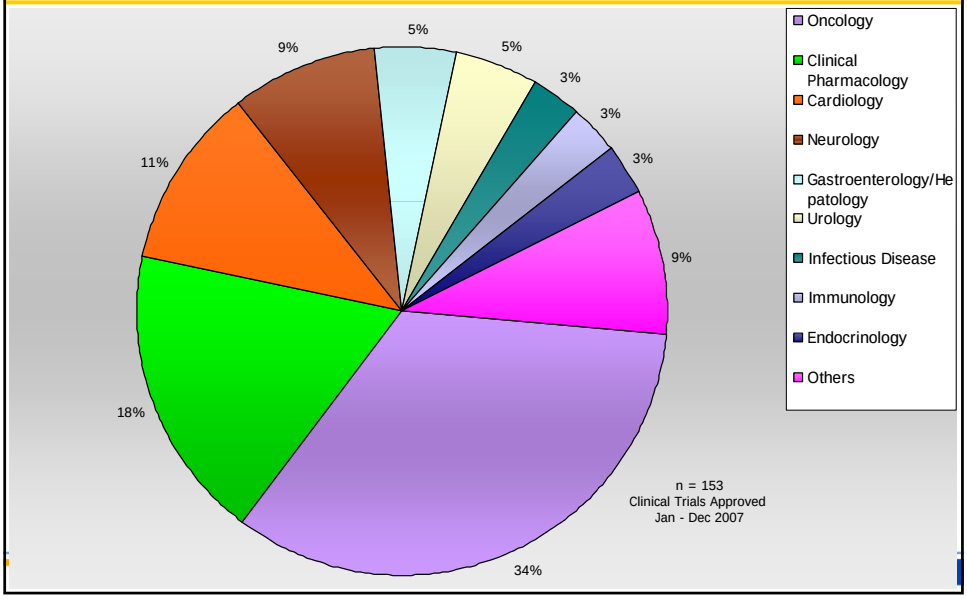
Clinical Trials Therapeutic Areas (2007)



Clinical Trials Trend

- 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: 30-35%
  - 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
- Growing phase I **Clinical Pharmacology** studies: 20-25%

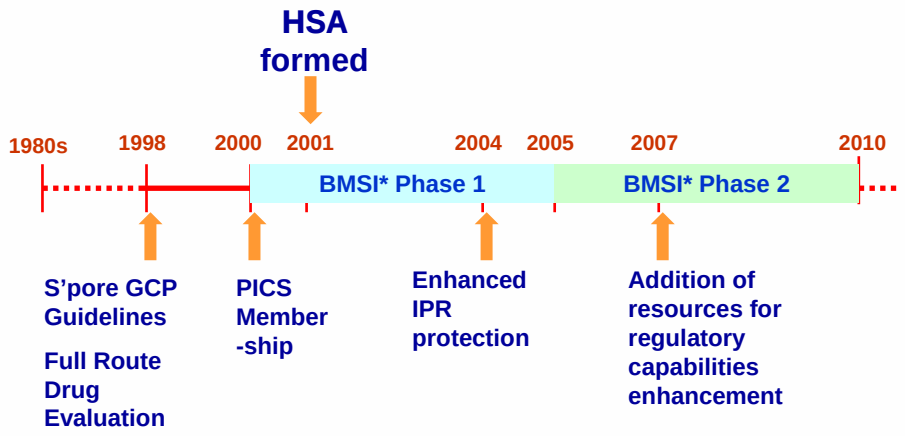
Clinical Trials Trend

Establishment of Phase 1 units in Singapore:

1. Lilly–NUS Centre for Clinical Pharmacology
2. Pfizer Clinical Research Unit, Raffles Hospital
3. Clinical Trials Research Unit, Changi General Hospital
4. Clinical Trials Unit, National University Hospital
5. Investigational Medicines Unit, Singapore GeneralHospital

- Availability of dedicated resources and facilities in providing full spectrum of scientific and technological expertise to conduct early phase drug development
- Singapore's Biomedical Sciences programme is key in enabling MNC companies to set up dedicated phase I centres in Singapore to conduct early phase clinical drug development
- Singapore will continue to support more of such studies to complement / strengthen strategy in knowledge-driven research

Regulatory Perspective



*Biomedical Sciences Initiatives

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Regulatory Perspective

In Singapore…

- Relative smallness of agency
  - Need to apply innovative approaches
- Biomedical Sciences Initiatives
  - Being an enabling regulator

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Regulatory Perspective

- Science-based, data-driven, risk-based approach
- Compliance to International Regulatory Standards
- Rigorous intellectual property framework
- Active promotion of Good Clinical Practice
- Continually enhancing capabilities to manage emerging technologies and therapies; attention to training and knowledge management in order to keep abreast of scientific advances
- Dialogues with stakeholders (sponsors)

Legislation Changes & GCP Inspection Updates

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Legislative Restructuring

Health Products Act

- To consolidate medicines control laws
- Modular approach – more responsive & flexible to deal with different degrees of risk
  - Tighter control for higher risk products
  - Lighter control for lower risk products

Proposed Changes to Clinical Trial Regulations

- To stipulate responsibilities of the sponsor in accordance with SG-GCP.
- To require both ethics and regulatory approval for conduct of clinical trials.
- To simplify the requirements for clinical trials in emergency situations.
- To exempt non-interventional trials.
- To clarify consent requirements for minors and persons of unsound mind.

Proposed Changes to Clinical Trial Regulations

- To convert CTC to lifetime licence.
- To clarify safety reporting requirements for sponsor and PI.
- To revise the clinical trial material labeling requirements.
- To remove ban on financial interest in clinical trial.
- To provide sufficient grounds to carry out GCP inspections.

GCP Inspection Updates

- Planned phase implementation of GCP Inspection Regulatory function
- Strengthen post-approval regulatory system for clinical drug trials with the capacity and capability to assess compliance by organisations and facilities involved in clinical trials to regulations and GCP guidelines.
- Target Q2 2009: Recruitment of qualified GCP inspectors & Drafting of procedures & communication to stakeholders
- Target Q3 2009: Commence GCP Inspections. The initial phase of the GCP Inspection programme will focus on training and education, and increasing quality assurance rather than strict enforcement, unless a blatant violation impacting on safety or rights of trial subjects, serious research misconduct or fraud is discovered.


HSA
Thank You!
visit us again: www.hsa.gov.sg
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TFDA

Thailand Update

by

Yuppadee JAVROONGRIT, Ph.D.

Head of International Affairs and Investigational Drug Group

Drug Control Division, TFDA, MOPH, Thailand

Advance workshop on GCP/ Clinical Research Inspection

Courtyard, Marriott Hotel, Bangkok, Thailand

02-06 March 2009

TFDA

Regulatory Infrastructure/Authority

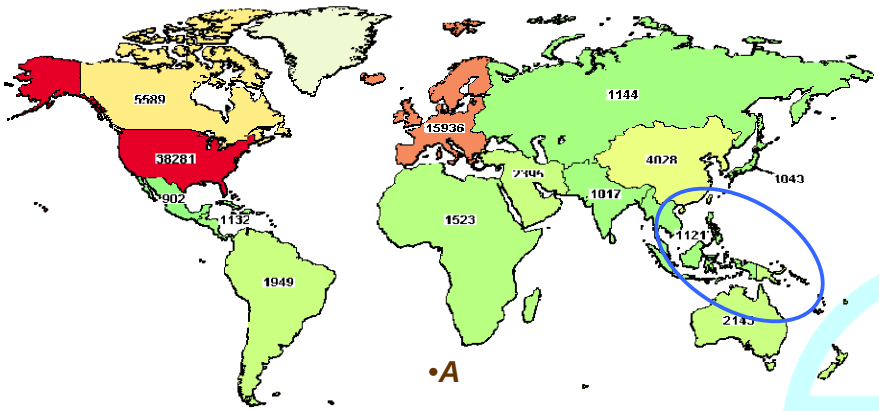
The Drives

- **Current & Trend**
  - **Increasing participation in…**
    - **Multinational Clinical Trials**
    - **Phase I trials**
    - **Pharmacogenetic study**
    - **big/major Public Clinical Trials**
  - **Increasing number of the Clinical Trials**
- **WHO's Pre-qualification Programme**
- **International Standards** – ***APEC, ASEAN, ICH&GCG***
- **Consumer protection**

TFDA

Global Clinical Trials

Ref.→ Feb.09 (www.ClinicalTrials.gov)



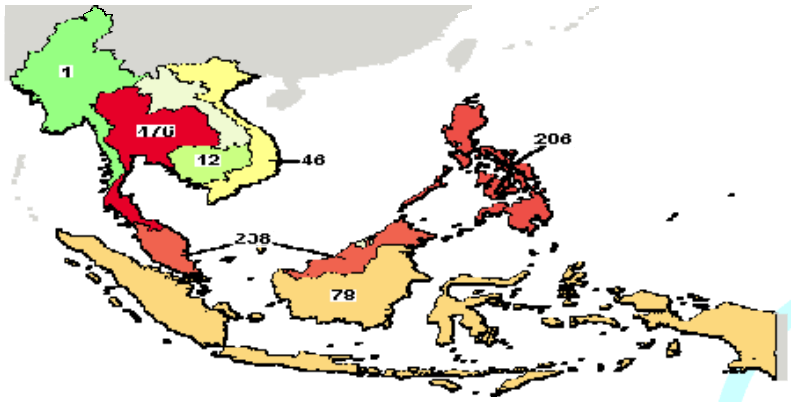
All 69,091 Clinical Studies = 1,121 Studies in ASEAN

Advance WS on GCP/Clinical Research Inspection

TFDA

Clinical Trials in ASEAN/Thailand

Ref.→ Feb.09 (www.ClinicalTrials.gov)



from 1,121 Clinical Studies in ASEAN
→ 476 Studies (.....Open Studies) are in Thailand

Advance WS on GCP/Clinical Research Inspection

TFDA

Regulatory Infrastructure/Authority

The Opportunity

- **Training Visit** – ***Health Canada***
- **Training Course** – ***US FDA-CDER***
- **Visiting Trips** – ***KFDA, EMEA***
- **Training Workshops**
  - **APEC-LSIF "Review of Drug Development in Clinical Trials" and "GCP / Clinical Research Inspection"**
  - **Industry "Drug Development" by Astra Zeneca "GCP Inspection" by Pfizer, …..**

TFDA

Regulatory Infrastructure/Authority

The Update *after Basic WS*

- **Amendment the Regulation …**
  - **requesting "compliance to GCP, GLP, GMP"**
  - **assigning "GCP Inspector Team"**
  - **working "for GCP Inspection in the Country"**
- **Coming activities…**
  - **formalize the GCP Inspection System**
  - **implementing Quality System**
  - **finalizing the Template/Check-list of the Inspection**
  - **preparation for the Inspection soon**

TFDA

Best Practice – Strategy for Inspection

The Update *after Basic WS*

- **The Principle & Target…**
  - compliance to GCP
  - subject protection
  - international standard
  - facilitate the Global-Clinical Trials/Drug Dev.
- **Strategy…**
  - developing Template & SOP for the inspection
  - strengthening the Inspectors
  - starting the real inspection

TFDA

Wish …

Advance WS

"GCP / Clinical Research Inspection"

Help complete

the "Know-how to Do GCP-Inspection"


ขอบคุณค่ะ
(Khob Khun Kha)
Thank You !!!

Good Clinical Practice (GCP) System in Vietnam

Department of Science and Training (DST)
Independent Ethics Committee (IEC)
Ministry of Health
T: + 844 6 273 22 49
F: + 844 6 273 22 43
E: quangbyt@yahoo.com

Our Team:

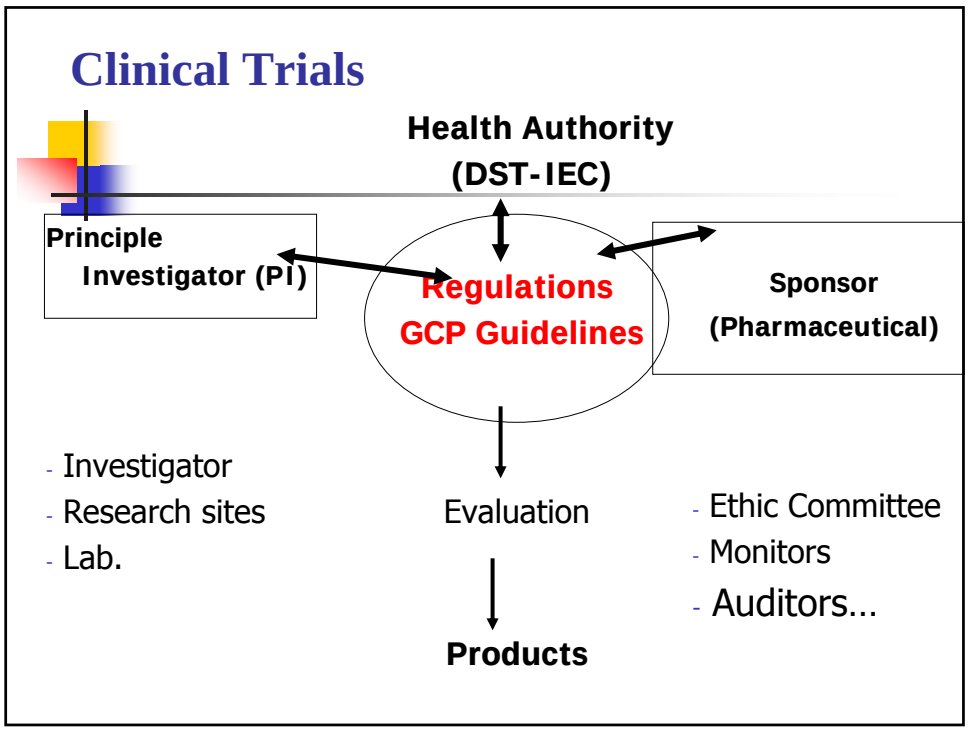
- Prof. Dr. **Van** Do Duc- Vice Chairman of IEC- MoH
- Dr. **Quang** Nguyen Ngo – Expert of DST, General Secretary of IEC- MoH

Main points:

1. Introduction
2. GCP System Development in Vietnam
3. What have been done in process...

I- Introduction:

- Relations among **Principle Investigator** (PI); **Health Authority- Government Officers and Sponsors** in the proposal, research and development of new medicines, vaccines and medical immuno-biological products
- The necessities for the standardization of Clinical research and application of GCP in Vietnam
- Harmonization and international integration



Legal bases:

- Laws on Medicines
- Laws on Science and Technology
- Decrees for the implementation of the laws
- Regulations No 01/2007/QĐ-BYT dated Nov. 1 2007
- Decision No 661/QĐ-BYT dated Feb.2 2008 and No 2626/QĐ-BYT dated Jul.22 2008
- GCP Guidelines (No QĐ 799/QĐ-BYT dated July. 3 2008)
- GCP/ICH.

II- The necessities for the standardization of clinical research

- **In reality:**
  - Great and urgent needs for drug trials both domestically and internationally
  - Legal bases for the safe and effective exposure to new medical products
  - Improving Scientist doctors' roles using international assistance funds
  - Requirements for the integration, acceptance and respect international rules on clinical trials.

The necessities for the standardization of clinical research

- The development of a clinical trial network in Vietnam is a difficult task requiring the health authority, investigators and sponsor's joint efforts.
- and also coordinate with other organizations and countries.

III. What have been done or are in process:

Regulation and Training:

- Developing and Issuing Regulations on Clinical Trials (GCP Regulation).
- Developing and Issuing GCP Guidelines follow ICH/ GCP Guideline.
- Training PI & investigators, health officers
- Training for CRA.

III. What have been done or are in process:

Independent Ethics Committee:

- Founding MOH Ethics Committee for the new term with clear definitions of roles, tasks (2008-2012)
- and SOPs for IEC.
- Regular meeting(1 day/month) for review the CL protocols.

III. What have been done or are in process:

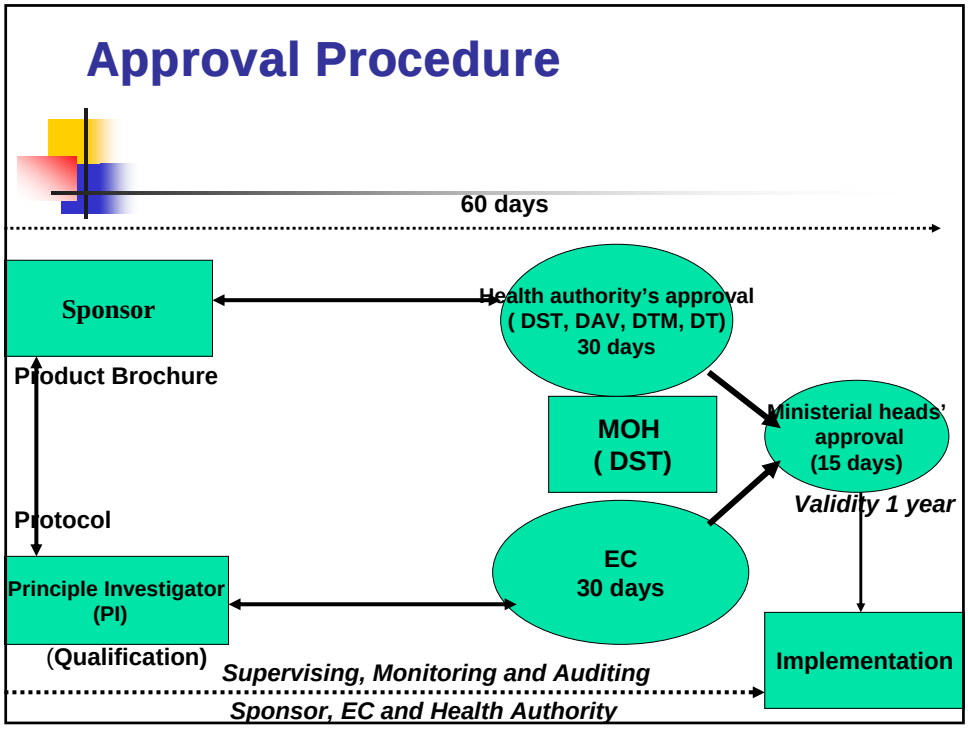
Supervision & Inspection:

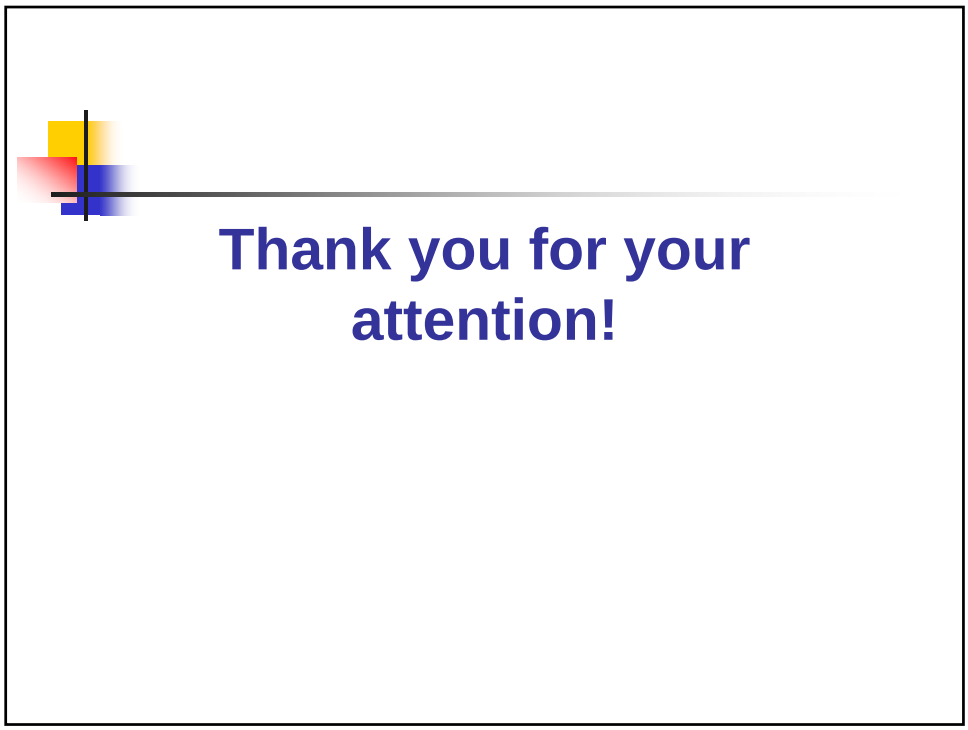
- Supervision and inspection of CLs running in Vietnam follow GCP standard.
- Set up the GCP inspection team under guidance of MoH.
- Data management and SAE report system/DST-MoH.

III. What have been done or are in process:

Develop GCP system:

- Setting up standards for GCP Units (11 Units)
- Evaluating and licensing GCP Units
- Developing a Project for the establishment of Clinical Research Centers (CRC).


Approval Procedure
60 days
Sponsor
Health authority's approval
(DST, DAV, DTM, DT)
30 days
Product Brochure
MOH
(DST)
Ministerial heads' approval
(15 days)
Validity 1 year
Protocol
EC
30 days
Principle Investigator
(PI)
(Qualification)
Supervising, Monitoring and Auditing
Implementation
Sponsor, EC and Health Authority


Thank you for your attention!

Update of GCP Laws/ Regulations in Saudi Arabia

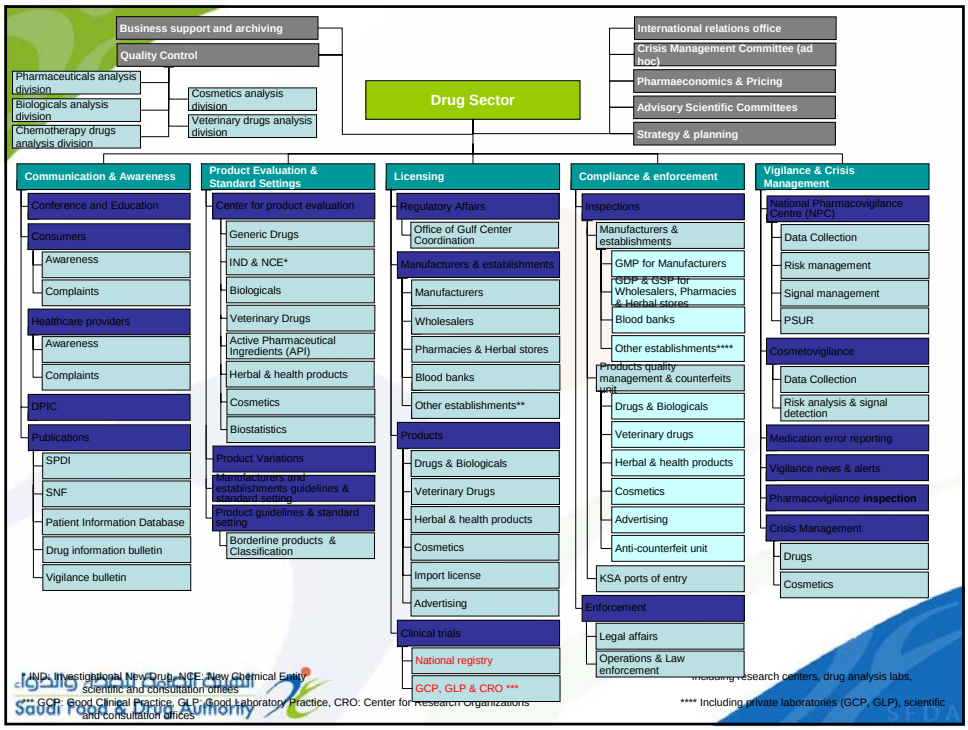
Abdulmohsen H. AL Rohaimi,
DDS, APC, MSc, Ph.D
Director of Research and Publication

March 2 – 6, 2009

GCP/ advance Clinical Research Inspection Workshop

Bangkok - Thailand

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 .

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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

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

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Saudi Food & Drug Authority

Opportunity & Needs

As of the first of jan 1st, 2010, the SFDA will require that all clinical trials in Saudi Arabia whether begun before or after that date must be registered with the Saudi Clinical Trial Registry.

Trials beginning after the first of jan 2010 must be registered before recruitment of the first patient“

All clinical trails **will** follow Saudi GCP guideline

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The Current Efforts for GCP Laws/ regulation in Saudi Arabia

Saudi Good Clinical Practice (GCP) principles was adapted from ICH guideline

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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

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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

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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

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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

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Saudi Food & Drug Authority

Thank you

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Saudi Food & Drug Authority

Review of Basic Workshop: Preparing for Inspection

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

APEC Advanced GCP Inspection Workshop

March 2, 2009

Key Elements in Preparing for CI Inspection -1-

- General review
  - Key activities in a clinical trial
  - Clinical investigator (CI) responsibilities under GCP
    - National regulations governing CIs
    - Investigator commitments, if applicable (e.g., Form FDA 1572 commitments)
  - Required (and additional) elements of informed consent

Key Elements in Preparing for CI Inspection -2-

- General Review (Continued)
  - Regulatory authority's "SOPs" for conducting and reporting a CI inspection
  - List of essential documents generally expected at the CI site

Key Elements in Preparing for CI Inspection -3-

- Inspection-specific materials
  - Assignment memo to the inspector
    - Correspondence to the inspected site pre-announcing the inspection
  - Study protocol
    - Investigator's brochure as needed (if available)
  - (Request) and review certain data listings and case report forms
    - Identify any potential problems

Key Elements in Preparing for CI Inspection -4-

- Develop an inspection/audit plan
  - Questions for opening interview
  - Data and records of (greatest) potential interest
    - Data (values/results) to compare with source
  - "Tools" to assist the inspector
  - Division of labor (especially if inspecting as a "team")

General Review

Key Activities in A Clinical Trial

- Reference: World Health Organization's (WHO) "Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation"
  - Identifies 15 key activities
  - CI contributes to most (nearly all) of these
  - Inspection should seek to understand each activity as it is performed at the trial site and the quality with which the CI/site performs that activity

WHO's 15 Key Activities -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, Qualified Investigators, and Study Site Staff

WHO's 15 Key Activities -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

WHO's 15 Key Activities -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

CI Responsibilities Under GCP -1-

- 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

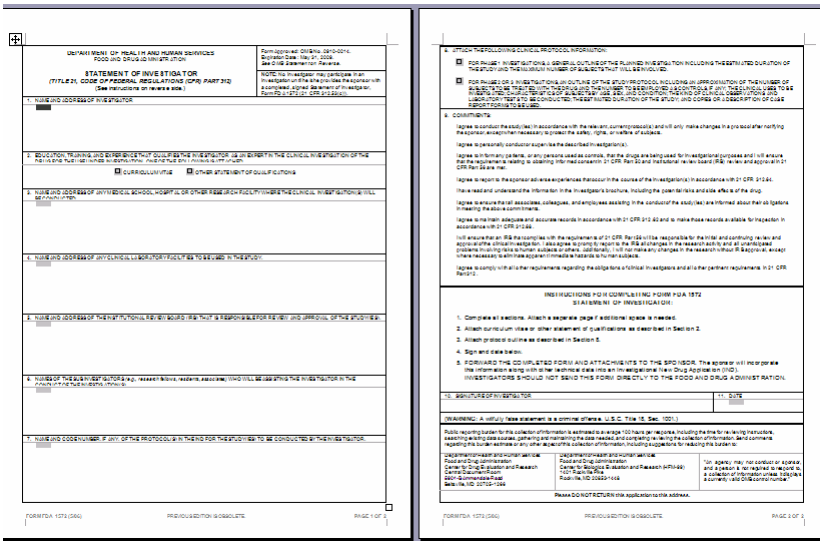
CI Responsibilities Under GCP -2-

- 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)

National Regulations Governing Conduct of CIs

- May impose additional requirements beyond (or more detailed than) those of international GCP, for example
  - U.S. requirement for Financial Disclosure by Clinical Investigators (21 CFR Part 54)
  - U.S. requirement for completion by CI of Investigator Statement (Form FDA 1572) for CIs/sites operating under a U.S. research permit (IND)
    - Available on-line at: www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf

Form FDA 1572: Statement of Investigator



STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

Form 1572: Includes Investigator Commitments and Signature

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

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

"SOPs" for Conducting a CI Inspection

- FDA Compliance Program Guidance Manuals (CPGMs)
  - Issued for each type of inspection
  - Current (12/2008) version for CI inspection http://www.fda.gov/ora/compliance_ref/bimo/7348_811/default.htm
  - Includes:
    - Background
    - Program management/Implementation instructions
    - **Inspectional procedures (Part III)**
    - Administrative (including classification) guidance
    - References and program contacts

Other Available "Model" SOPs for CI Inspecting

- European Medicines Agency (EMEA)
  - "Inspection procedures and guidance for GCP inspections conducted in the context of the Centralised Procedures"
  - Access at: http://www.emea.europa.eu/Inspections/GCPproc.html
- Pan American Health Organization (PAHO)
  - GCP Document of the Americas, Annex 4: A Guide to Clinical Investigator Inspections
  - Access at:
    - www.paho.org/english/ad/ths/ev/GCP-Eng-doct.pdf (English)
    - www.paho.org/spanish/ad/ths/ev/BPC-doct-esp.doc (Spanish)

Essential Documents at the CI Site

- ICH GCP (E6) Section 8 provides a list of "Essential Documents for the Conduct of a Clinical Trial" and guidance on where each document should be filed (with investigator/institution, with sponsor, or with both)
  - Useful as a guide in preparing for the "records inventory" component of an inspection

From ICH E6: Essential Documents at the CI Site -1-

- Investigator's Brochure, including updates
- Protocol, amendments, revisions, (sample CRF)
- Information given to the study subjects
  - Informed Consent form (+ any revisions)
  - Any other written information
- 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

From ICH E6: Essential Documents at the CI Site -2-

- (Regulatory authority authorization[s])
- Curriculum vitae
  - Clinical Investigator
  - Subinvestigators/site staff (List of duties)
- (Laboratory information; normal values, both initial and any updates)
- Shipping records for investigational product and study-related materials
- Instructions for handling investigational product
- Appropriate labeling of investigational product
- Decoding procedures for blinded studies
- (Monitoring reports: study initiation, monitoring visits, close-out)

From ICH E6: Essential Documents at the CI Site -3-

- Relevant communications with sponsor
- Signed and dated Informed Consent forms
- (Signed) Copy of completed CRFs
- Documentation of CRF corrections
- Notification to sponsor (and IEC) of serious adverse events
- Notification by sponsor to CI re: important safety information
- Interim reports to IEC
- 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

Inspection-Specific Materials

Assignment memo

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE ISSUED: *[leave blank for date stamp]* **FACTS#**

TO: Bioresearch Monitor
xxx District Office

(or for International)
International Operations Branch
Division of Field Investigations

FROM: *DSI Reviewer Name, Title*

THROUGH: Branch Chief, Good Clinical Practice Branch
Division of Scientific Investigations

SUBJECT: FY 2008 - High Priority CDER User Fee NDA Pre-Approval, Clinical Investigator Data Validation (*Domestic or Foreign*) Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811), *linked to Sponsor or IRB inspection (include if applicable)*

EIR Due Date: Select one:
45 days from issuance date *for domestic*
60 days from issuance date *for foreign*

RE:
NDA#:
Sponsor: Name
Address
City, State/Country, Mail Code
Telephone:
Fax:
Email:
Drug: brand name (generic name)
New Molecular Entity (NME): Yes/No
Protocol: # and Title
Type of Population: i.e., adult, pediatric, geriatric, or other special population
Subjects < 18 years: Yes/No ***[note for each protocol]***

Note: **Please fax a copy of any Form FDA 483 issued as soon as it is available.**

Assignment Memo to the Inspector -1-

- Subject of the assignment
- Inspection due date
- Background information
  - Investigational product, route of administration, disease/proposed indication
  - Description of protocol to be inspected
- Site(s) for inspection
  - Rationale for site selection
  - Previous inspectional history
  - Other sites for the same protocol

Assignment Memo to the Inspector -2-

- General instructions to the inspector
  - Guidelines (from CPGM) on what should be reviewed during the inspection
  - Guidance on how much to review
- Specific instructions
  - Any specific concerns of application reviewer(s), identified in a complaint, or identified during development of the inspection assignment
- Headquarters contact information

Study Protocol

- Sections most useful
  - Background (to investigational product; study)
  - Inclusion/Exclusion Criteria
  - Key datapoints/endpoints
  - Objective vs. subjective datapoints
  - Study flow chart
  - Investigational product handling
  - Monitoring plan (if included)
  - Sample CRF and informed consent document

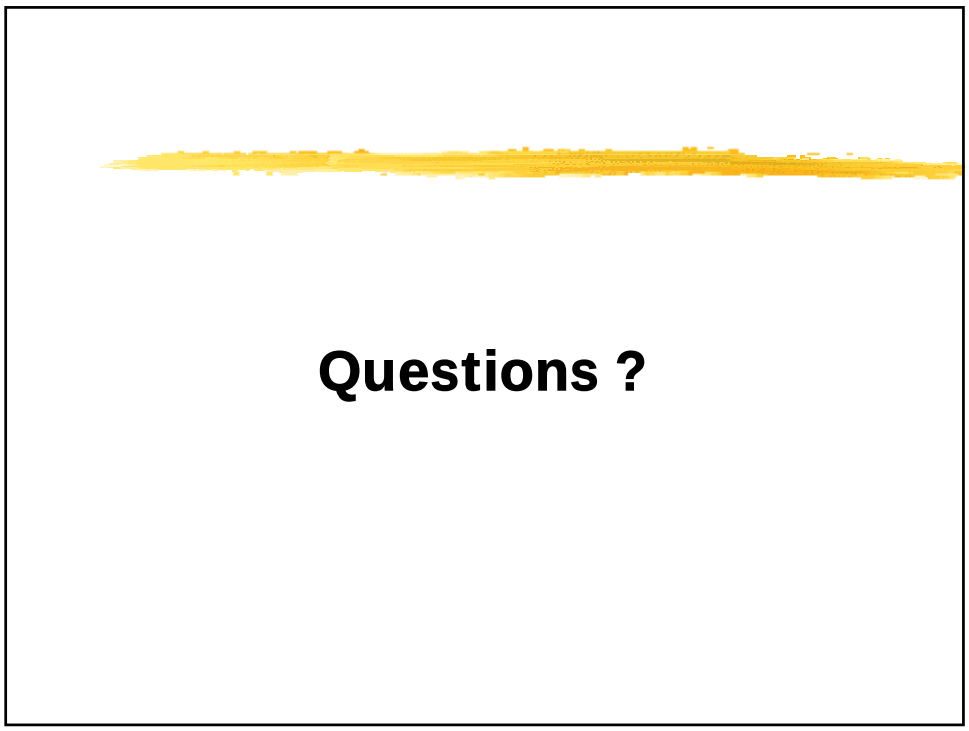
Specific Research Subject Data Listings and/or CRFs

- May be included with the inspection assignment
  - Randomly chosen or “for cause”
- Should generally be available (upon request) for advance review
  - Through application reviewer/team and/or
  - From sponsor

Inspection / Audit Plan

The Inspection/Audit Plan

- An inspection/audit plan is critical to efficient use of time and resources
- FDA does not have or prescribe the use of checklists
  - However, many FDA inspectors will develop/use checklists for their individual purposes
- Learn from our mock inspection exercise
  - Be prepared to discuss during report-out (Day 5)


Questions ?

Review of Basic Workshop: Conducting an Inspection

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

APEC Advanced GCP Inspection Workshop

March 2, 2009

A Good Inspection is Built on the "Scientific Method"

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

Conducting the Inspection -1-

- Pre-announced [...or not]
- Present authority/credentials to inspect
- Opening interview (investigator)
- Meet key site staff
  - Plan for secondary interviews of site staff
- Identify a work site

Conducting the Inspection -2-

- Inventory the study records
- Process/systems review: Key trial activities
- Conduct the data audit
  - Verify research subject protection/ethics
    - Informed Consent (forms and process)
    - IEC review and communications
  - Verify investigational product handling and accountability

Conducting the Inspection -3-

- Identify specialized tests, diagnostic testing facilities, and supporting laboratories
  - Consider facilities tour(s)
- Be sure to consider each of the investigator's responsibilities under GCP (and applicable regulations)

Conducting the Inspection -4-

- Document what was done during the inspection
- Document objectionable findings (deviations from GCP/regulation)
  - Collect "exhibits" to support each observation
  - Protect subject confidentiality in records collected
- Verify and develop a written list of (any) objectionable findings
- Close-out meeting with the clinical investigator

Getting Started –
In Greater Detail

Notice of Inspection (Form 482)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1431 Harbor Bay Parkway
Alameda, CA 94502-7070
408-291-7332

2. NAME AND TITLE OF INDIVIDUAL
Robert E. Thompson, Plant Manager

3. DATE
9-10-06

4. FIRM NAME
Garden City Nut Shellers

5. TIME
8:30 a.m.

6. NUMBER AND STREET
3704 Sellers Ave

7. CITY AND STATE ZIP CODE
San Jose, CA 95131

8. PHONE # & AREA CODE
408-213-4587

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264]

9. SIGNATURE (Food and Drug Administration Employee(s))
Sidney H. Rogers

10. TYPE OR PRINT NAME AND TITLE (FDA Employee(s))
Sidney H. Rogers, Investigator

* Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704. (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414 when the Secretary has a reasonable belief that an article of food (other than infant formula for which a notice or other information is required by law) is adulterated within the meaning of section 402(a)(1) or 402(a)(2) and presents a threat of serious adverse health consequences or death to humans or animals, subject to the limitations established in section 414(b). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use or restricted devices which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such plant, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (2) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or 519, section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale by wholesale, or which do not sell such drugs or devices at wholesale, or (B) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704. (b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) is otherwise unfit for food, drug, or cosmetic purposes, or (3) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records, and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person

FORM FDA 482 (7/06) PREVIOUS EDITION IS OBSOLETE (Continued on Reverse) NOTICE OF INSPECTION

Notice of Inspection

- Standard format/form delivered to the inspected party on arrival of the inspector
  - Form FDA 482; available at: http://www.fda.gov/ora/inspect_ref/iom/exhibits/5-1.pdf
- Form includes:
  - FDA field office address and phone number
  - Inspected party: identifying information
  - Date and hour notice was presented
  - Signature of the FDA inspector
  - Statement notifying of inspection and legal authority for the inspection

Inspection Refusals

- May include
  - Refusal of Entry
  - Refusal of Information
- Procedures should be addressed in regulatory agency's SOPs
  - May include procedure for (a pre-emptive or a follow-up) inspection warrant

Opening Interview: General

- Interview is between the inspector and the inspected party
  - Inspector decides whether others can be present
- CI may want to deliver a “prepared” presentation
  - Try to limit these: i.e., to the extent these are useful to the inspector
  - Don’t let a prepared presentation substitute for an opening interview
- Expect to spend 45-60 minutes with the CI

Opening Interview: Setting the Tone

- 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

Opening Interview: Getting Started

- Communicate 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

Opening Interview: Some Sample Questions -1-

- Focus on learning about the CI, his/her experiences with the study, and an orientation to the site, staff, and records
  - How many studies has the CI previously conducted ?
  - Did the sponsor provide any training ?
  - Who else is working for the CI on the study ?
  - Who is doing what (when and where) ?
  - Were there any problems with recruiting subjects ?
  - Any requests for exception to inclusion/exclusion criteria ?

Opening Interview: Some Sample Questions -2-

- Any problems with subjects coming in for visits ?
- Any difficulties with the protocol/complying ?
- Any problems with blinding the study ? Could subjects predict which study arm ?
- Any serious/unexpected adverse events at the site ?
- Did the sponsor come to monitor ? Effectiveness ?
- Any computer systems used at the site ?
- Who organized the files we will be looking at ?

Opening Interview: Ending the Interview

- Give CI opportunity to ask questions about the inspection
- Indicate that CI need not be physically present the entire day
  - Establish meeting times with the CI (e.g., end of day AND at end of inspection)
  - Identify key site staff available for assistance if/as needed
- Inspector should request a quiet work space
  - Access to a photocopier

Records Inventory and Process/Systems Review

Records Inventory: To Start

- Often useful for knowledgeable site staff to provide initial orientation to the available records
  - 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

Records Inventory: Assessment

- Be guided by inspection SOPs and a listing of Essential Documents expected at the site
  - Are any Essential Documents missing/unavailable ?
- Identify "source" data/documents
  - Working definition of "source": The first place that the data are committed to durable medium
  - Distinguish clearly from transcribed data/documents
- Assure that "source" really is "source"
  - Not just created after-the-fact for the inspector/ regulator

Process/Systems Review -1-

- Be guided by the key activities (e.g., WHO's list of "15 key activities") in a clinical trial
- Review the investigator's/site's involvement in each key trial activity and approaches to ensuring the quality of each activity by the CI and at the site
  - Identify any weaknesses that might impact the quality of a key activity
    - Are there associated regulatory violations ?

Process/Systems Review -2-

- Process/systems review should also seek to gauge the GCP compliance of the sponsor/CRO and IEC from information available at the CI site
  - Is a follow-up sponsor/CRO or IEC inspection warranted ?

Data Audit

Data Audit: Which Data and How Much ? -1-

- Initial guide:
  - Inspection SOPs and Assignment Memo
    - In general, review records for 1/3 to 1/2 of the total number of subjects at the site
    - If number of subjects randomized at the site is less than 25, inspector may review proportionally more (or even all) subjects
    - If number of subjects is very large, an appropriate but smaller fraction of subjects will be reviewed

Data Audit: Which Data and How Much ? -2-

- Initial guide (Continued)
  - Inspector's review of protocol and identification of key subjects, data, and timepoints
    - Examples to consider:
      - Subjects who have discontinued prematurely
      - More objective/corroborating data
      - Key endpoints at time zero and at time prescribed in the protocol for primary data analysis

Data Audit: Which Data and How Much ? -3-

- Be sure that the data audit addresses:
  - Verification of research subject protection
    - Inclusion/exclusion criteria are met
    - Reporting of safety (and not just efficacy) data
    - Informed consent audit
  - Verification of investigational product handling and accountability

Data Audit: General Approach

- Compare original source data to the CRF entries and/or to the final report(s) submitted by the investigator to the sponsor
- Assess data for quality (ALCOA) and for integrity (3 “C’s”)
- If a significant problem is identified, expand the inspection in that area

Data Quality

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

Data Integrity

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

Facilities Tours

Facilities Tours -1-

- Determined by inspector (not “required” under FDA’s CI CPGM)
- Possibilities:
  - Examining rooms/equipment
  - Site of specialized procedures
  - Clinical laboratory(-ies)
  - Pharmacy
  - Shipping and Records departments

Facilities Tours -2-

- Purpose
  - Does the facility exist ?
  - Indicator of the site's general organization and functioning
  - Can the facility support GCP, protocol compliance, and the development of adequate and accurate subject data/case histories ?
  - [Follow-up to subject complaints]
- Generally not within the scope/jurisdiction of the inspector to "qualify the facility"

Inspector's On-Site Documentation

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
  - Diary should 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 supporting any observations of a GCP violation
- Include when, where, and from whom copies were obtained and that it is a true copy of a source document: inspector's diary should make note that the authenticity of source copied was verified

Exhibits -2-

- Confidentiality is essential and FDA works to maintain confidentiality, but subject identifiers are often essential – reason for essential element in informed consent
- Exhibit pages are identified with an exhibit number, name of inspected party, date(s) of inspection, and FDA inspector's initials
- Identifying information must not cover, deface, or obliterate any data on the record/document

Close-Out Meeting and List of Inspector's Observations

Close-Out Meeting

- Explain what was inspected
- Present the written list of objectionable findings, (FDA Form 483), if applicable
  - Discuss and explain each finding
- Separately discuss and explain additional findings that were not included on the written list
- Provide the CI with an opportunity to respond to the findings orally or in writing
- Explain additional levels of review before any final decision/classification of the inspection

Form FDA 483

- Listing of inspector's observations
  - Observations should be significant (GCP violations) and based on pertinent national regulations
  - Observations should not reference guidance (...only violations of regulation)
  - Should not be issued when there are no significant GCP deviations
- Not a final report

Conducting an Inspection: Overall Considerations

Overall Considerations -1-

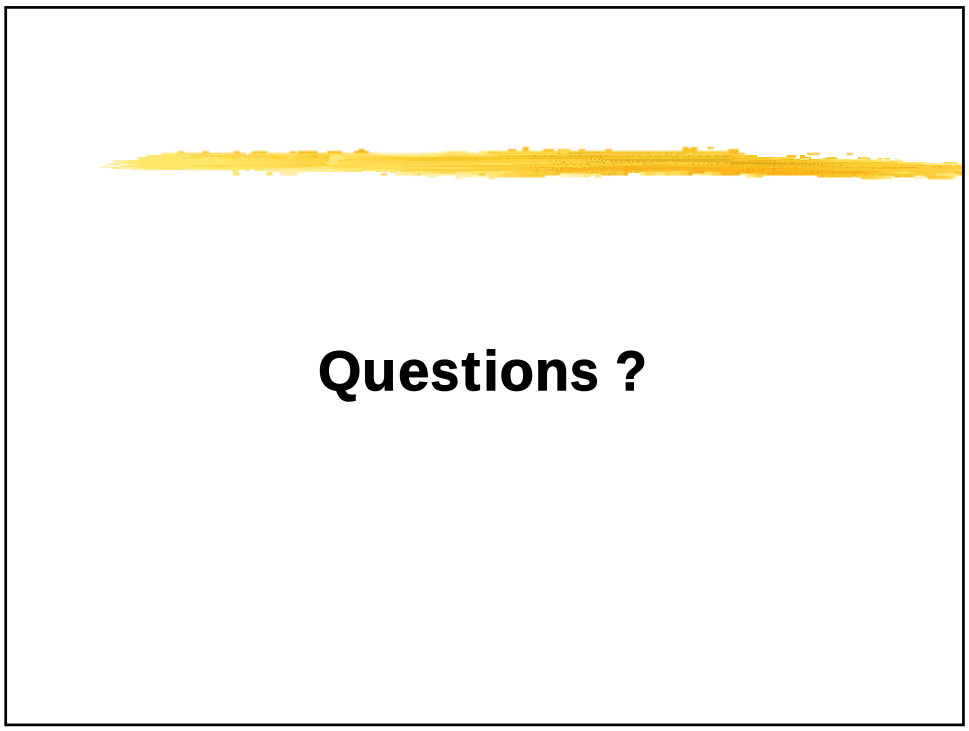
- Let the inspection build (or diminish) your confidence in the site
- Don't be intimidated
- Work forward (from inspection preparation and audit plan), in real time (from any violative or suspicious observations), and backward (from what is required for the inspection report)

Overall Considerations -2-

- Be prepared to get technical
  - Medical/scientific support as needed
- Query chain of custody (e.g., subject CRF; investigational product) and/or the sequence of steps in a process
- Don't be afraid to count/add

Overall Considerations -3-

- Don't just inventory --- **read** some of the essential documents (e.g., subject/patient clinic charts; monitoring reports; IEC correspondence)
- Be on the lookout for pages out of order and/or suspicious changes in handwriting or "ink"


Questions ?

Review of Basic Workshop: Inspection Reporting and Classification

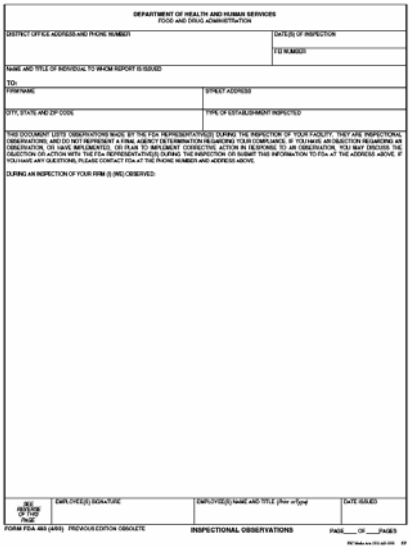
David A. Lepay, M.D., Ph.D.

APEC Advanced GCP Inspection Workshop

March 3, 2009

U.S. Food and Drug Administration

Form FDA 483



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION | FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME | STREET ADDRESS

CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I (WE) OBSERVED:

PAGE OF PAGES | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (Type or Print) | DATE ISSUED

FORM FDA 483 (4/97) PREVIOUS EDITION OBSOLETE | INSPECTIONAL OBSERVATIONS | PAGE ___ OF ___ PAGES

Form FDA 483

- Listing of inspector's observations presented to the inspected party at the close-out meeting
  - Observations should be significant (GCP violations) and based on pertinent national regulations
- Not a final report

Due Process: Inspected Party's Opportunity to Respond

- Inspected party may respond orally, in writing, or both
  - Response may occur at the close-out discussion or at any time after the inspection
- Response at the close-out discussion should be documented in the inspector's diary
- Response will become part of the Establishment Inspection Report

FDA and TURBO

- Computerized system (software) for recording inspectional observations (FDA Form 483) and preparing Establishment Inspection Reports (EIRs)
- Standardizes the language used for reporting inspectional observations
  - Assures link to pertinent regulation
- Presently used for most GCP inspections

TURBO Cites: General Format

- "Failure to....(language of violated regulation). Specifically..."
- "An investigation was not...(requirement not fulfilled). Specifically..."
- Study drug was not...(requirement)... Specifically..."
- Clinical investigator did not...(requirement). Specifically..."

Establishment Inspection Report (EIR)

References

- CPGM Program 7348.811: Part III (Inspectional), Section “P” (EIRs)
- FDA Investigations Operations Manual, Section 5.10
  - Available at http://www.fda.gov/ora/inspect_ref/iom/ChapterText/5_10.html#SUB5.10

Establishment Inspection Report (EIR) -1-

- Prepared after the inspection
- 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

Narrative Report

- May be a “Summary of Findings” if no violative conditions were found
- Same basic areas are always covered (just more abbreviated if no violative conditions)
  - Reason for inspection
  - Administrative information
  - Scope of the inspection
  - Individual responsibilities
  - Inspectional findings
  - Close-out discussion with investigator

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

Administrative Information -1-

- FDA Application number
- Name of investigational product
- Study sponsor
- Protocol title and number
- Dates of study (overall; at site)
- Name of the CI/inspected party
- Location of study site inspected
- Identity of the Ethics Committee

Administrative Information -2-

- 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

Scope of the Inspection

- Statement about comparison of data (CRFs or line listings) with the CI's source documents
- State what records were covered
  - Clinic Charts
  - Hospital Records
  - Laboratory slips; Radiology/Pathology Reports
  - Other Source Documents (ECGs; X-rays)
- Number of files and CRFs Reviewed (out of the total site and study population)

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: General Statements

- Statement about test article accountability
  - Including identification of records that were reviewed
- Statement whether there was evidence of under-reporting of adverse experiences
- Statement about protocol adherence

Inspection Findings: Specifics

- Significant observations (if any) ....
  - Violations of regulations/GCP

Statement of the Close-Out Discussion

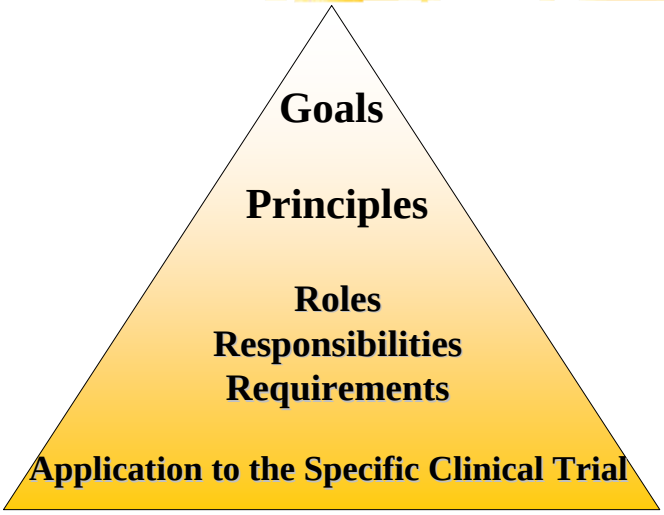
- Summarize the discussion of "483" observations and non-483 observations
  - Include identification of who was present at this closing interview
- Summarize the investigator's response to these observations

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

Classifying the Inspection/ Inspection Findings

The Hierarchy of GCP



Classifying the Inspection General -1-

- Inspectional observations/findings are NOT all of equal significance and impact
  - Those that violate the goals and principles of GCP are the most significant
    - Require the most thorough documentation on inspection
    - Are most likely to lead to official (vs. voluntary) enforcement action

Classifying the Inspection General -2-

- Classification should be done (only) after supervisory review and concurrence
  - FDA inspectors can recommend a classification for GCP inspections, but
  - 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

Approaches to GCP Inspection Classification -1-

- Single classification for the inspection as a whole
  - U.S. FDA approach
    - NAI: No Action Indicated (GCP compliant)
    - VAI: Voluntary Action Indicated
    - OAI: Official Action Indicated (compromise to goals of GCP)

Examples of Violations that May Warrant OAI Classification

- Inadequate Human Subject Protection
  - Failure to inform subjects that they could refuse to participate
  - Subject's request to withdraw was denied
  - Missing consent documents
  - No documentation of IEC approval
  - Failure of CI to supervise the study with resultant exposure of subjects to unreasonable and significant risk or injury

Examples of Violations that May Warrant OAI Classification

- Submission of false information to FDA or the sponsor
  - Study records are fabricated, altered, or concealed
  - False or misleading reports were prepared and/or submitted
  - Inadequate CI supervision of study personnel who, in turn, fabricated, altered, or contributed false information to study records or reports

Examples of Violations that May Warrant OAI Classification

- Repeated or Deliberate Failure to Comply with the Regulations
  - For example, repeatedly or deliberately enrolling subjects who do not meet entrance criteria because they have conditions that put them at increased risk
  - Repeated or deliberate use of an investigational product by an unauthorized individual
- Promotion or commercialization of investigational products

Approaches to GCP Inspection Classification -2-

- Grading of each inspectional finding
  - EMEA Approach
    - Critical
    - Major
    - Minor
  - (Note: U.S. FDA does not classify each individual finding)

EMEA Definitions: Grading of Findings -1-

- Critical
  - Conditions, practices or processes that **adversely affect** the rights, safety, or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable
  - Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

EMEA Definitions: Grading of Findings -2-

- Major
  - Conditions, practices, or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles
  - Remark: Observations classified as major may include a pattern of deviations and/or numerous minor observations

EMEA Definitions: Grading of Findings -3-

- Minor
  - Conditions, practices, or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data
  - Indicate the need for improvement of conditions, practices, and processes
  - Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences

Mock Inspection Exercise

Mock Inspection: Written Report

- Each team will prepare a written inspection report
  - Form and format of an EIR
  - Covering all basic components of the EIR
    - Reason for inspection
    - Administrative information
    - Scope of the inspection
    - Individual responsibilities
    - Inspectional findings
    - Close-out discussion with investigator

Mock Inspection: Oral Report-Out

- Each team will prepare an oral report-out for presentation on Friday (Day 5)
  - 20 minutes in length – not longer
    - Ability to concisely summarize the inspection is important
- Reports should not cite product or company names
  - Refer to investigational products as “IP” (or IP1, IP2)
  - Refer to sponsor as “Company x”

Elements of Day 5 Oral Report-Out -1-

- Few sentence description of the study
  - Most important points for inspection
- Team’s approach to preparing for inspection
  - Inspection plan and division of labor
- Brief orientation to the CI and site
- What was inspected
- Comment on each of the key trial activities as observed at the site

Elements of Day 5 Oral Report-Out -2-

- Compliance with investigator's responsibilities
  - Any violations of GCP ?
- Brief summary of close-out meeting
- Final comments from the team
  - Any areas of difficulty or surprises during the inspection ?

Questions ?

In Vivo Bioequivalence

Martin K. Yau, Ph.D.
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Compliance, CDER

Clinical Bioresearch
Monitoring BR2001A

Outline

- What is bioequivalence (BE)?
  - significant endpoint data in a BE study
  - BE study design
- Role of BE in the approval process
- Critical points to consider when conducting an clinical study site inspection
- CDER's BE inspection program

What is bioequivalence?

In plain English...

- Two drug products with the same active ingredient/moiety are considered bioequivalent if they achieve similar drug concentration - time profile in the systemic blood circulation when administered at the same dose

Regulatory Definition

- Bioavailability and Bioequivalence Requirements, 21 CFR Part 320
  - 21 CFR 320.1(a)
    - Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the the site of action.

Regulatory Definition

- Bioavailability and Bioequivalence Requirements, 21 CFR Part 320
  - 21 CFR 320.1(e)
    - Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

- Since measuring the rate and extent to which the active moiety becomes available to the site of drug action is usually not feasible we rely upon the existence of a relationship (when it occurs) between safety/efficacy and concentration of drug in the systemic circulation to demonstrate BE

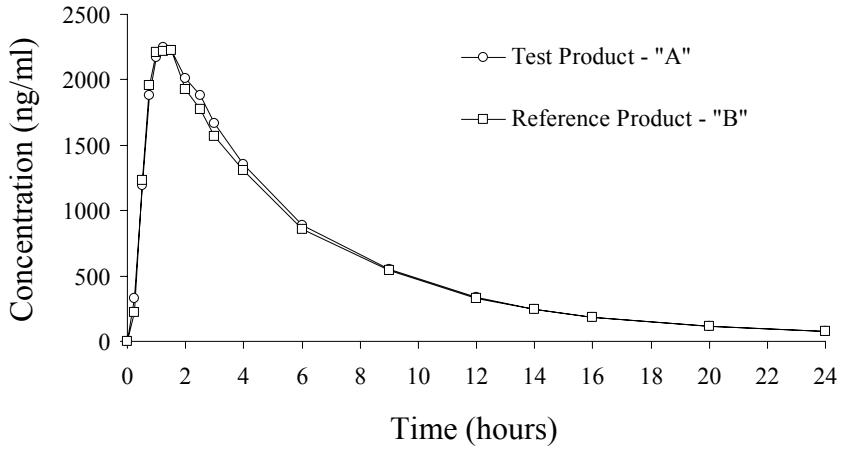
How is BE demonstrated?

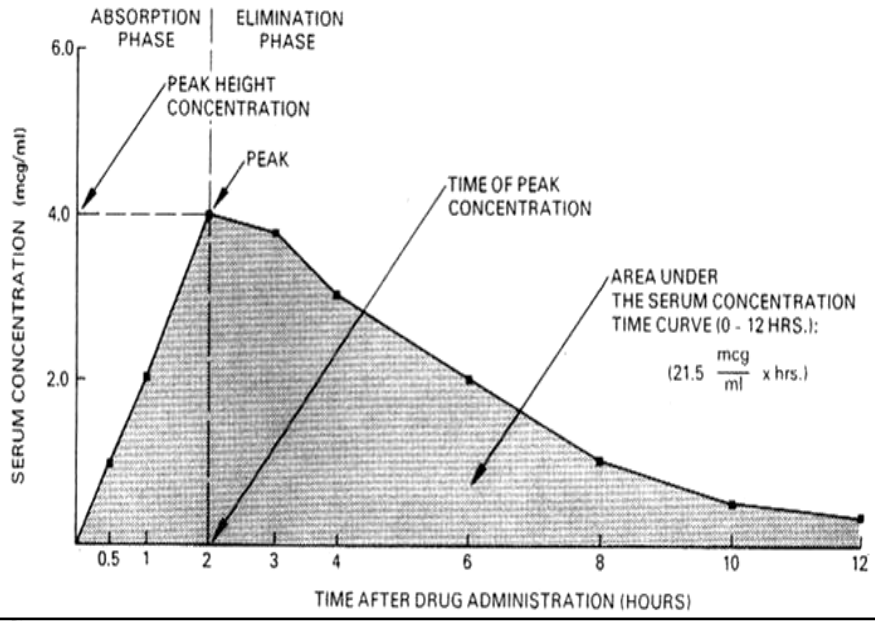
- Same group of Subjects (n=18-36) are administered test (A) and reference (B) drug products in separate dosing periods
- Serial samples of biologic fluid (plasma, serum, urine) are collected from subjects just before and at various times after dosing (e.g., 0.5, 1, 1.5, 2, 2.5,3,3.5,4,6,9,12,14,16,20, and 24 hr post dose)

- The samples are analyzed for drug and/or active metabolite concentrations
- The concentration data are used to generate a drug concentrations-time profile (i.e., a systemic exposure profile)

Systemic Exposure Profile

time course of a drug in the body





- Pharmacokinetic measures of peak and total exposure of the drug of interest and/or its active metabolite(s) in the systemic circulation are used to demonstrate BE
  - Cmax
    - peak drug concentration achieved
    - rate and extent of absorption
  - AUC
    - Area Under the Curve
    - total amount of drug in the systemic circulation

Other pharmacokinetic parameters determined in a BE study

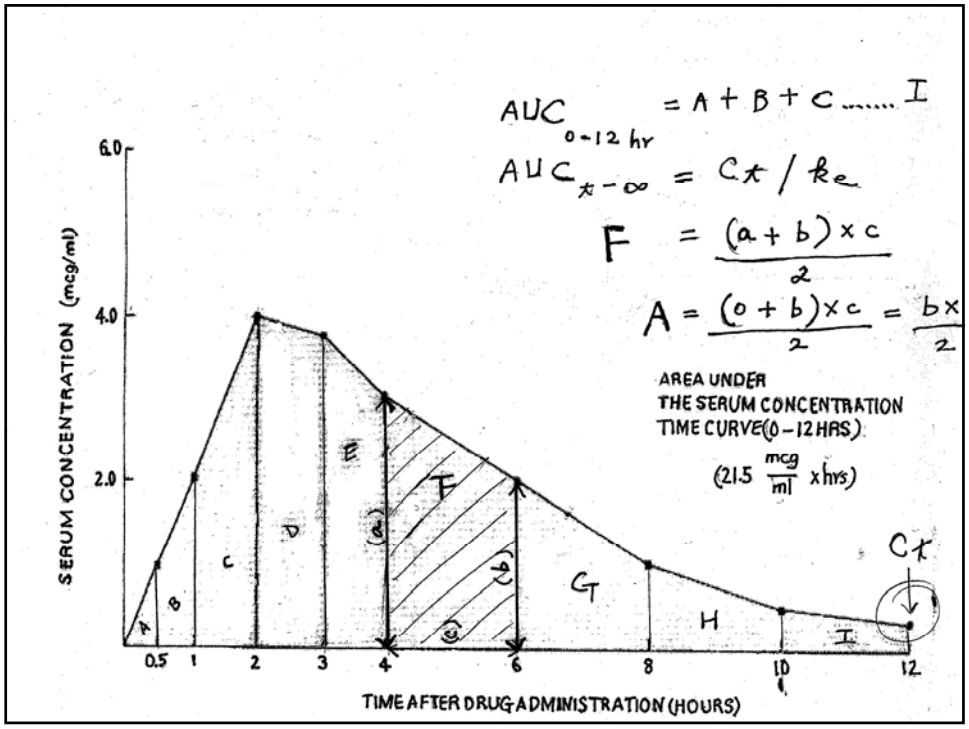
- Tmax (rate of absorption)
  - Time when Cmax is achieved
- Elimination rate constant, ke
  - Determined by linear regression of data point in the elimination phase
- Elimination half-life, $t_{½}$
  - $t_{½} = 0.693 / ke$

AUC

AUC $0-\infty$ = AUC 0-t + AUC $t-\infty$

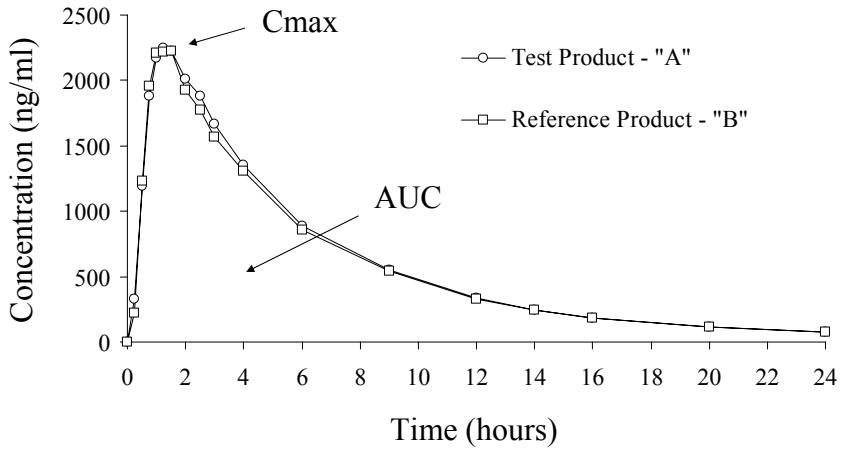
AUC 0-t = AUC from zero time to time when last plasma sample is collected

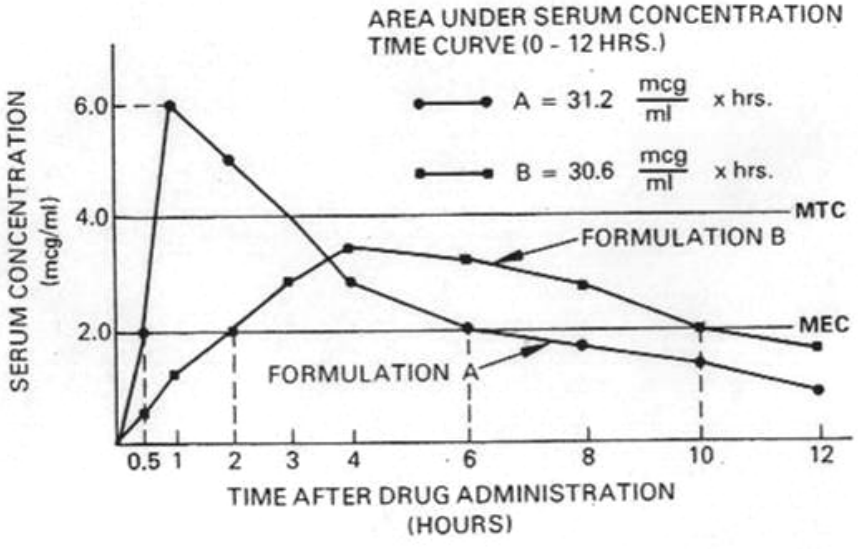
AUC $t-\infty$ = AUC from time t to infinity
= C t / ke
(Ct = concentration of the last collected plasma sample)

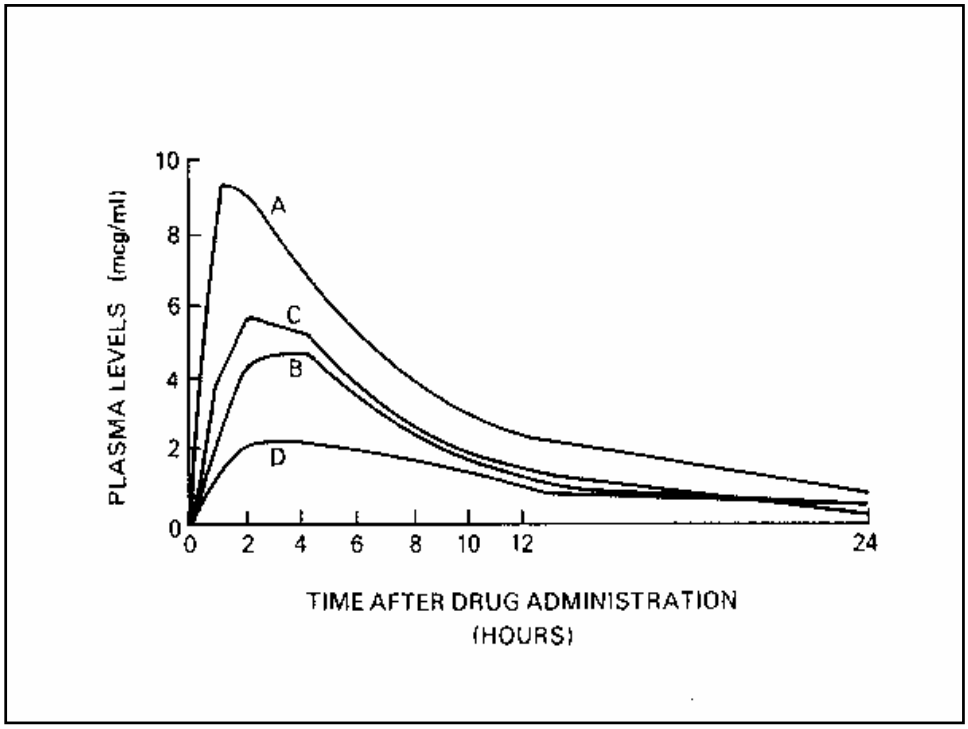


- Cmax and AUC undergo statistical analysis to determine whether these pharmacokinetic measurements demonstrate BE
  - test (A) and reference (B) products are considered bioequivalent when the 90% confidence intervals for (i) Cmax (A/B) ratio and (ii) AUC (A/B) ratio are within 80-125%

Systemic Exposure Profile






PLASMA LEVELS (mcg/ml)
10
8
6
4
2
0
A
C
B
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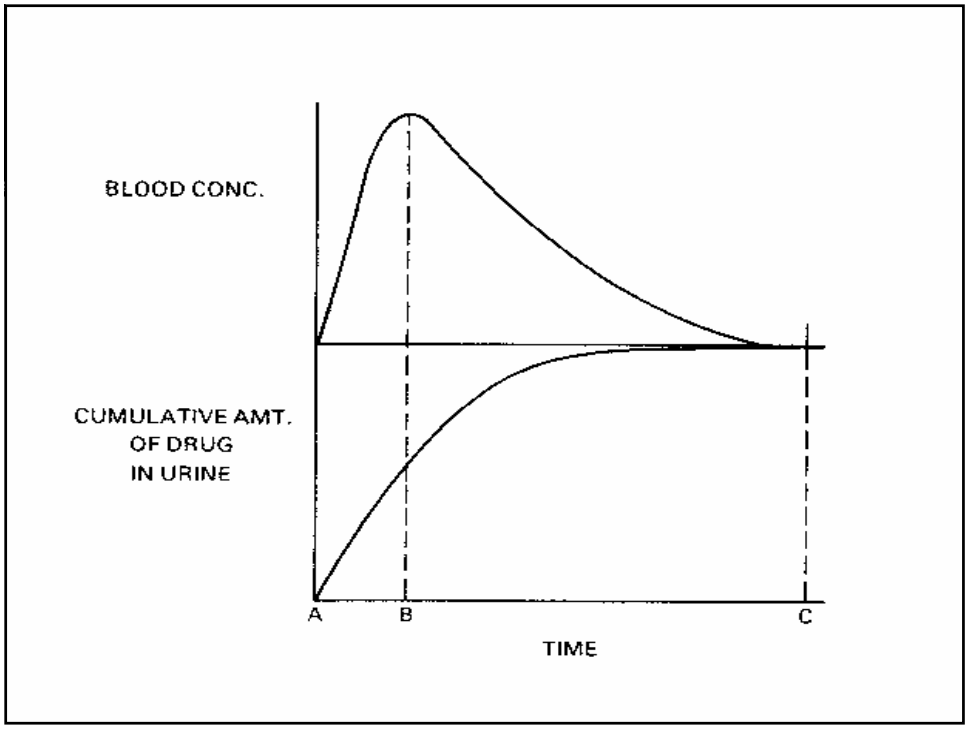
8
10
12
24
TIME AFTER DRUG ADMINISTRATION
(HOURS)


BLOOD CONC.
CUMULATIVE AMT.
OF DRUG
IN URINE
A
B
C
TIME

Study Design

- BE studies include clinical, analytical and statistical portions
  - clinical
    - subjects are dosed, blood samples are collected
  - analytical
    - blood samples are analyzed for drug concentration
  - statistical
    - analysis of the resulting concentration data
  - may be the same or different facilities

- BE studies usually employ 18-36 normal healthy subjects
  - number of subjects enrolled depends upon the variability of the drug
  - subjects with the target disease are sometimes used
  - All subjects should be audited!

TYPICAL BE STUDY

- Single dose, randomized, crossover study in a fasted state
  - each subject receives the test (A) and reference (B) drug products in separate dosing periods
    - length of time between dosing periods (washout) depends upon the elimination half life of the drug
  - subjects/clinical staff are generally not blinded
  - assignment to dose sequence is random

BE STUDIES -Variations

- Single-dose food study
- Multi-dose study
- Pharmacodynamic (PD) or clinical endpoint BE study
  - drug not intended for systemic absorption, or measurement in the blood not feasible
    - antifungal cream for tinea pedis (athlete's foot)
      - cure rate, both clinical and mycological cure
    - usually a double blind study

BE and the Approval Process

- BE studies are conducted for both NDAs and ANDAs
- NDAs
  - clinical trial versus to-be-marketed formulation
    - links the formulation used in demonstrating safety and efficacy to the formulation that will be marketed
  - change in dosage form
    - tablet already approved, sponsor wants to market a capsule, suspension, or extended release formulation

- ANDAs
  - generic versus innovator formulation
    - if the concentration of the drug in plasma is the same, it is assumed that the generic formulation will demonstrate the same safety and efficacy as the innovator product

Critical Points to Consider When Conducting an Clinical Study Site Inspection

Clinical Conduct

- Regulatory perspective
  - requirements for clinical studies in general
    - 21 CFR Part 50, Protection of Human Subjects
    - 21 CFR Part 56, Institutional Review Boards
    - 21 CFR Part 312, Investigational New Drug Application
- Compliance Program Guidance Manual
  - Program 7348.001, In Vivo Bioequivalence

- Many BE studies for ANDAs do not require an IND [21 CFR Part 320.31(d)]
  - the study is conducted in compliance with Parts 50 and 56
  - reserve samples of the test and reference drug are retained
    - when exempt from the IND regulations, Form 1572 is not required

- Regardless of whether an IND is required, BE inspection must verify the accuracy, quality and integrity of the data
  - All observations that impact study outcomes should be cited on the Form FDA-483

Critical Points

- Subject safety
- Dosing
- Drug products
- Blood draw time
- Sample processing
- Adverse events
- Protocol adherence
- Reserve samples

Subject Safety

- Were the rights, health and welfare of the subjects protected?
  - Was informed consent obtained?
    - verify 100% of the informed consent forms
  - Was adequate medical supervision provided?

Dosing

- Who got what?
  - actual treatment administered
    - "A" or "B"
    - Was the randomization scheme adhered to?
- When did they get it?
  - actual dosing time
  - Who administered it?
    - CI or designee

Drug Products

- Accountability
  - numbers of tablets dispensed, returned, remaining
- Lot numbers
  - verify information provided to FDA
- Control of drug storage area
  - security, temperature, humidity

Blood Draw Time

- Were draw times documented at the time of the event?
  - Were changes justified?
- Were deviations reported?

Sample Processing

- Were samples processed according to the protocol?
  - temperature, centrifugation, within specified time frame
- Were processed (e.g., plasma, serum or urine) samples stored appropriately?
  - storage temperature, location

Adverse Events

- Were all adverse events reported?

Protocol Adherence

- Inclusion/exclusion criteria
  - Were inclusion/exclusion criteria met?
- Were protocol-required screening, in-study and post-study activities conducted?
  - e.g., clinical chemistry/hematology/urinalysis, pregnancy tests, vital signs, EKGs, physical exams

- Was adherence to protocol restrictions documented at each dosing period?
  - BE protocols commonly exclude
    - Rx and OTC drugs 7-14 days prior to dosing and throughout the study
    - caffeine (xanthines)/alcohol 24-48 hours prior to dosing

Reserve Samples

- Retained samples that are representative of the actual drug products used in the study
  - reserve samples help FDA more fully investigate instances of possible fraud in BE testing
    - fraudulent substitution, "the generic drug scandal"

What's the regulation?

- Reserve sample requirements are defined by
  - 21 CFR Part 320.38 and 320.63 "Retention of BA Samples" and "Retention of BE Samples"
    - Federal Register Notice, Vol. 58, No. 80 (April 28, 1993) "Retention of BA and BE Testing Samples"

- Guidance document from DSI
  - "Handling and Retention of BA and BE Testing Samples"
    - http://www.fda.gov/cder/guidance/guidance.htm
      - under the heading "Generics (Draft)"

Core Elements

- Reserve samples must be
  - randomly selected at the study site
  - positively identified as having come from the same sample used in the BE study
  - maintained in sufficient quantity
    - 5x all of the release tests required by the application

- Reserve samples must be
  - stored under conditions consistent with product labeling
    - reserve samples cannot be returned to the sponsor
  - retained for 5 years after the approval of the application

- The request to collect reserve samples is specific to the BE study you are inspecting
  - the reserve samples should be sent to FDA Division of Pharmaceutical Analysis (DPA) in St. Louis for analysis

- These critical points will be discussed in more detail in BE clinical Inspection technique session.

FDA
CENTER OF DRUG EVALUATION AND RESEARCH (CDER) 's BA/BE Inspection Program

CDER'S BA/BE INSPECTION PROGRAM

- The BA/BE inspection program is a part of the CDER Bioresearch Monitoring (BIMO) program.
- BIMO program was established in 1977 to provide oversight of the conduct of studies with regulated drug products in the U.S.

THE CDER's BA/BE INSPECTION PROGRAM IS LOCATED IN:

- **GLP and Bioequivalence Investigations Branch**
  Division of Scientific Investigations
  Office of Compliance
  Center for Drug Evaluation and Research
  U.S. Food and Drug Administration
  Building 51, 5th Floor
  10903 New Hampshire Avenue
  Silver Spring, Maryland 20993
  USA

MEMBERS OF THE BA/BE INSECTION PROGRAM

C. T. Viswanathan, Ph.D. (Chief)

Michael F. Skelly, Ph.D.
Jacqueline A. O'Shaughnessy, Ph.D.
John Kadavil, Ph.D.
Xikui Chen, Ph.D.
Lisa Capron
Dylan Yao, Ph.D.
Gopa Biswas, Ph.D.
Carolyn Lopez, Ph.D.
Linda Kaufman
Martin K. Yau, Ph.D.
Sriram Subramaniam, Ph.D.
Hyojong Kwon, Ph.D.
Samuel Chan, Ph.D.
Abhijit Raha, Ph.D.
Sean Kassim, Ph.D.
Arindam Dasgupta, Ph.D.
Zhou, Chen, Ph.D.

THE OBJECTIVES OF THE BA/BE INSPECTION PROGRAM ARE:

- To verify the quality, integrity, and accuracy of scientific data submitted in support of CFR Part 320 - BA and BE requirements
- To assure the protection of the right & welfare of the study subjects

THE OBJECTIVES OF THE BA/BE INSPECTION PROGRAM ARE:

- To promote quality & consistency across the studies conducted by the pharmaceutical industry, generic & innovators alike
- To foster voluntary compliance

WHAT KIND OF STUDIES DO WE INSPECT?

- BA and BE studies pivotal to support approval of an application.
  - New Drug Application (NDA)
  - NDA supplement
  - Abbreviated New Drug Application (ANDA)

NEW DRUG APPLICATION (NDA)

- BA Studies
  - Oral solid dosage form vs. solution
- BE Studies
  - New formulation vs. marketed formulation
  - Formulation used in clinical trials vs. to be marketed formulation
  - New route of drug administration (e.g., IV, subcutaneous vs. oral)

NEW DRUG APPLICATION (NDA)

- Other Phase I studies that are important to support labeling:
  - Pharmacokinetic (PK) studies
  - Pharmacodynamic (PD) studies
  - PK-PD link studies
  - In vitro drug metabolism and drug-drug interaction studies

ABBREVIATED NEW DRUG APPLICATION (ANDA)

- BE Studies (generic product vs. innovator product)
  - In Vivo
    - Single-dose fasting study
    - Multi-dose fasting study
    - Food study
  - In Vitro
    - Nasal aerosols and nasal sprays

WHO DO WE INSPECT?

- Contract Research Organizations (CROs)
- Universities
- Study Sponsors (In-house studies)

REASONS FOR INSPECTING A STUDY SITE

- OAI classification on last inspection
- No inspection history (new sites)
- Suspicion of false or fraudulent data
- Complaint
- Pivotal study

TYPE OF INSPECTIONS

- Domestic Inspection
  - Routine inspections
  - For cause inspections
- Foreign Inspections

FOR CAUSE INSPECTION

- The study contains data that appear unrealistic.
- Questions about the integrity or quality of the BA/BE data, and/or results of drug assays.
- There are evidences of selective reporting of study data.

INSPECTION TEAM

- FDA field investigator from the Office of Regulatory Affairs (ORA)
  - Domestic inspections: investigator selected from ORA District Office where the study site is located
  - Foreign inspections: investigator selected from the ORA foreign inspection cadre
- FDA scientist from the Division of Scientific Investigations (DSI), CDER

INSPECTION NOTIFICATION

- Routine domestic inspections
- Routine foreign inspections
- For cause inspections

INSPECTION PROCEDURE

- Inspection Opening Meeting
  - Issue of the Notice of Inspection (Form FDA-482)
    - For domestic inspection only
  - Credential of FDA investigators
- Inspection of source document and records
- Inspection Closing Meeting
  - Discussion Items
  - Objectionable inspection findings (Form FDA-483)

CDER's INSPECTION CLASSIFICATION

- OAI Classification
- VAI Classification
- NAI Classification

INSPECTION REFERENCE DOCUMENT

- Compliance Program Guidance Manual (CPGM), 7348.001- InVivo Bioequivalence
  - This CPGM describes the procedures used by FDA staff in performing BA, BE, and/or PK study inspections.

INSPECTION REFERENCE DOCUMENT

- FDA Guidance for Industry, Bioanalytical Method Validation
- FDA Guidance for Industry, Handling and Retention of BA and BE Testing Samples
  - Http:www.fda.gov/cder/guidance/index.htm
- 21 CFR Part 320 - Bioavailabilty and Bioequivalence Requirements

CLINICAL AND ANALYTICAL SITE INSPECTION

- BA/BE study inspection will be conducted at the clinical site and/or analytical site:
  - Clinical site
    - Clinical testing facility where subjects are dosed and blood samples are collected.
  - Analytical site
    - Analytical laboratory where biological fluid collected in the BA/BE studies are analyzed for drug concentration.

INSPECTION COVERAGE

- Part 1: Facilities and Procedures
  - Applicable to clinical and analytical facilities
- Part 2 : Clinical data and operations
- Part 3: Analytical data and operations

Questions?

In Vivo Bioequivalence Inspection Techniques

Martin K. Yau, Ph.D.
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (DSI)
Office of Compliance, CDER

Clinical Bioreseach
Monitoring BR2001A

Objectives

- Provide techniques for auditing an *in vivo* bioequivalence (BE) study
  - What records should you review?
    - use the compliance program as your guide
- Explain how to document findings on the 483 and in the Establishment Inspection Report (EIR)
  - examples from DSI Bioequivalence (DSI-BE) inspections

CP 7348.001 - *In Vivo* BE

- This Compliance Program Guidance Manual describes the procedures used by FDA staff in performing BA, BE, and/or pharmacokinetic study inspections.

Program Objectives

- Your inspection should...
  - verify the accuracy, quality and integrity of data from BE studies submitted to FDA, Center for Drug Evaluation and Research (CDER)
  - ensure that the rights and welfare of human research subjects are protected
  - ensure compliance with the regulations
    - 21 CFR Parts 320, 312, 50 and 56

CP 7348.001 - Attachment A

- Describes the inspectional focus in general identifies the minimum information that must be obtained during an BA/BE inspection
  - please note...
    - DSI-BE inspection assignment memos usually provide additional instructions specific to the study or site.

- Attachment A is divided into three parts
  - Part I - Facilities and Procedures
    - applicable to clinical and analytical facilities
  - Part II - Clinical Data and Operations
  - Part III - Analytical Data and Operations

- Inspection must include a comparison of the source data at the clinical site with the data submitted to Regulatory Agency
  - Regulatory Agency will provide the background documents for comparison.
    - Please document the number of records reviewed and whether any discrepancies were found.

What records should you review?

First and foremost...

- Review records that directly impact study outcomes
  - Dosing
    - Can you unambiguously verify "Who got what?"
  - Specimen sampling (e.g., blood draws, urine collection)
    - Documentation contemporaneous with event?
    - Are changes justified?
  - Specimen handling, processing and storage

Next verify whether the site...

- Adhered to the protocol
  - inclusion/exclusion criteria (IEC)
  - protocol restrictions
    - abstention from Rx/OTC drugs, caffeine
    - fasting requirements
  - pre-, in- and post-study activities
- Accounted for drug receipt and use

Then compare...

- Source documents to the final report
  - drug lots used
    - document any discrepancies
  - adverse events
    - All reported?
      - look for AEs such as vomiting or diarrhea soon after dosing
  - concomitant medications or intercurrent illness
    - Were these accurately reported?

Then compare...

- Source documents to the final report
  - pharmacokinetic (PK) blood draw times and results of protocol required testing
    - spot check, expand review if problems found
      - The actual sampling time should be used in determining the PK parameters.

Don’t forget the...

- Correspondence file
  - can provide a wealth of information
    - problems with study conduct
    - requests to exclude specific data

Finally, determine whether...

- The site complied with the regulations
  - Was subject safety protected?
    - informed consent forms
      - review informed consent forms of all subjects and document your review in the EIR
    - medical supervision/delegation of authority
    - records of IRB approval of the protocol
  - Were reserve samples randomly selected and retained on site?

Documenting your findings

- We'll provide specific DSI-BE inspectional findings that focus on the critical points to consider for a BE study inspection
  - FDA Form-483s and EIR exhibits

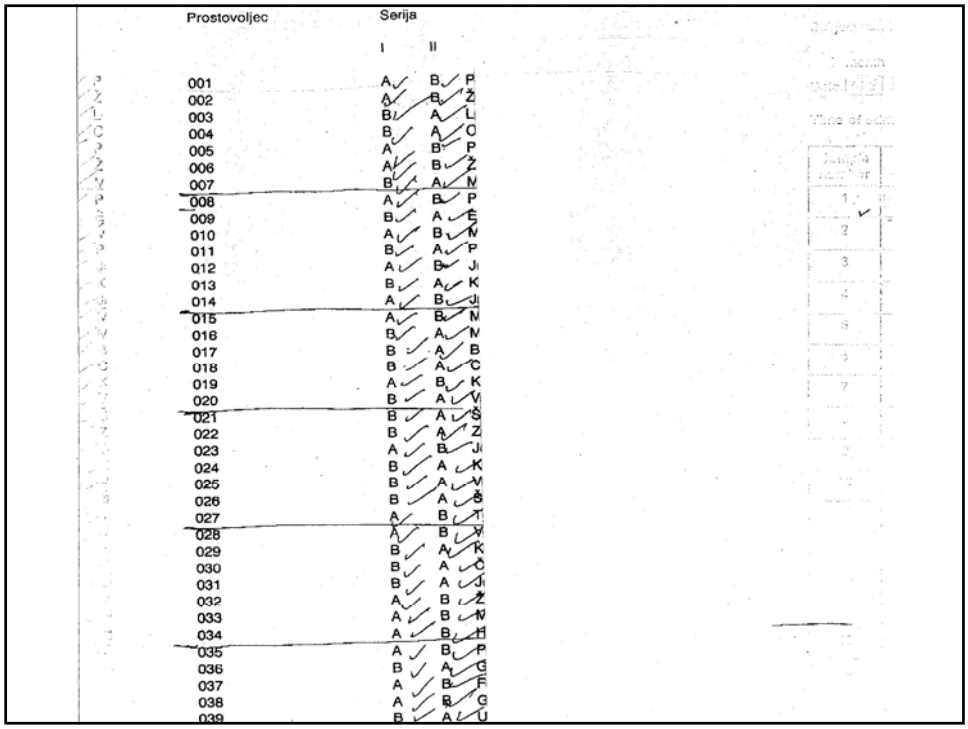
- Your inspection should thoroughly address the issues raised in the following slides
  - please document your findings concerning these issues in the EIR

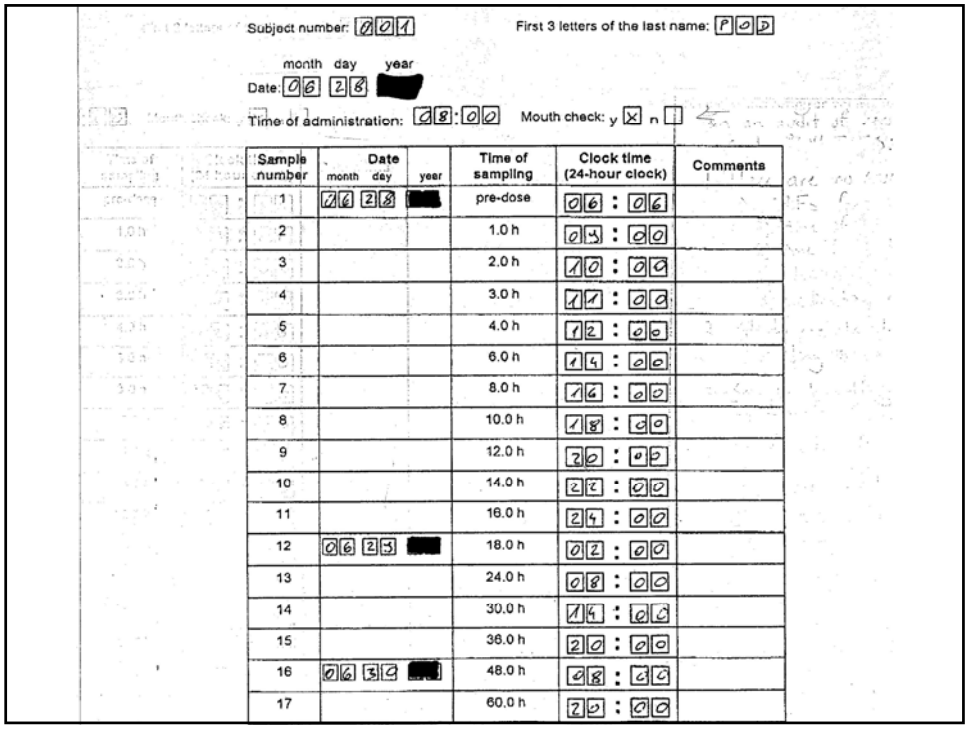
Dosing Records

- Was the treatment administered to each subject documented at the time of dosing?
  - open-label versus blinded studies
- Was the actual dosing time documented?

DSI-BE Inspection Findings

- Example: Inspection at Eastern Europe
  - "A" or "B" not documented
    - randomization scheme is the intended dose and not the actual dose
    - Who got what? must be unambiguous
  - Actual dosing time not documented
    - impact on PK calculations
  - Form FDA-483



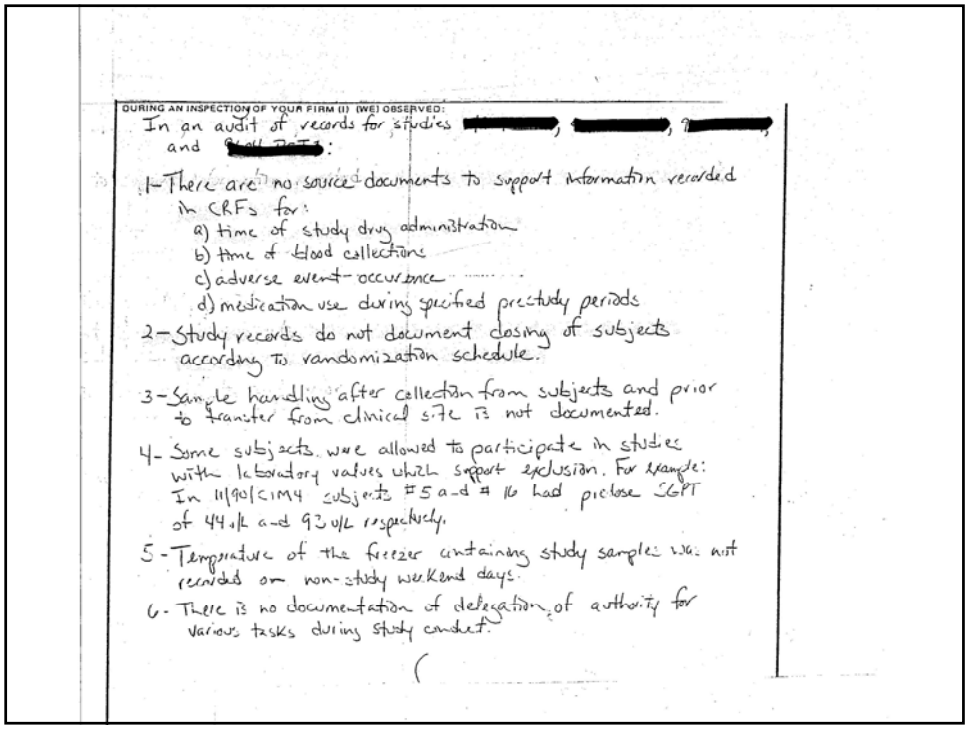


Subject number: 001 First 3 letters of the last name: POD

Date: month 06 day 28 year [redacted]

Time of administration: 08:00 Mouth check: y [X] n [ ]

Sample number	Date month	day	year	Time of sampling	Clock time (24-hour clock)	Comments
1	06	28	[redacted]	pre-dose	06 : 06	
2				1.0 h	07 : 00	
3				2.0 h	10 : 00	
4				3.0 h	11 : 00	
5				4.0 h	12 : 00	
6				6.0 h	14 : 00	
7				8.0 h	16 : 00	
8				10.0 h	18 : 00	
9				12.0 h	20 : 05	
10				14.0 h	22 : 00	
11				16.0 h	24 : 00	
12	06	25	[redacted]	18.0 h	02 : 00	
13				24.0 h	08 : 00	
14				30.0 h	14 : 00	
15				36.0 h	20 : 00	
16	06	30	[redacted]	48.0 h	08 : 00	
17				60.0 h	20 : 00	



DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

In an audit of records for studies [redacted], [redacted], [redacted], and [redacted]:

1- There are no source documents to support information recorded in CRFs for:
   a) time of study drug administration
   b) time of blood collections
   c) adverse event occurrence
   d) medication use during specified pre-study periods

2- Study records do not document dosing of subjects according to randomization schedule.

3- Sample handling after collection from subjects and prior to transfer from clinical site is not documented.

4- Some subjects were allowed to participate in studies with laboratory values which support exclusion. For example: In 11/90/CIM4 subjects #5 and #16 had pre-dose SGPT of 44 u/L and 93 u/L respectively.

5- Temperature of the freezer containing study samples was not recorded on non-study weekend days.

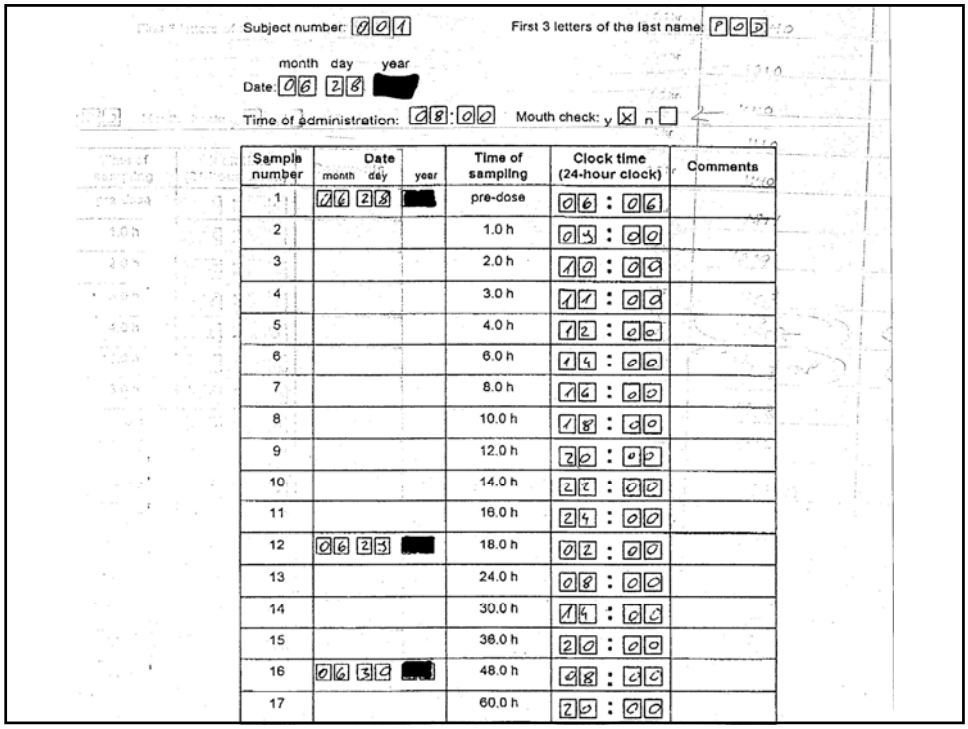
6- There is no documentation of delegation of authority for various tasks during study conduct.

Blood Draw Records

- Was the actual time of the PK blood draws documented?
- Were deviations from scheduled draw times reported?

DSI-BE Inspection Findings

- Blood draw times not documented
  - see example of inspection in Eastern Europe
- Blood draw times changed without justification
  - see example at Baltimore, MD (minocyclcine)
  - consequences on PK calculations
  - Form FDA-483s

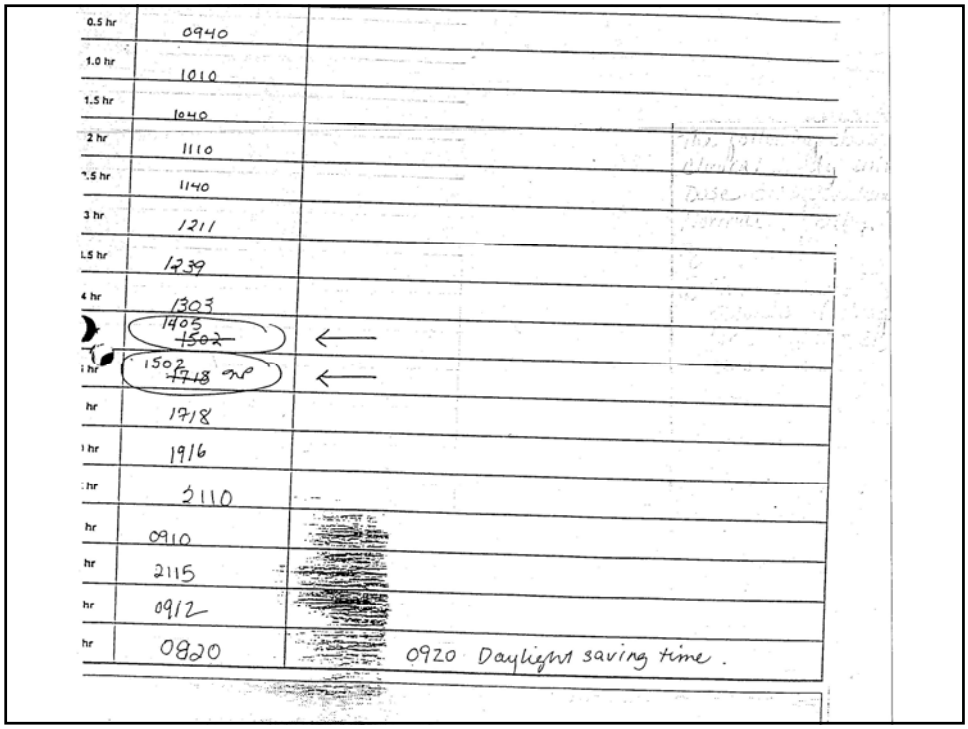


Subject number: 001 First 3 letters of the last name: PAD

month day year
Date: 06 28 [redacted]

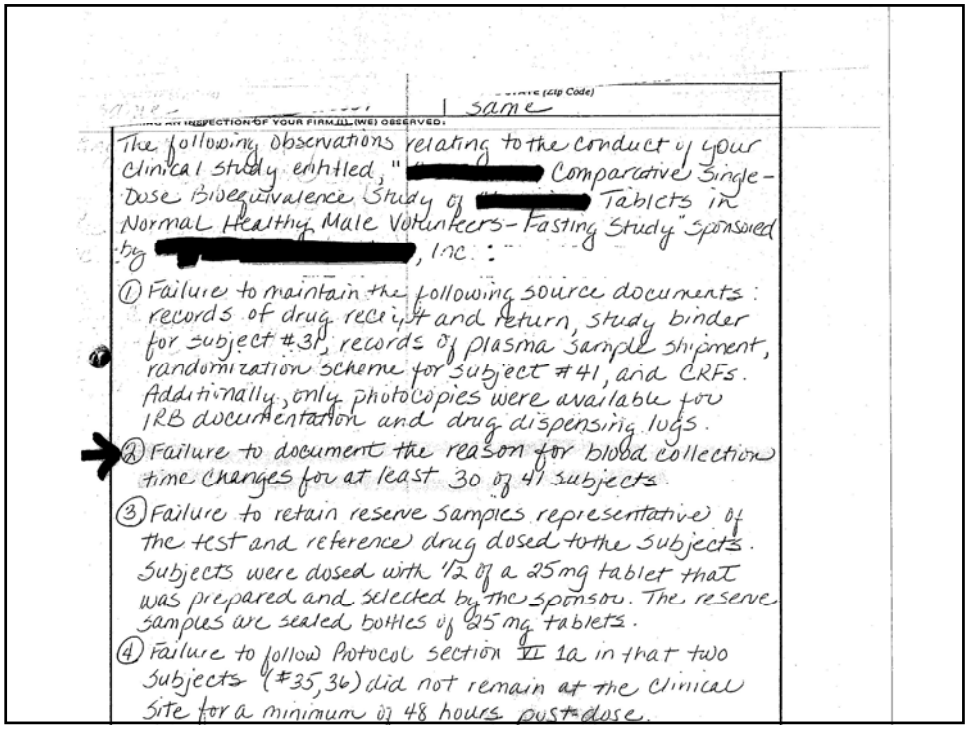
Time of administration: 08:00 Mouth check: y ☒ n ☐

Sample number	Date month	day	year	Time of sampling	Clock time (24-hour clock)	Comments
1	06	28	[redacted]	pre-dose	06 : 06	
2				1.0 h	07 : 00	
3				2.0 h	10 : 00	
4				3.0 h	11 : 00	
5				4.0 h	12 : 00	
6				6.0 h	14 : 00	
7				8.0 h	16 : 00	
8				10.0 h	18 : 00	
9				12.0 h	20 : 00	
10				14.0 h	22 : 00	
11				16.0 h	24 : 00	
12	06	29	[redacted]	18.0 h	02 : 00	
13				24.0 h	08 : 00	
14				30.0 h	14 : 00	
15				36.0 h	20 : 00	
16	06	30	[redacted]	48.0 h	08 : 00	
17				60.0 h	20 : 00	



0.5 hr	0940
1.0 hr	1010
1.5 hr	1040
2 hr	1110
.5 hr	1140
3 hr	1211
.5 hr	1239
4 hr	1303
	1405 ~~1502~~ ←
hr	1502 ~~1718~~ ←
hr	1718
hr	1916
hr	2110
hr	0910
hr	2115
hr	0912
hr	0820

0920 Daylight saving time.



same

The following observations relating to the conduct of your clinical study entitled, "[redacted] Comparative Single-Dose Bioequivalence Study of [redacted] Tablets in Normal Healthy Male Volunteers- Fasting Study" sponsored by [redacted], Inc.:

① Failure to maintain the following source documents: records of drug receipt and return, study binder for subject #31, records of plasma sample shipment, randomization scheme for subject #41, and CRFs. Additionally, only photocopies were available for IRB documentation and drug dispensing logs.

② Failure to document the reason for blood collection time changes for at least 30 of 41 subjects.

③ Failure to retain reserve samples representative of the test and reference drug dosed to the subjects. Subjects were dosed with 1/2 of a 25mg tablet that was prepared and selected by the sponsor. The reserve samples are sealed bottles of 25 mg tablets.

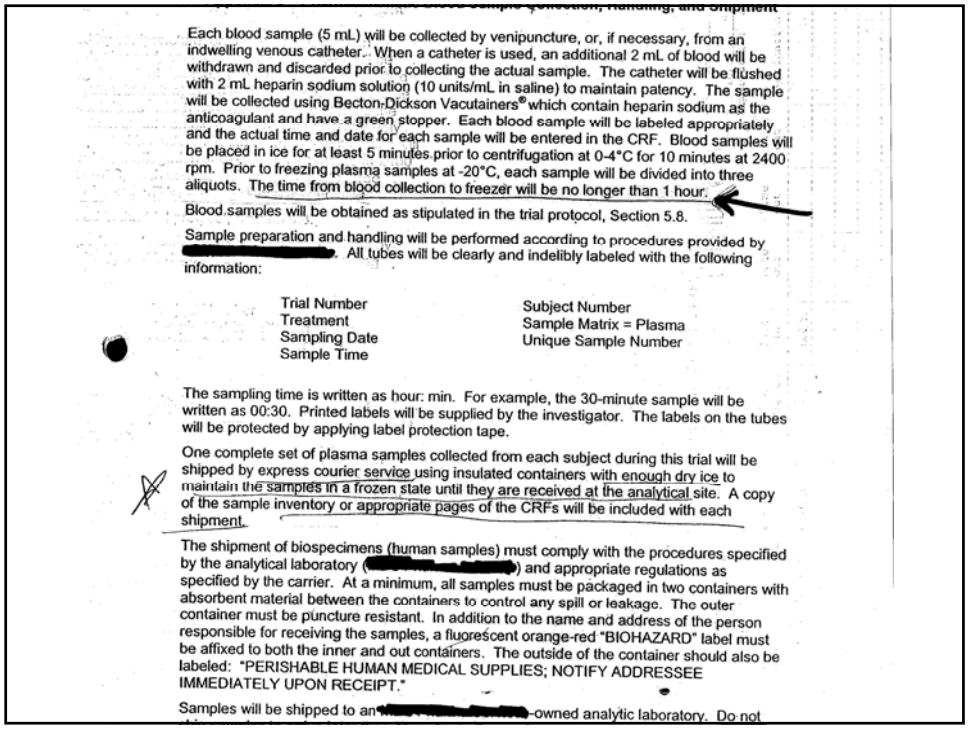
④ Failure to follow Protocol section VI 1a in that two subjects (#35, 36) did not remain at the clinical site for a minimum of 48 hours post-dose.

Specimen Handling

- Are there procedures for linking subjects and specimens?
- Are there procedures for processing collected specimens?
  - Any specific stability concerns for the analyte of interest (e.g., temperature, light)?
- Were there acceptable storage conditions before and after processing, as well as during transit to the analytical laboratory?

DSI-BE Inspection Findings

- See example regarding inspection at Phoenix, AZ
  - subject samples not processed within the protocol required timeframe
    - include description of processing blood to serum or plasma, anticoagulants
  - analytical consequences
    - affected 25% of the subject samples
  - Form FDA-483



Each blood sample (5 mL) will be collected by venipuncture, or, if necessary, from an indwelling venous catheter. When a catheter is used, an additional 2 mL of blood will be withdrawn and discarded prior to collecting the actual sample. The catheter will be flushed with 2 mL heparin sodium solution (10 units/mL in saline) to maintain patency. The sample will be collected using Becton-Dickson Vacutainers® which contain heparin sodium as the anticoagulant and have a green stopper. Each blood sample will be labeled appropriately and the actual time and date for each sample will be entered in the CRF. Blood samples will be placed in ice for at least 5 minutes prior to centrifugation at 0-4°C for 10 minutes at 2400 rpm. Prior to freezing plasma samples at -20°C, each sample will be divided into three aliquots. The time from blood collection to freezer will be no longer than 1 hour.

Blood samples will be obtained as stipulated in the trial protocol, Section 5.8.

Sample preparation and handling will be performed according to procedures provided by [redacted]. All tubes will be clearly and indelibly labeled with the following information:

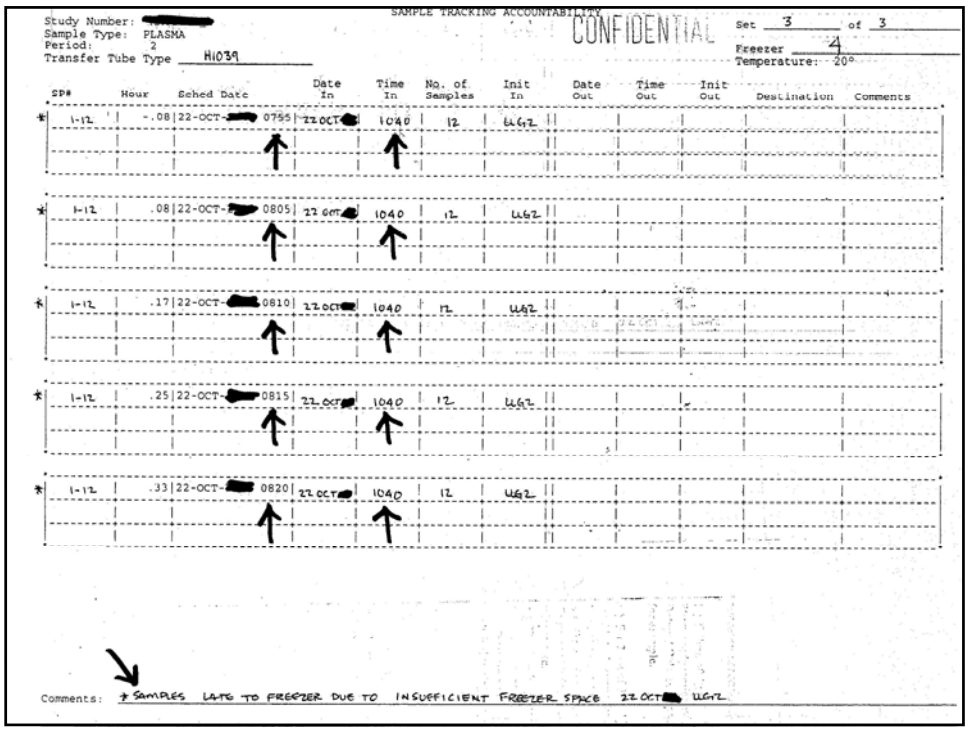
Trial Number
Treatment
Sampling Date
Sample Time
Subject Number
Sample Matrix = Plasma
Unique Sample Number

The sampling time is written as hour: min. For example, the 30-minute sample will be written as 00:30. Printed labels will be supplied by the investigator. The labels on the tubes will be protected by applying label protection tape.

One complete set of plasma samples collected from each subject during this trial will be shipped by express courier service using insulated containers with enough dry ice to maintain the samples in a frozen state until they are received at the analytical site. A copy of the sample inventory or appropriate pages of the CRFs will be included with each shipment.

The shipment of biospecimens (human samples) must comply with the procedures specified by the analytical laboratory ([redacted]) and appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged in two containers with absorbent material between the containers to control any spill or leakage. The outer container must be puncture resistant. In addition to the name and address of the person responsible for receiving the samples, a fluorescent orange-red "BIOHAZARD" label must be affixed to both the inner and out containers. The outside of the container should also be labeled: "PERISHABLE HUMAN MEDICAL SUPPLIES; NOTIFY ADDRESSEE IMMEDIATELY UPON RECEIPT."

Samples will be shipped to an [redacted]-owned analytic laboratory. Do not



SAMPLE TRACKING ACCOUNTABILITY

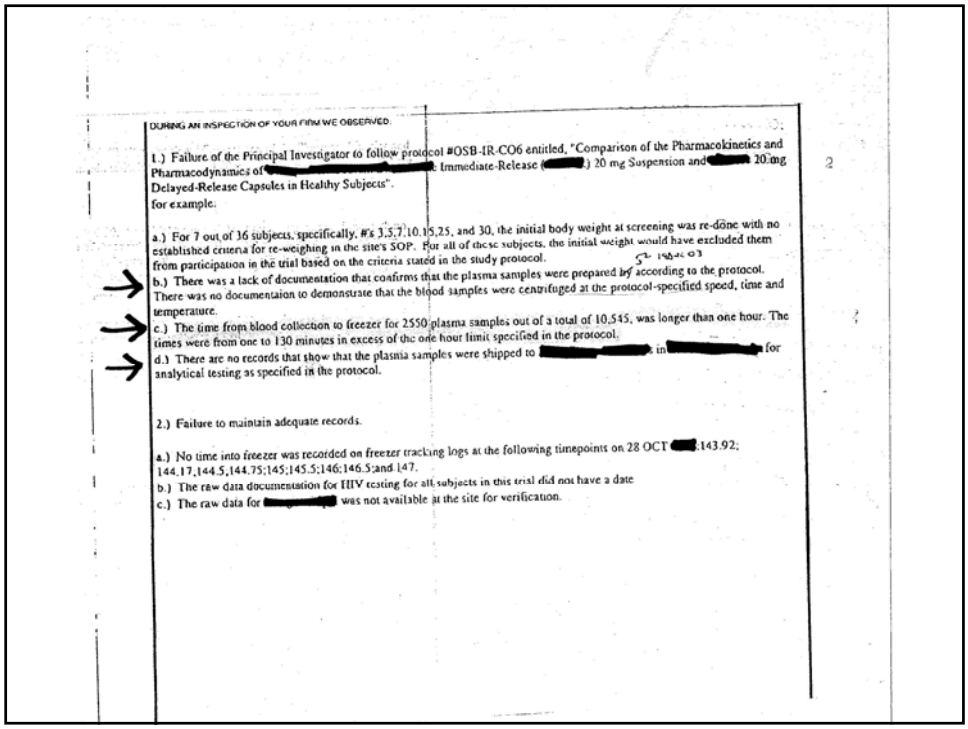
CONFIDENTIAL

Study Number: [redacted]
Sample Type: PLASMA
Period: 2
Transfer Tube Type: Hi039

Set 3 of 3
Freezer 4
Temperature: -20°

SP#	Hour	Sched Date	Date In	Time In	No. of Samples	Init In	Date Out	Time Out	Init Out	Destination	Comments
* 1-12	-.08	22-OCT-[redacted] 0755	22 OCT[redacted]	1040	12	UGZ					
* 1-12	.08	22-OCT-[redacted] 0805	22 OCT[redacted]	1040	12	UGZ					
* 1-12	.17	22-OCT-[redacted] 0810	22 OCT[redacted]	1040	12	UGZ					
* 1-12	.25	22-OCT-[redacted] 0815	22 OCT[redacted]	1040	12	UGZ					
* 1-12	.33	22-OCT-[redacted] 0820	22 OCT[redacted]	1040	12	UGZ					

Comments: 7 SAMPLES LATE TO FREEZER DUE TO INSUFFICIENT FREEZER SPACE 22 OCT[redacted] UGZ



DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1.) Failure of the Principal Investigator to follow protocol #0SB-IR-CO6 entitled, "Comparison of the Pharmacokinetics and Pharmacodynamics of [redacted] Immediate-Release ([redacted]) 20 mg Suspension and [redacted] 20 mg Delayed-Release Capsules in Healthy Subjects".
for example:

a.) For 7 out of 16 subjects, specifically, #'s 3,5,7,10,15,25, and 30, the initial body weight at screening was re-done with no established criteria for re-weighing in the site's SOP. For all of these subjects, the initial weight would have excluded them from participation in the trial based on the criteria stated in the study protocol.

b.) There was a lack of documentation that confirms that the plasma samples were prepared according to the protocol. There was no documentation to demonstrate that the blood samples were centrifuged at the protocol-specified speed, time and temperature.

c.) The time from blood collection to freezer for 2550 plasma samples out of a total of 10,545, was longer than one hour. The times were from one to 130 minutes in excess of the one hour limit specified in the protocol.

d.) There are no records that show that the plasma samples were shipped to [redacted] in [redacted] for analytical testing as specified in the protocol.

2.) Failure to maintain adequate records.

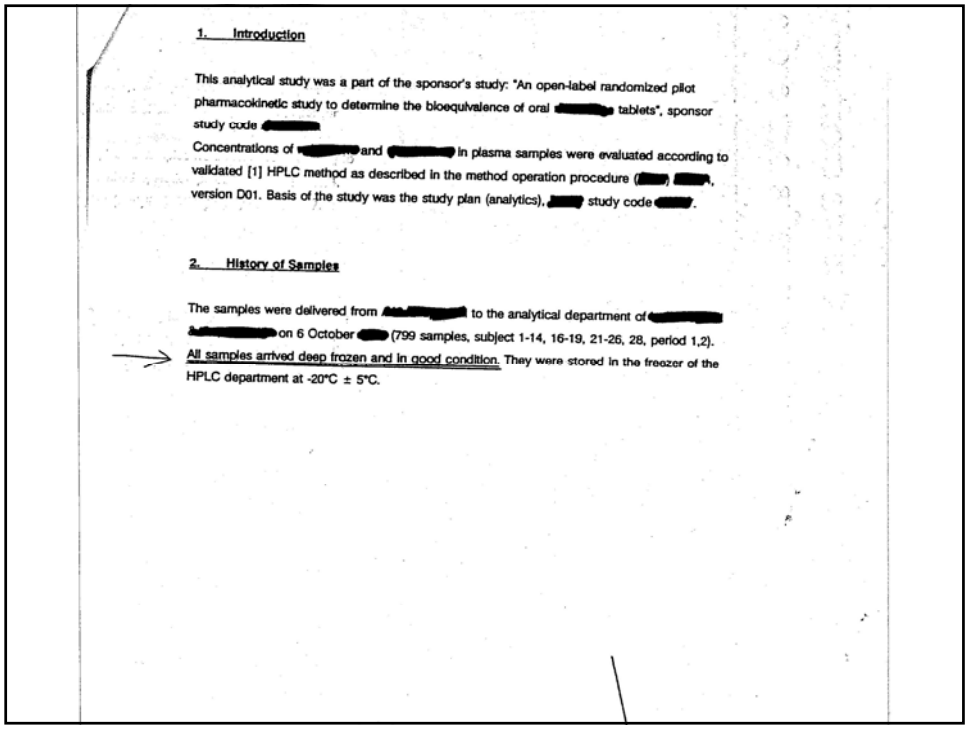
a.) No time into freezer was recorded on freezer tracking logs at the following timepoints on 28 OCT [redacted]:143.92; 144.17,144.5,144.75;145;145.5;146;146.5;and 147.

b.) The raw data documentation for HIV testing for all subjects in this trial did not have a date

c.) The raw data for [redacted] was not available at the site for verification.

DSI-BE Inspection Findings

- Example at Research Triangle Park, NC
  - thawed samples received by analytical lab
  - analytical consequences
  - Form FDA-483

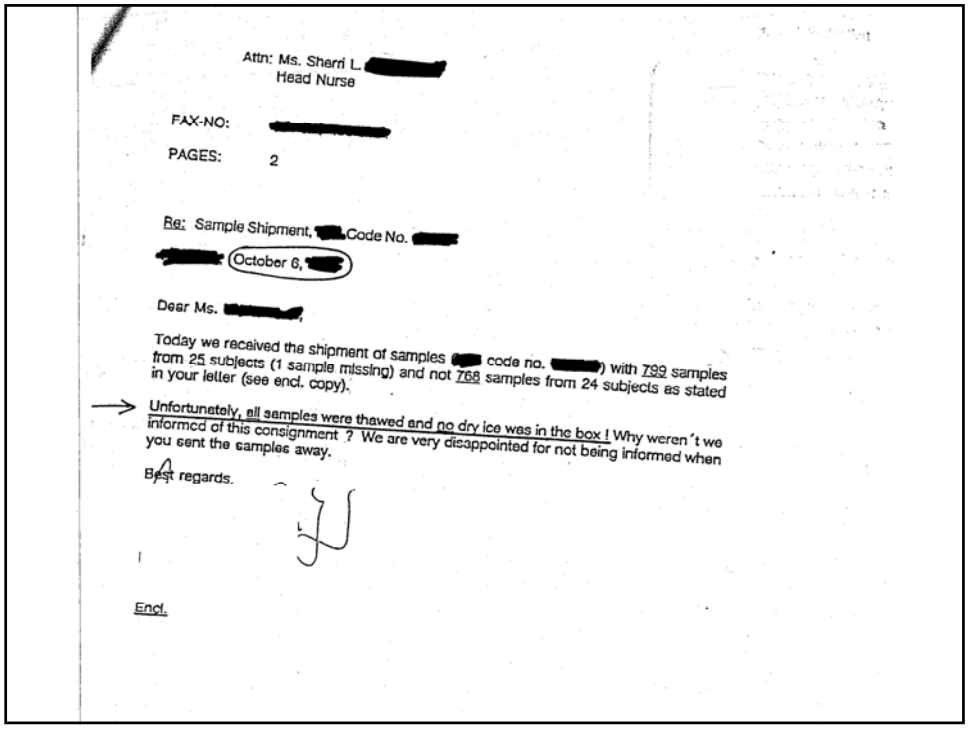


1. Introduction

This analytical study was a part of the sponsor's study: "An open-label randomized pilot pharmacokinetic study to determine the bioequivalence of oral [redacted] tablets", sponsor study code [redacted].
Concentrations of [redacted] and [redacted] in plasma samples were evaluated according to validated [1] HPLC method as described in the method operation procedure ([redacted]), [redacted], version D01. Basis of the study was the study plan (analytics), [redacted] study code [redacted].

2. History of Samples

The samples were delivered from [redacted] to the analytical department of [redacted] on 6 October [redacted] (799 samples, subject 1-14, 16-19, 21-26, 28, period 1,2).
All samples arrived deep frozen and in good condition. They were stored in the freezer of the HPLC department at -20°C ± 5°C.



Attn: Ms. Sherri L. [redacted]
Head Nurse

FAX-NO: [redacted]

PAGES: 2

Re: Sample Shipment, [redacted] Code No. [redacted]

[redacted] October 6, [redacted]

Dear Ms. [redacted],

Today we received the shipment of samples [redacted] code no. [redacted]) with 799 samples from 25 subjects (1 sample missing) and not 768 samples from 24 subjects as stated in your letter (see encl. copy).

→ Unfortunately, all samples were thawed and no dry ice was in the box ! Why weren´t we informed of this consignment ? We are very disappointed for not being informed when you sent the samples away.

Best regards.

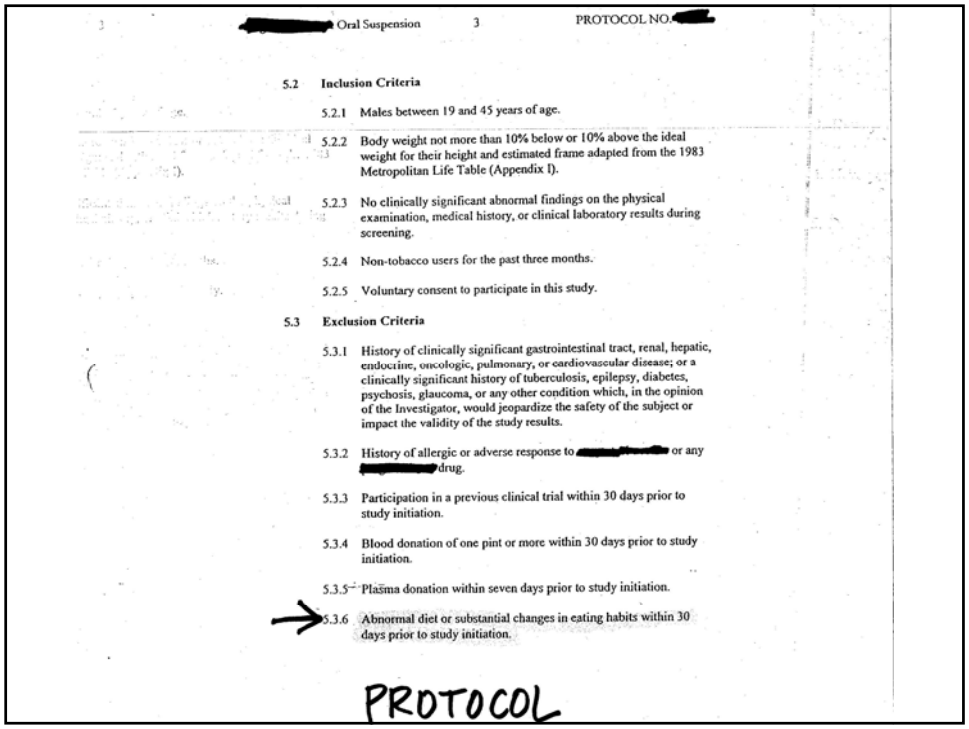
Encl.

Protocol

- Were the inclusion/exclusion criteria followed?
- Were protocol-required screening, in-study and post-study activities conducted?

DSI-BE Inspection Findings

- See example regarding megestrol acetate, at Lincoln, NE
  - protocol exclusion criteria not followed
    - subjects with a vegetarian diet enrolled in the study, discuss potential impact on study
    - recommended excluding these subjects



[redacted] Oral Suspension 3 PROTOCOL NO. [redacted]

5.2 **Inclusion Criteria**

5.2.1 Males between 19 and 45 years of age.

5.2.2 Body weight not more than 10% below or 10% above the ideal weight for their height and estimated frame adapted from the 1983 Metropolitan Life Table (Appendix I).

5.2.3 No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during screening.

5.2.4 Non-tobacco users for the past three months.

5.2.5 Voluntary consent to participate in this study.

5.3 **Exclusion Criteria**

5.3.1 History of clinically significant gastrointestinal tract, renal, hepatic, endocrine, oncologic, pulmonary, or cardiovascular disease; or a clinically significant history of tuberculosis, epilepsy, diabetes, psychosis, glaucoma, or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

5.3.2 History of allergic or adverse response to [redacted] or any [redacted] drug.

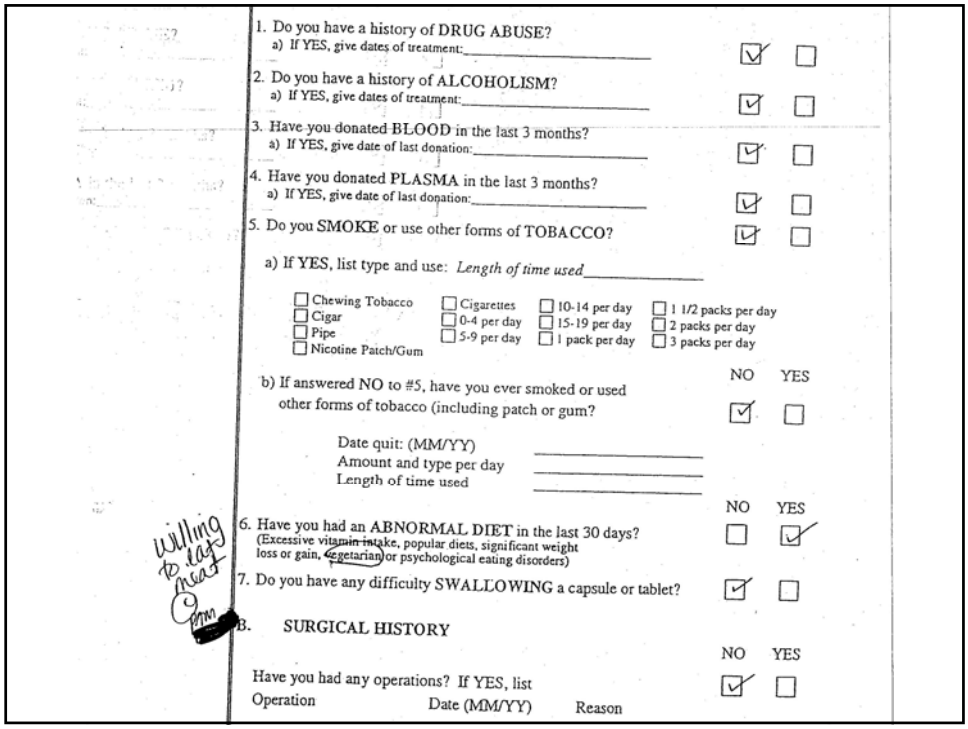
5.3.3 Participation in a previous clinical trial within 30 days prior to study initiation.

5.3.4 Blood donation of one pint or more within 30 days prior to study initiation.

5.3.5 Plasma donation within seven days prior to study initiation.

5.3.6 Abnormal diet or substantial changes in eating habits within 30 days prior to study initiation.

PROTOCOL



1. Do you have a history of DRUG ABUSE? ☑ NO ☐ YES
   a) If YES, give dates of treatment:_____
2. Do you have a history of ALCOHOLISM? ☑ NO ☐ YES
   a) If YES, give dates of treatment:_____
3. Have you donated BLOOD in the last 3 months? ☑ NO ☐ YES
   a) If YES, give date of last donation:_____
4. Have you donated PLASMA in the last 3 months? ☑ NO ☐ YES
   a) If YES, give date of last donation:_____
5. Do you SMOKE or use other forms of TOBACCO? ☑ NO ☐ YES
   a) If YES, list type and use: *Length of time used*_____

   ☐ Chewing Tobacco ☐ Cigarettes ☐ 10-14 per day ☐ 1 1/2 packs per day
   ☐ Cigar ☐ 0-4 per day ☐ 15-19 per day ☐ 2 packs per day
   ☐ Pipe ☐ 5-9 per day ☐ 1 pack per day ☐ 3 packs per day
   ☐ Nicotine Patch/Gum

   b) If answered NO to #5, have you ever smoked or used other forms of tobacco (including patch or gum)? ☑ NO ☐ YES

   Date quit: (MM/YY)_____
   Amount and type per day_____
   Length of time used_____

6. Have you had an ABNORMAL DIET in the last 30 days? ☐ NO ☑ YES
   (Excessive vitamin intake, popular diets, significant weight loss or gain, ~~V~~egetarian or psychological eating disorders)
7. Do you have any difficulty SWALLOWING a capsule or tablet? ☑ NO ☐ YES

willing to try again

B. SURGICAL HISTORY

Have you had any operations? If YES, list ☑ NO ☐ YES

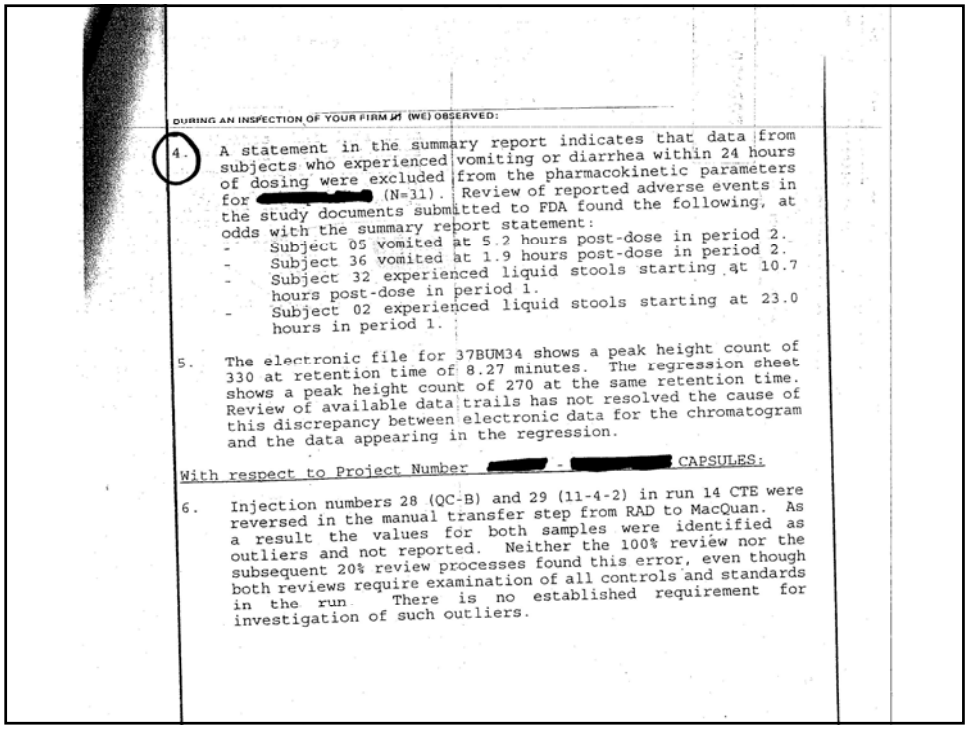
Operation | Date (MM/YY) | Reason

Subjects' Records

- Were all adverse events reported?
- Was there any unreported concomitant medication or intercurrent illness?

DSI-BE Inspection Findings

- Example regarding clomipramine in Canada inspection
  - inconsistent handling of subjects that vomited
    - protocol required exclusion of subjects that vomited within 24 hrs of dose, only one of three subjects that vomited were excluded
    - impact on drug absorption
    - Form FDA-483



DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED:

4. A statement in the summary report indicates that data from subjects who experienced vomiting or diarrhea within 24 hours of dosing were excluded from the pharmacokinetic parameters for [redacted] (N=31). Review of reported adverse events in the study documents submitted to FDA found the following, at odds with the summary report statement:
   - Subject 05 vomited at 5.2 hours post-dose in period 2.
   - Subject 36 vomited at 1.9 hours post-dose in period 2.
   - Subject 32 experienced liquid stools starting at 10.7 hours post-dose in period 1.
   - Subject 02 experienced liquid stools starting at 23.0 hours in period 1.

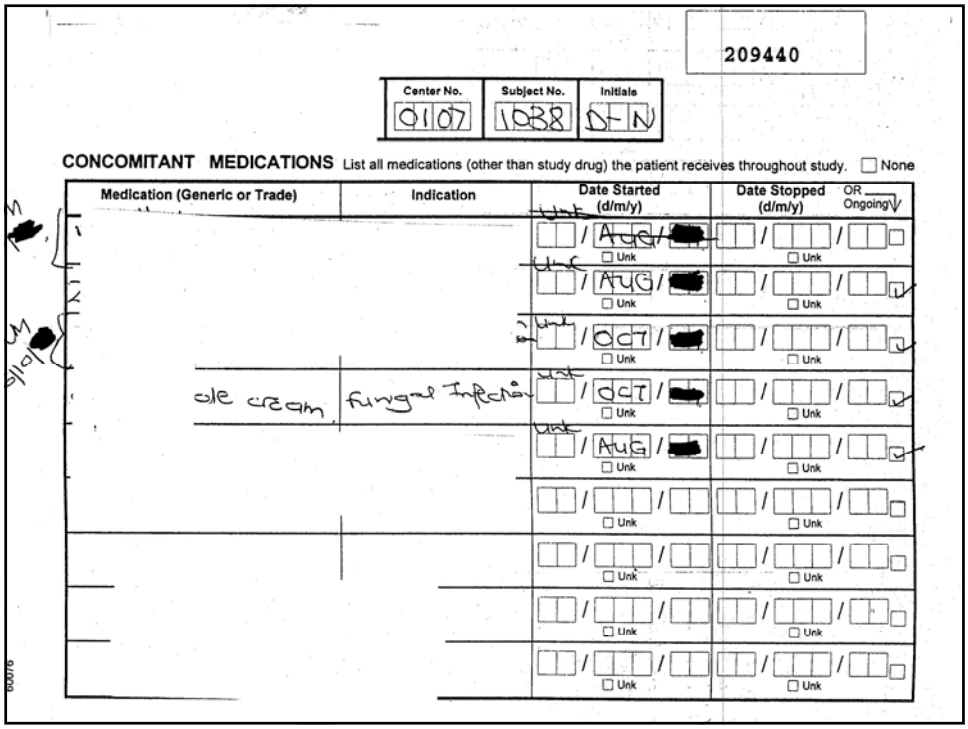
5. The electronic file for 37BUM34 shows a peak height count of 330 at retention time of 8.27 minutes. The regression sheet shows a peak height count of 270 at the same retention time. Review of available data trails has not resolved the cause of this discrepancy between electronic data for the chromatogram and the data appearing in the regression.

With respect to Project Number [redacted] - [redacted] CAPSULES:

6. Injection numbers 28 (QC-B) and 29 (11-4-2) in run 14 CTE were reversed in the manual transfer step from RAD to MacQuan. As a result the values for both samples were identified as outliers and not reported. Neither the 100% review nor the subsequent 20% review processes found this error, even though both reviews require examination of all controls and standards in the run. There is no established requirement for investigation of such outliers.

DSI-BE Inspection Findings

- Example regarding clotrimazole troche in South Africa inspection
  - subject received a concomitant drug that contained the same active ingredient as the study medication

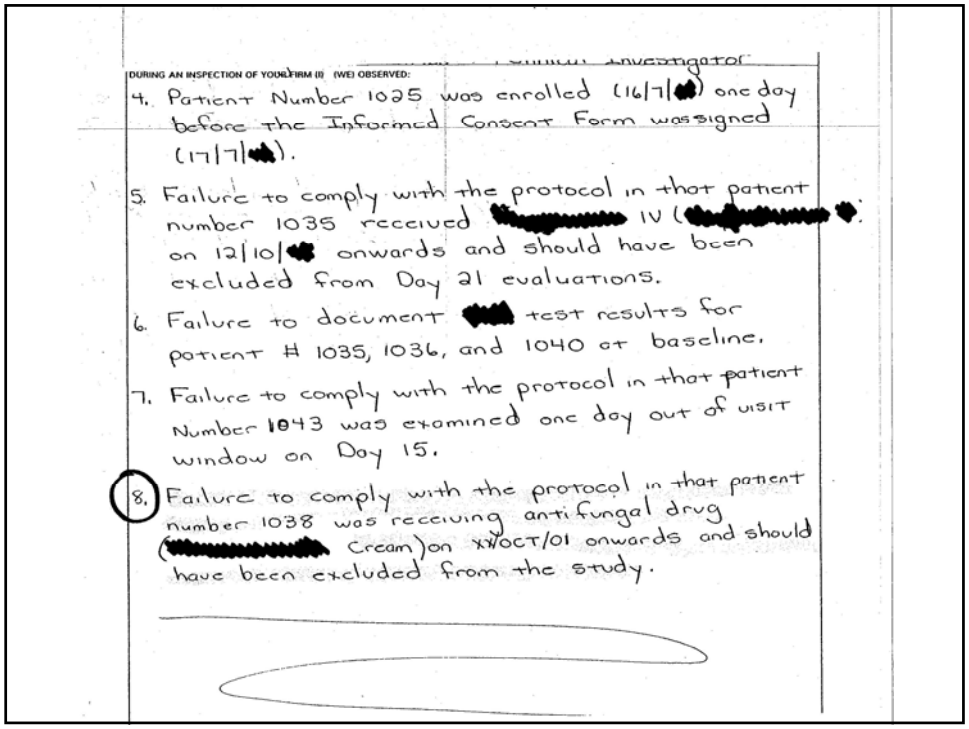


209440

Center No.	Subject No.	Initials
0107	1038	[redacted]

CONCOMITANT MEDICATIONS List all medications (other than study drug) the patient receives throughout study. ☐ None

Medication (Generic or Trade)	Indication	Date Started (d/m/y)	Date Stopped (d/m/y) OR Ongoing
		Unk / AUG / [redacted] ☐ Unk	/ / ☐ Unk
		Unk / AUG / [redacted] ☐ Unk	/ / ☐ Unk
		Unk / OCT / [redacted] ☐ Unk	/ / ☐ Unk
ole cream	fungal Infecti	Unk / OCT / [redacted] ☐ Unk	/ / ☐ Unk
		Unk / AUG / [redacted] ☐ Unk	/ / ☐ Unk
		/ / ☐ Unk	/ / ☐ Unk
		/ / ☐ Unk	/ / ☐ Unk
		/ / ☐ Unk	/ / ☐ Unk
		/ / ☐ Unk	/ / ☐ Unk



DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

4. Patient Number 1025 was enrolled (16/7/[redacted]) one day before the Informed Consent Form was signed (17/7/[redacted]).

5. Failure to comply with the protocol in that patient number 1035 received [redacted] IV ([redacted]) on 12/10/[redacted] onwards and should have been excluded from Day 21 evaluations.

6. Failure to document [redacted] test results for patient # 1035, 1036, and 1040 at baseline.

7. Failure to comply with the protocol in that patient Number 1043 was examined one day out of visit window on Day 15.

8. Failure to comply with the protocol in that patient number 1038 was receiving antifungal drug ([redacted] Cream) on xx/OCT/01 onwards and should have been excluded from the study.

Drug Products

- Are there adequate records concerning the receipt and use of study drugs?
- Are the lot numbers the same as those reported to FDA?

Reserve Samples

- Are the reserve samples representative of the products used in the study?
  - Positively identified?
    - please collect a written assurance that the reserve samples came from the same samples as used in the BE study
      - as per 21 CFR 320.38(g)

Requirements

- Randomly selected at the testing facility performing the BE study
  - both test and reference products
    - pre-selection by a sponsor, third-party packager, SMO or CRO managing the study is not allowed

Requirements

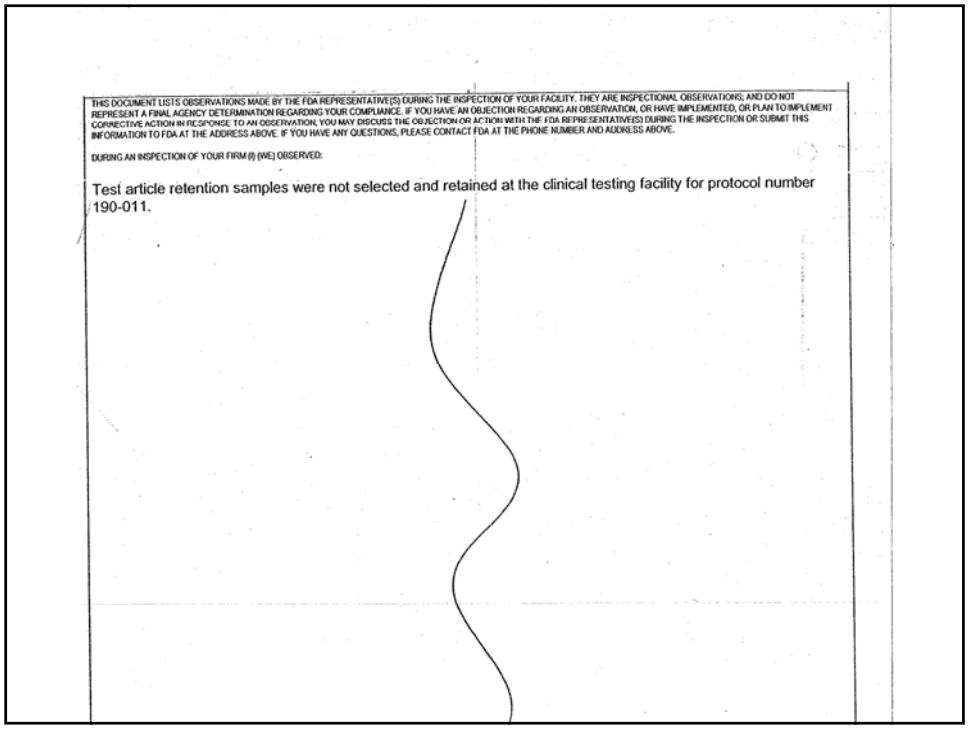
- Appropriate storage
  - retained at the testing facility under conditions consistent with product labeling
    - reserve samples cannot be returned to the sponsor
    - storage by an independent, third-party following dosing is permitted
- Retention period
  - 5 years after the approval of the application

Special Considerations

- Unit dose packaging
  - minimum 24 unit doses plus bulk
- Blinded studies
  - enough labeled sets to conduct the study and retain as reserve samples
  - sealed code for use by FDA
- Additional shipments
  - select reserve samples from each shipment

DSI-BE Inspectional Findings

- Example:
  - clinical site failed to select and retain reserve samples
  - correspondence file contained a memo stating that “The sponsor releases Contract Research Organization (CRO) from any obligation to collect reserve samples.”



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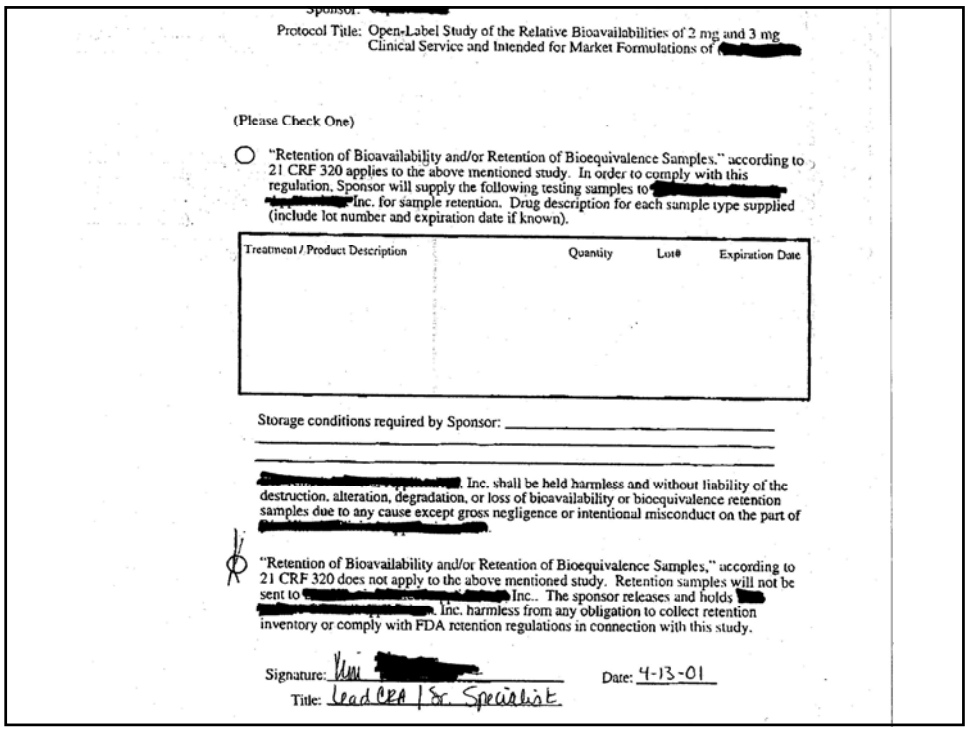
DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Test article retention samples were not selected and retained at the clinical testing facility for protocol number 190-011.



Protocol Title: Open-Label Study of the Relative Bioavailabilities of 2 mg and 3 mg Clinical Service and Intended for Market Formulations of [redacted]

(Please Check One)

○ "Retention of Bioavailability and/or Retention of Bioequivalence Samples," according to 21 CRF 320 applies to the above mentioned study. In order to comply with this regulation, Sponsor will supply the following testing samples to [redacted] Inc. for sample retention. Drug description for each sample type supplied (include lot number and expiration date if known).

Treatment / Product Description	Quantity	Lot#	Expiration Date

Storage conditions required by Sponsor: _____

[redacted] Inc. shall be held harmless and without liability of the destruction, alteration, degradation, or loss of bioavailability or bioequivalence retention samples due to any cause except gross negligence or intentional misconduct on the part of [redacted].

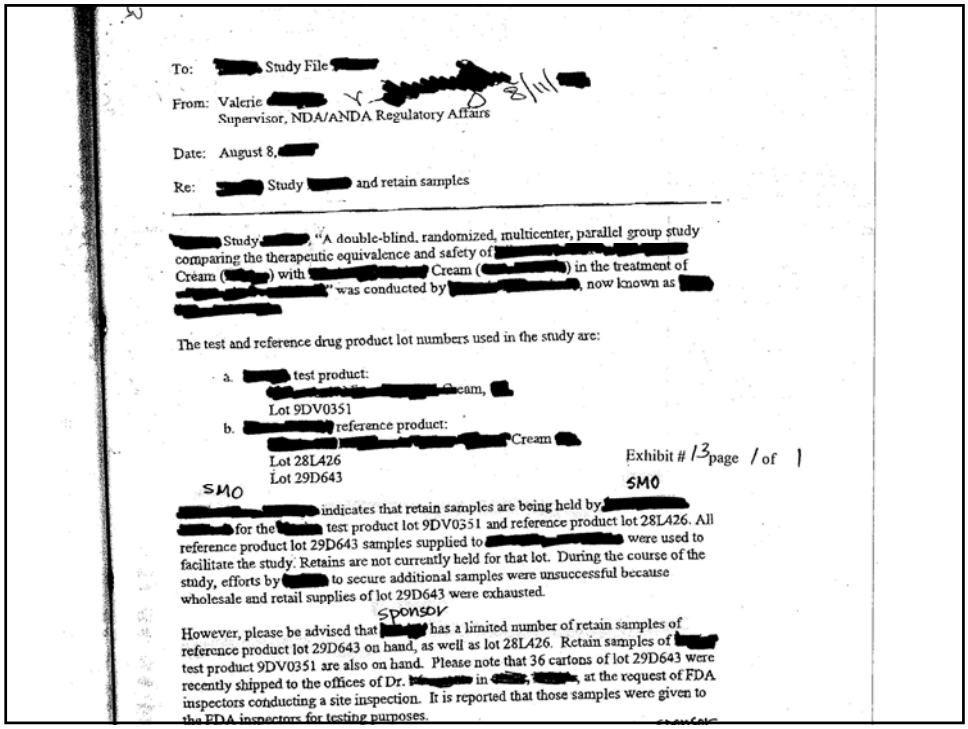
⊘ "Retention of Bioavailability and/or Retention of Bioequivalence Samples," according to 21 CRF 320 does not apply to the above mentioned study. Retention samples will not be sent to [redacted] Inc.. The sponsor releases and holds [redacted] Inc. harmless from any obligation to collect retention inventory or comply with FDA retention regulations in connection with this study.

Signature: [redacted] Date: 4-13-01

Title: Lead CRA / Sr. Specialist

DSI-BE Inspection Findings

- Example regarding miconazole inspection
  - SMO selected and retained reserve samples instead of the clinical site
  - discuss lack of sealed code for FDA to break the blind
  - multi-site clinical endpoint blinded study



To: [redacted] Study File [redacted]

From: Valerie [redacted]
Supervisor, NDA/ANDA Regulatory Affairs

Date: August 8, [redacted]

Re: [redacted] Study [redacted] and retain samples

[redacted] Study [redacted], "A double-blind, randomized, multicenter, parallel group study comparing the therapeutic equivalence and safety of [redacted] Cream ([redacted]) with [redacted] Cream ([redacted]) in the treatment of [redacted]" was conducted by [redacted], now known as [redacted]

The test and reference drug product lot numbers used in the study are:

a. [redacted] test product:
[redacted] Cream, [redacted]
Lot 9DV0351

b. [redacted] reference product:
[redacted] Cream [redacted]
Lot 28L426
Lot 29D643

Exhibit # 13 page 1 of 1

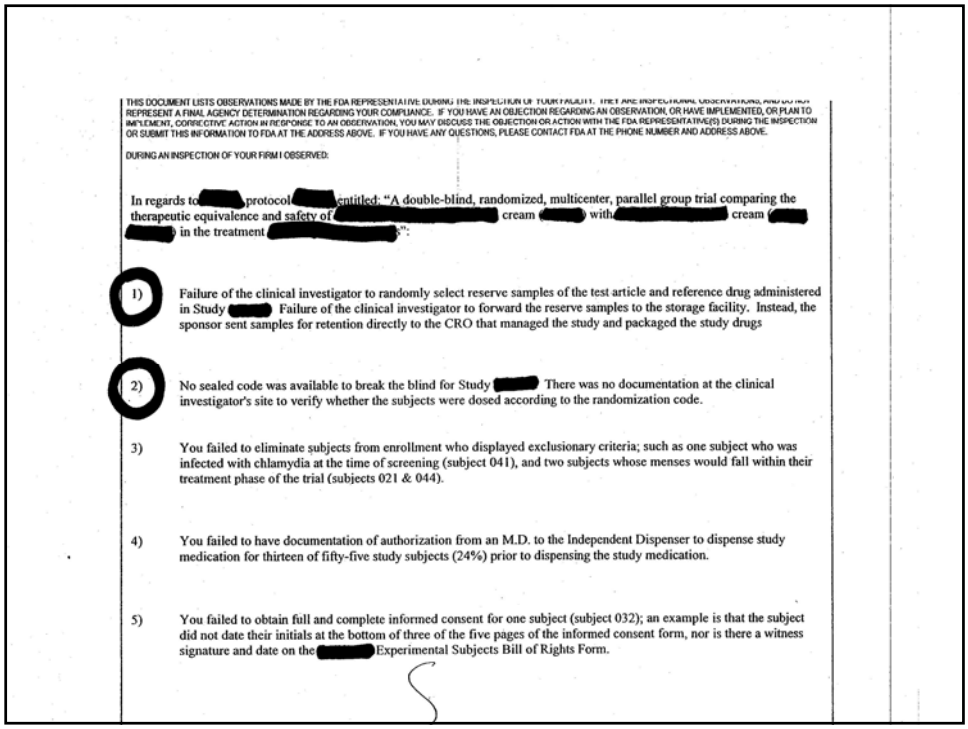
SMO

SMO

[redacted] indicates that retain samples are being held by [redacted] for the [redacted] test product lot 9DV0351 and reference product lot 28L426. All reference product lot 29D643 samples supplied to [redacted] were used to facilitate the study. Retains are not currently held for that lot. During the course of the study, efforts by [redacted] to secure additional samples were unsuccessful because wholesale and retail supplies of lot 29D643 were exhausted.

SPONSOR

However, please be advised that [redacted] has a limited number of retain samples of reference product lot 29D643 on hand, as well as lot 28L426. Retain samples of [redacted] test product 9DV0351 are also on hand. Please note that 36 cartons of lot 29D643 were recently shipped to the offices of Dr. [redacted] in [redacted], at the request of FDA inspectors conducting a site inspection. It is reported that those samples were given to the FDA inspectors for testing purposes.



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DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

In regards to [redacted] protocol [redacted] entitled: "A double-blind, randomized, multicenter, parallel group trial comparing the therapeutic equivalence and safety of [redacted] cream [redacted] with [redacted] cream [redacted] in the treatment [redacted]":

1) Failure of the clinical investigator to randomly select reserve samples of the test article and reference drug administered in Study [redacted] Failure of the clinical investigator to forward the reserve samples to the storage facility. Instead, the sponsor sent samples for retention directly to the CRO that managed the study and packaged the study drugs

2) No sealed code was available to break the blind for Study [redacted] There was no documentation at the clinical investigator's site to verify whether the subjects were dosed according to the randomization code.

3) You failed to eliminate subjects from enrollment who displayed exclusionary criteria; such as one subject who was infected with chlamydia at the time of screening (subject 041), and two subjects whose menses would fall within their treatment phase of the trial (subjects 021 & 044).

4) You failed to have documentation of authorization from an M.D. to the Independent Dispenser to dispense study medication for thirteen of fifty-five study subjects (24%) prior to dispensing the study medication.

5) You failed to obtain full and complete informed consent for one subject (subject 032); an example is that the subject did not date their initials at the bottom of three of the five pages of the informed consent form, nor is there a witness signature and date on the [redacted] Experimental Subjects Bill of Rights Form.

Additional Points to Consider

Please comment on...

- Quality of the source documents
  - Are they organized, complete, legible?
  - Do they provide an assurance that all subjects existed?
- Protocol changes
  - Were they approved by the IRB before implementation?
    - please document any differences between the protocol at the site and the one provided by DSI-BE

Please comment on...

- Competency of the study personnel
  - Is staff trained to perform assigned tasks?
    - If inadequate training impacts study outcomes, please document your findings on the 483.
      - particularly important for clinical endpoint BE studies
    - (Example: tretinoin cream, 1998 inspection, non-physician staff responsible for scoring acne lesions in a clinical endpoint BE not adequately trained, no documentation on site to verify validation of the individual.)

Please comment on...

- Facility conditions
  - Is there adequate work space, separation of operations?
  - Are there written procedures for study conduct?
  - Is the clinic arranged to prevent ingress of unauthorized food, drugs, etc.?
    - (Example: CRO in Miami, subjects had access to food preparation areas)

Please comment on...

- Electronic records/signatures
  - Is an electronic system used to collect data?
    - identify the system and summarize its use
    - Example: Inspection at Austin, TX. Inspected high level systems documentation, trustworthiness of the software, qualifications of persons developing/supporting computerized systems

Please comment on...

- Sponsor monitoring visits
  - only applicable to studies under an IND
    - reminder: many BE studies are exempt from the IND regulations

To sum it all up...

What should you look for?

- Examples of non-compliance
  - failure to document “Who got what”
  - failure to accurately document PK blood sampling times
  - PK blood samples compromised
    - improper identification, handling, storage

What should you look for?

- Examples of non-compliance
  - failure to report AEs
    - especially vomiting and diarrhea, which may affect absorption and elimination of drugs
  - failure to report concomitant medications or intercurrent illness
  - protocol inclusion/exclusion criteria not followed
  - protocol restrictions not met

What should you look for?

- More examples of non-compliance
  - inadequate or missing informed consent forms
  - inadequate medical supervision
  - inadequate drug accountability
  - failure to randomly select and retain reserve samples

Quiz Questions

In Vivo Bioequivalence Inspection Techniques

Critical issues to address during an *in vivo* bioequivalence study inspection include:

A. Who got what drug treatment?
B. When were specimens collected (e.g., PK blood draws)?
C. Where's Waldo?
D. both A and B

In Vivo Bioequivalence Inspection Techniques

Dosing records in an open-label *in vivo* bioequivalence study must document:

A. the treatment administered to each subject at the time of dosing
B. the actual time the treatment was administered
C. both A and B
D. none of the above

In Vivo Bioequivalence Inspection Techniques

Reserve samples for an *in vivo* bioequivalence study conducted at a CRO must be:

A. randomly selected by the sponsor
B. positively identified as having come from the same sample used in the bioequivalence study
C. retained by the sponsor
D. all of the above

In Vivo Bioequivalence Inspection Techniques

Examples of non-compliance for an *in vivo* bioequivalence study:

A. failure to document "Who got what"
B. integrity of PK blood samples compromised
C. failure to report AEs (especially vomiting and diarrhea, which may affect drug absorption)
D. all of the above

In Vivo Bioequivalence

What is Cmax?

A. the point in time at which the maximum plasma concentration of the test drug is achieved
B. the maximum concentration of the test drug achieved in the plasma
C. the rate and extent to which a drug is made available at the site of action
D. the area under the plasma concentration curve

In Vivo Bioequivalence

What is Tmax?

A. the time at which the maximum plasma concentration of the test drug is achieved
B. the maximum concentration of the test drug achieved in the plasma
C. the area under the plasma concentration curve
D. none of the above

In Vivo Bioequivalence

In vivo bioequivalence studies are important to the approval process of:

A. NDAs (e.g., clinical trial *vs.* to-be-marketed formulation)
B. ANDAs (e.g., generic *vs.* innovator formulation)
C. both A and B
D. none of the above

In Vivo Bioequivalence

Which Pharmacokinetic parameter represent both the rate and extent of absorption?

A. Tmax
B. Cmax
C. AUC (area under the plasma concentration curve)
D. All of the above

ANALYTICAL COMPONENT OF BIOEQUIVALENCE INSPECTIONS

Martin K. Yau, Ph.D.
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Compliance, CDER

1

Objectives

- **To show that the bioanalytical portion is an important component of BE studies and BE inspections**
- **To provide basic concept of validating a bioanalytical method for BA, BE, and PK studies**
  - **A method should be validated before it is used to analyze biological specimens (e.g., plasma, serum, etc.)**
  - **scope of validation experiments**

2

Objectives

- To show the concept of using calibration standards, and quality control samples (QCs) for accepting or rejecting an analytical run, during analysis of study specimens, to ensure accuracy of BA/BE/PK study data
- To provide examples of objectionable observations (483 items) in bioanalytical inspections.

3

Reminder

- BA/BE/PK study inspections are conducted at the clinical site and/or analytical site:
  - Clinical site
    - Clinical testing facility where subjects are dosed and blood samples are collected.
  - Analytical site
    - Analytical laboratory where biological specimens collected in the BA/BE/PK studies are analyzed for drug concentration.

4

Reminder: How is BE Demonstrated?

- Same group of subjects (n=18-36) are administered test (A) and reference (B) drug products in separate dosing periods
- Serial samples of biologic fluid (plasma, serum, urine) are collected from subjects just before and at various times after dosing (e.g., 0.5, 1, 1.5, 2, 2.5,3,3.5,4,6,9,12,14,16,20, and 24 hr post dose)

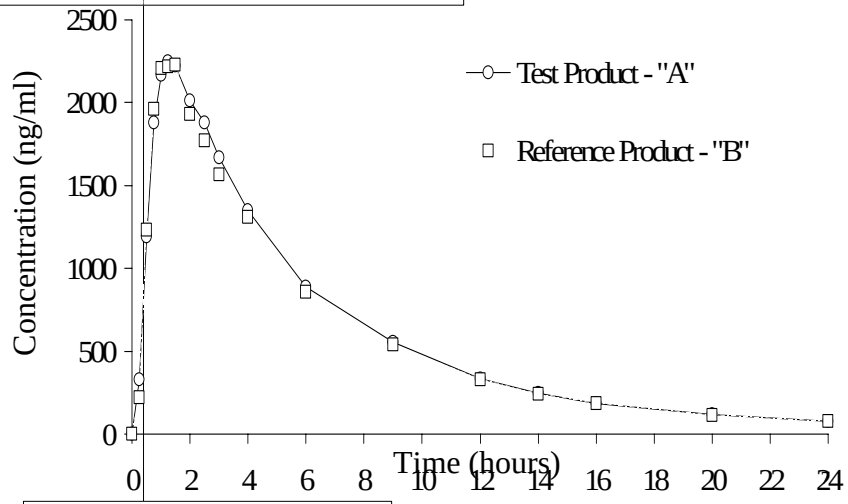
5

Reminder: How is BE Demonstrated?

- The samples are analyzed for drug and/or active metabolite concentrations
- The drug concentration data are used to generate a concentrations-time profile (i.e., a systemic exposure profile)

6

Time Course of a Drug in the Body



Please note that ...

- **<u>Precise and accurate</u> determination of drug concentrations in biological specimens (e.g., plasma, serum) is critical in BA/BE/PK studies**

8

Use FDA CPGM as a Guidance

- **Compliance Program Guidance Manual (CPGM) 7348.001 - *In Vivo* BE**
  - **This Compliance Program Guidance Manual describes the procedures used by FDA staff in performing BA, BE, and/or PK study inspections.**

9

CPGM 7348.001 - Attachment A

- ***Part 1: Facilities and Procedures***
  - ***Applicable to clinical and analytical facilities***
- ***Part 3: Analytical data and operations***
- Part 2 : Clinical data and operations **(already discussed)**

10

Focus on the Bioanalytical Method Used in the Study

- The biological specimens are analyzed for drug and/or active metabolite concentrations using different types of bioanalytical methods
  - chromatographic assays (e.g., LC/MS/MS, HPLC)
  - Ligand binding assays (e.g., RIA, ELISA)
- The data generated are used in BA/BE/PK assessments to support IND, NDA, ANDA applications

11

Two Major Components

- Analytical method validation
- Analysis of biological specimens (e.g., plasma, serum, etc.) obtained in a study for analyte (drug) concentration
  - Reference paper: FDA Guidance for Industry, Bioanalytical Method Validation

12

Concept for Validation of Chromatographic Assays (e.g., LC/MS/MS, HPLC)

13

General Concept

- In a validation experiment, calibration standard (CS) and quality control samples (QCs) of different concentrations are prepared by spiking known amount of analyte and internal standards (IS) into blank biological samples (e.g. plasma or serum)
- CS and QCs are then processed according to the assay procedure developed
- Following sample processing (e.g. protein precipitation, liquid/liquid extraction, solid phase extraction, etc), a small volume (e.g., 100 ul) of CS and QCs in extracted samples are injected into analytical system (e.g. LC/MS)

14

General Concept (cont..)

- Note the relationship between instrumental response and analyte concentrations.
- Based on the relationship between instrument response to known concentrations of the analyte in the CS, a calibration (standard) curve is generated
- Results of QCs are back calculated from the standard curve
  - Back calculated QC concentrations are compared to the known QC concentrations (nominal values) to determine outcomes of the validation experiment.

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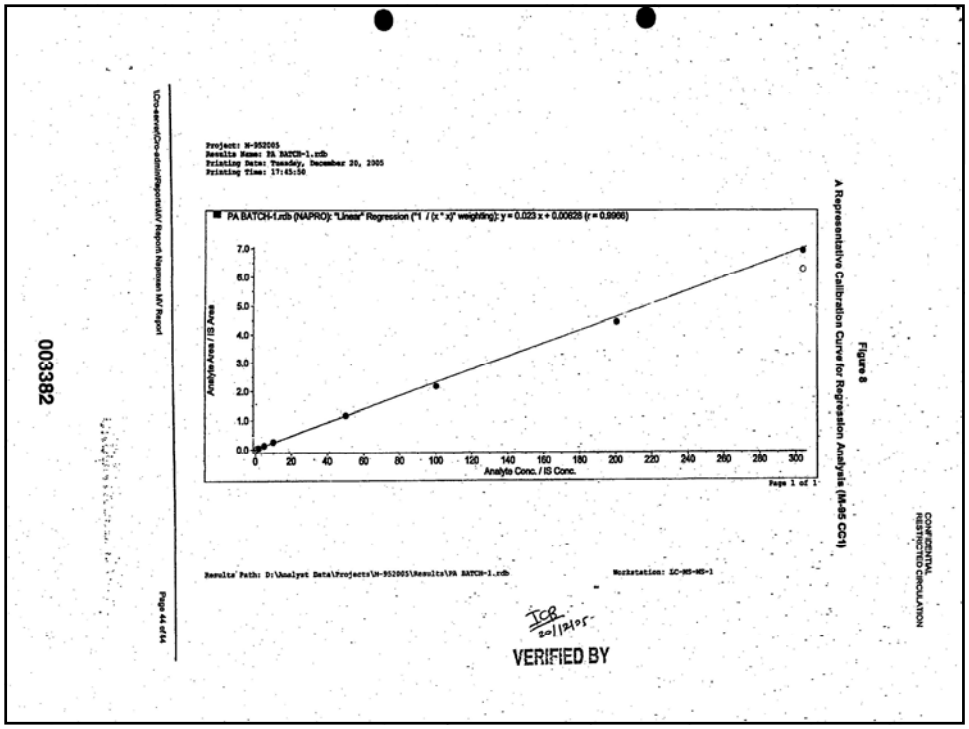

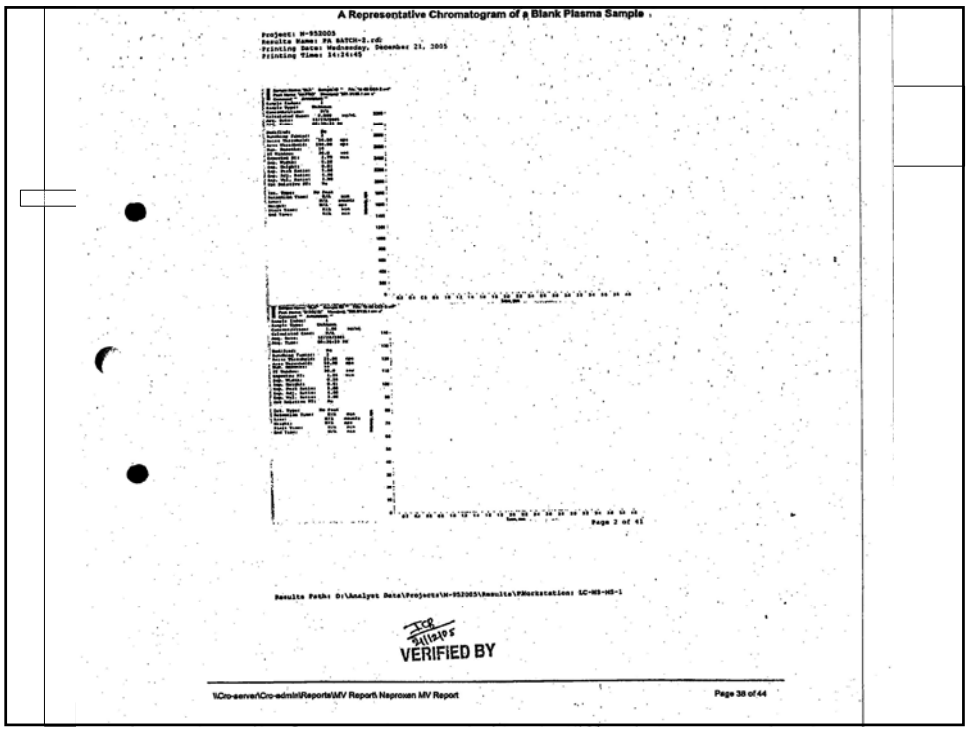
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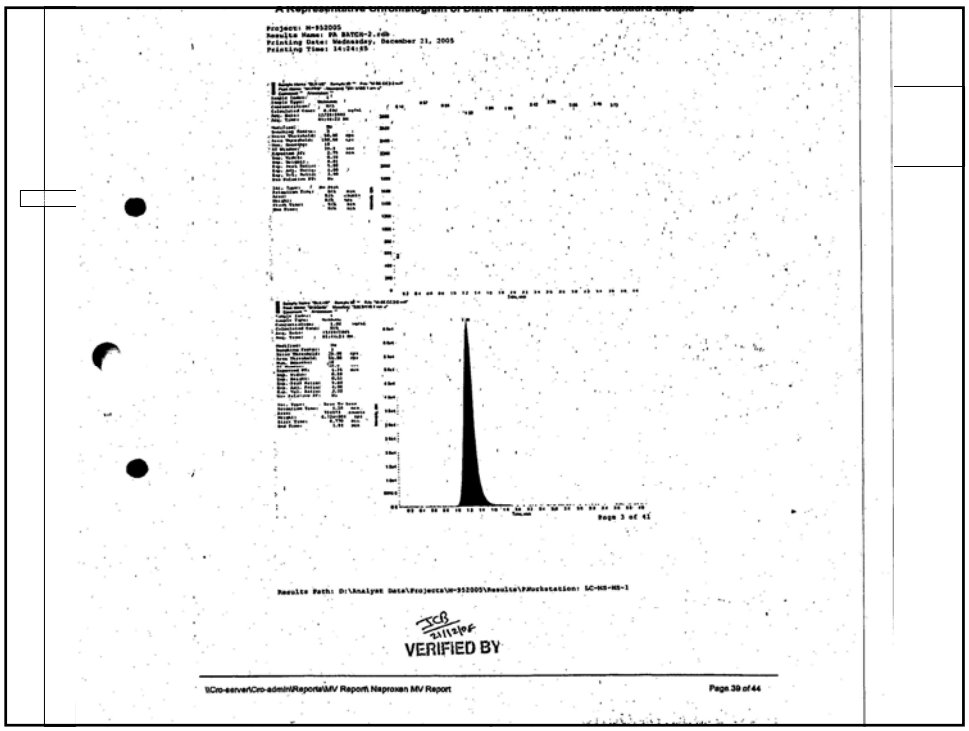
Page 38 of 44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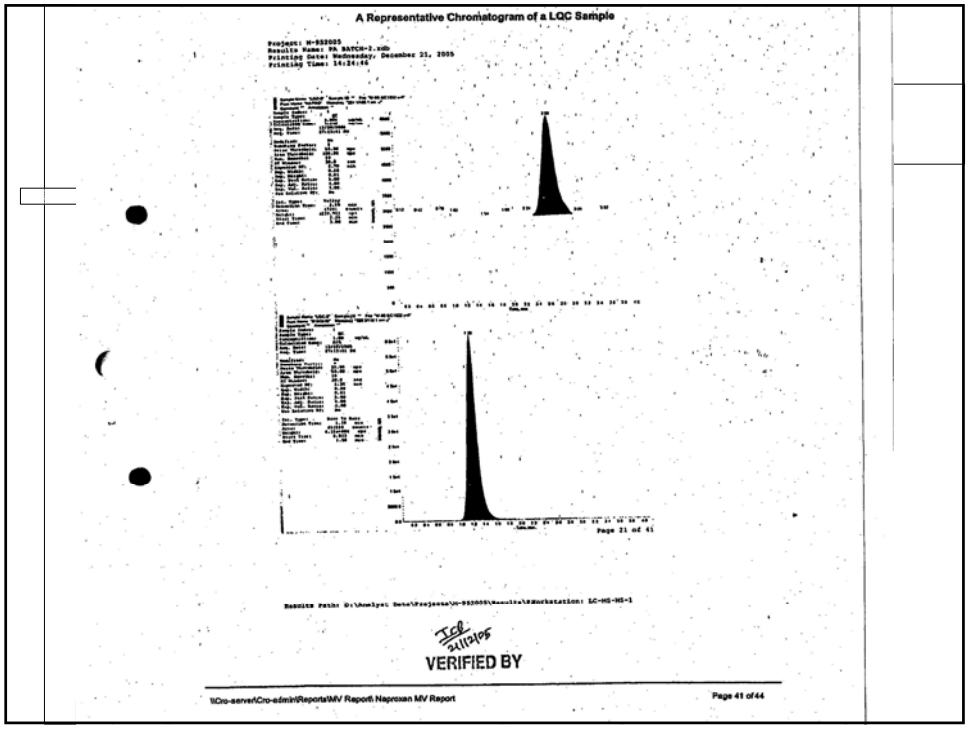
Page 39 of 44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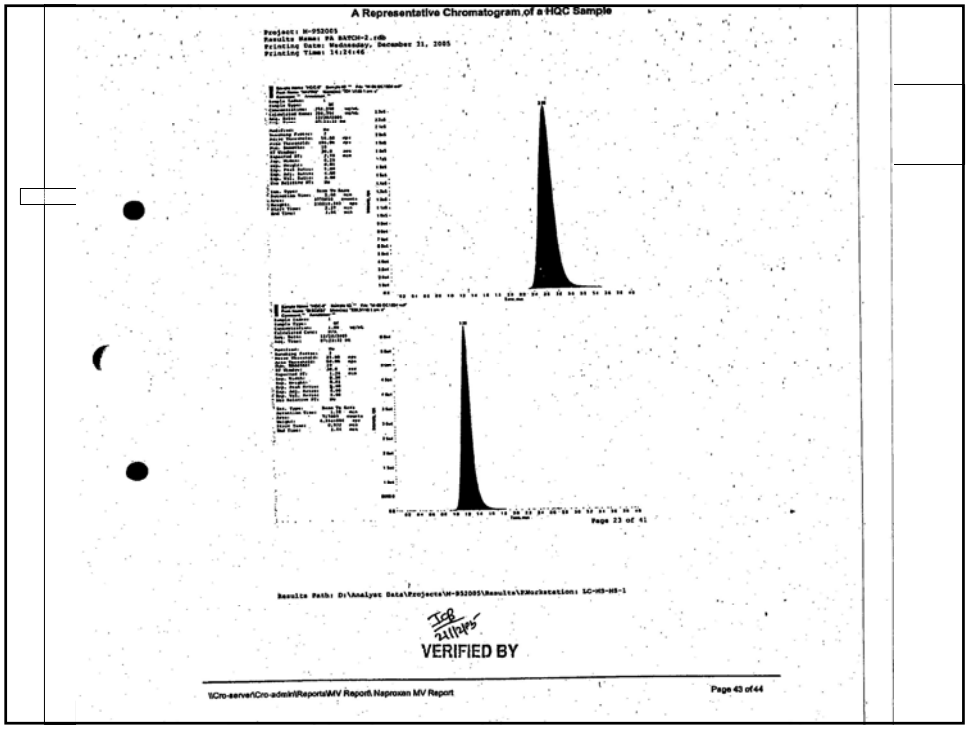
Page 41 of 44


A Representative Chromatogram of a HQC Sample
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Page 43 of 44

Method Validation

- Validate assay selectivity, sensitivity, accuracy, precision, recovery, and dilution integrity of the assay
- Validate stability of analyte and its internal standard
- Method should be validated before it is used to analyze biological specimens (e.g., plasma, serum, etc.)

21

Assay Selectivity

- Selectivity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample.
- To validate:
  - use blank samples in appropriate matrix (e.g., plasma, serum, urine) from six sources.
  - examine chromatograms of all blank samples for interference (look for interference peak at the retention time of the analyte)
  - Selectivity should be ensured at the lower limit of quantification (LLOQ).

22

Assay Accuracy and Precision

- **Validated Bioanalytical method should generate precise and accurate data**
  - **Accuracy: closeness of mean test results obtained by the method to the true value of the analyte (i.e, % deviation from the nominal value).**
  - **Precision: % Coefficient of variation from the mean value (i.e, % CV)**
    - **Note that data may be precise but inaccurate**

23

Assay Accuracy and Precision

- **Demonstrated by analysis of replicate sets of analyte samples of known concentrations (i.e., QC samples)**
- **Should be validated using a minimum of 3 QC concentrations in the range of expected concentrations (low, mid, and high concentrations ; n=5 samples for each concentration)**

24

Assay Accuracy and Precision

- For accuracy, the validation results (i.e., mean value) should be within 15% of the nominal value; within 20% for lower limit of quantification (LLOQ)
- For precision, validation results should not exceed 15% CV; <20% CV for LLOQ
- Assay sensitivity is the lowest concentration that can be reliably quantified with accuracy and precision that met the above criteria (i.e., LLOQ).

25

Assay Recovery

- Recovery is the extraction efficiency of an analytical process reported as % of the known amount of an analyte carried through the sample extraction and processing steps of the method.
- Unextracted standard represent 100% recovery
- Conducting recovery experiments is recommended.
- Assay recovery need not be 100%

26

Assay Dilution Integrity

- **Experiments conducted to assure the bioanalytical method remain precise and accurate when samples are diluted**
  - **Validate diluted samples (e.g., 2x, 5x, 10x) with high and low concentrations; 5 samples for each concentration**
  - **If validated, sample dilution should have no significant effect on assay accuracy and precision.**

27

Stabilities Studies

- **Stabilities of analyte and internal standard (IS) in *study samples, calibration standards (CS), quality control (QC) samples*, and stabilities of *reagents* used in an analytical method are critical data to *insure data integrity***
- **Stability experiments should be conducted to demonstrate stability of analyte and IS.**

28

Scope of Stability Studies

- Long term frozen storage stability study of analyte in matrix of biological specimens (i.e., study samples)
- Studies investigating other factors that may affect integrity of study samples:
  - freeze/thaw stability
  - bench-top stability
  - extract stability
  - auto-injector stability
  - Stock solution stability
- The above stability studies are normally conducted during assay validation

29

Long Term Frozen Storage Stability Study

- Cover the time period when study samples were collected to the time when study samples were analyzed
- Stability samples store under same condition as study samples (-20^{O}C or -70^{O} C)*
- Matrix of stability samples same as the study samples*
- Use same anticoagulant as in study samples*
- Documentation of :
  - Storage duration and conditions of stability samples*
  - Location of stability samples*
  - Failed stability studies*

* also apply to other stability studies

30

Freeze/Thaw (F/T) Stability Study

- F/T cycles should cover the # of times study samples are subjected to re-assay
- F/T conditions same as processing study samples
- Documentation of F/T conditions

31

Bench-Top Stability Study

- Cover the time period that study samples are placed on bench-top before sample processing
- Conducted under same temperature for storage of study samples on bench-top (usually room temperature)
- Light sensitive compounds
- Documentation of temperature and time period when stability samples are placed on bench-top

32

Sample Processing Stability Studies

- **Extract stability study**
  - Cover time period after extraction to the time when study extract samples are placed in the auto-injector for assay
  - Conduct under temperature used for storage of extract samples (usually refrigerated temperature)
  - Documentation of temperature and time for storage of extract stability samples
- **Auto-injector stability study**
  - Cover duration of the longest analytical run

33

Stock Solutions Stability Study

- Stability of stock solutions for analyte and IS used for the preparation of calibration standards and QC samples need to be demonstrated
  - Assure assay linearity if peak height/area to IS ratios are used to evaluate stock solution stability.
- QC samples and calibration standards should be prepared from different stock solutions

34

Standard Curve in Stability Studies

- Freshly prepared standard curve is recommended particularly for long-term frozen storage and F/T stability studies
  - Calibration standards prepared from stock solutions:
    - freshly made
    - previously made, but within the time period demonstrated by stock solution stability data
- Standard curve should not be generated from calibration standards stored under the same condition as the stability samples

35

Reagents

- Reagents used in the analytical method should not be deteriorated or expired.
- Bottles containing reagents should be properly labeled and should include expiration dates.

36

Remember ….

- Source data generated in all validation experiments need to be documented
- Source data of validation experiments are usually recorded in laboratory notebooks or forms
- All source data are subjected to audit during a FDA inspection
- Follow the SOP for assay validation
- Summarized method used and results of all validation experiments in a Bioanalytical Method Validation Report

37

Analysis of Biological Specimens Obtained in Bioavailability (BA), Bioequivalence (BE) or Pharmacokinetic (PK) Studies

38

Analytical Run (or Batch)

- Biological specimens (study samples) collected in a study are analyzed in analytical runs
- An analytical run is a complete set of analytical and study samples with appropriate # of standards and QCs for their validation.
- All study samples collected from a subject should be analyzed in the same analytical run; an analytical run may contain samples from one or more subjects

39

Standard Curve

- A calibration (standard) curve is the relationship between instrument response to known concentrations of the analyte.
- Standard curve should be generated for each analyte in an analytical run and be used to calculate the concentration of the analyte in the biological specimens (i.e., study samples with unknown analyte concentration) in the run

40

Standard Curve

Standard curve should be prepared

- **in the same biological matrix as the samples to be analyzed**
- **by spiking the matrix with different known concentrations of the analyte**

- **Sufficient # of calibration standards (CS) should be used to define the curve**
  - **6 to 8 non zero concentrations**

41

Standard Curve

- **CS concentrations should be chosen based on the concentration range expected in a particular study**

- **Should use scientifically sound procedure to accept/reject a calibration standard point and/or a standard curve**
  - **Reject or exclude a standard point if result is >15% deviation from the nominal value; >20% for LLOQ**
  - **To accept a standard curve, 75% or a minimum of 6 non-zero standards should meet the above criteria.**

42

Quality Control (QC) Samples

- A QC sample is a spiked sample with known concentration
- QC samples are used to monitor the performance of a bioanalytical method, and to assess the integrity and validity (i.e., acceptability) of the results of the subject samples analyzed in an analytical run

43

Quality Control (QC) Samples

- QCs replicated (at least once) at a minimum of 3 concentrations (low, mid, and high QCs) should be incorporated into each analytical run.
- QC concentrations should be representative of concentrations in study subject samples
- QCs are processed and analyzed in the same way as subject samples
- QCs should be interspersed throughout the entire analytical run

44

Quality Control (QC) Samples

- **A QC sample failed if the result is >15% deviation from the nominal value**
- **The results of QC samples provide the basis of accepting or rejecting an analytical run.**

  To accept an analytical run:
  - **At least 67% (e.g., 4 out of 6) of all QC samples in an analytical run should pass;**
  - **At least 50% (e.g., 1 out of 2) of QC samples in each QC concentration should pass**

45

Quality Control (QC) Samples

- **The minimum # of QC samples (in multiples of three) should be at least 5% of the # of subject samples or six total QC samples, whichever is greater.**

46

Note that….

- **Only data generated in an analytical run that meet the run acceptance criteria can be accepted for regulatory review.**

47

Remember ….

- **Source data generated in all analytical runs are subjected to audit during a FDA inspection**
  - **Document preparation of stock solutions of analyte, internal standard, and other reagent solutions**
  - **Document preparation of calibration standards and QCs used in analytical runs**
  - **Document processing of subject samples, calibration standards, and QCs in all analytical runs**
  - **Document # of analyst involved in sample processing and their roles**

48

Remember ….

- Chromatograms of samples in all analytical runs need to be available
- Follow SOP for analysis of study samples
- Summarized method used and all analytical results in an Analytical Study Report

49

Other Areas Covered During the Inspection

50

Repeat Sample Analysis

- Important to establish an SOP for repeat analysis and for data acceptance/reporting criteria
- SOP should provide objective criteria or reasons for re-assay (e.g., sample processing errors, equipment failure, poor chromatography, inconsistent PK data, sample outside of assay range etc.)
- Samples do not meet the re-assay criteria should not be re-analyzed.
- The rationale for the repeat analysis and the report of the repeat analysis should be clearly documented.

51

Chromatograms

- Check sample chromatograms for
  - Significant interference
    - All acceptance chromatograms should be free of significant interference
  - Manual re-integration
    - Is there a reason to justify manual re-integration?
  - Integration consistency
    - Compare integration of calibration standards and QCs vs those of subject samples
    - Check integration of calibration standards and QCs with borderline results

52

Reference Standard Material

- Reference standard material of analyte and internal standard (IS) are used to prepare calibration standards and QC samples, and the purity of the reference standard can affect study data.
- Reference standards used should not be expired
  - USP reference standards
    - Current lots
  - Non-USP reference standards, need
    - Purity
    - Expiration date
  - Extension of expiration date need to be support with recertify certificate of Analysis

53

Incurred Sample Reproducibility (ISR)

- FDA in BE inspections found lack of reproducibility sometimes seen on reanalysis of study samples.
- ISR issue was discussed in Bioanalytical Conferences in the US
  - Crystal City III Conference in 2006 resulted in a white paper that emphasized the need for conducting ISR studies
  - AAPS ISR Workshop in Feb 2008 discussed how best to conduct ISR studies (AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples – Implication of Crystal City Recommendations)

54

Current Expectation on ISR for US Bioanalytical Labs

- Establish ISR Program.
- Acceptance criteria be explicit
  - Two-thirds ≤ 20% difference recommended for small drug molecules
  - Other criteria needs to be justified
- Sample size considerations
  - target percentage of total sample size
  - 5%-10% recommended
- Samples selection is done *a priori*
- If ISR failed, conduct investigation

55

Current Expectation on ISR for US Bioanalytical Labs

- Follow-up and resolution of ISR will be necessary
- When ISR fails, the bioanalytical data is on hold until an investigation is completed and follow up action is done
- Documentation is essential

56

Also check…

- Major pieces of analytical and storage instruments involved in a bioanalytical assay (e.g., HPLC systems, LC/MS/MS systems, balances, freezers, refrigerators, pipettes, centrifuges, etc)
  - Calibration and maintenance records
  - Repair/service records
  - Unexpected event logs.
- Site should establish SOPs for instrument calibration/standardization and maintenance schedule

57

Receipt and Storage of Study Samples

- Check the following areas:
  - shipping invoice for date of receipt and conditions of study samples upon receipt (samples frozen?)
  - accountability of all samples upon receipt (any missing samples or broken tubes?)

58

Receipt and Storage of Study Samples

- Check the following areas:
  - location (freezer id) for storage of study samples, and time and date when samples were put into the freezer
  - freezer for storage of study samples (freezer equipped with continuous temperature monitoring device and alarm?)
  - freezer temperature records over the period of sample storage.

59

Software used in Analytical Labs

- Software for instrument control, data acquisition, data processing
- Audit trail function in software should not be disabled. Audit trial can assures integrity of electronic records.
  - Ensure only authorized changes in electronic records have occurred
  - Reconstruct significant events of study conduct and/or data collection, to verify data quality and integrity

60

Software

- **Be aware of system software security**
  - **Limited access (authorized staff only)**
  - **Individual account for each user**
  - **Limit the # of log-in attempts**
  - **Change user password at established intervals**

61

Example of Inspection Observations

62

Example of Inspection Observations

- Inconsistencies between data reported to FDA and at the site
- Inadequate or missing validation of assay with respect to assay selectivity, sensitivity, accuracy, precision, dilution integrity, and stabilities of analyte and its internal standard
- Failure to employ calibration standards, and QCs

63

Example of Inspection Observations

- Lack of objective criteria for acceptance/rejection of calibration standards, QCs
- Samples were allowed to remain for prolonged periods of time without proper storage.

64

Example of Inspection Observations

- Failure to maintain source data
  - For example, source data written on scrap paper and/or discarded in trash after transferring to analytical document
- Inadequate or no written procedures for receipt and handling of study drug
- Inadequate or missing standard operating procedures

65

Example of Inspection Observations

- Long term frozen (-20°) stability data for analyte are not adequate to cover the storage duration of subject samples.
- Experiment to validate F/T stability did not mimic sample handling conditions.

66

Example of Inspection Observations

- The firm failed to demonstrate stability of analyte during F/T cycles. Experiments to validate F/T stability could not be supported by notebook entries, specifically the duration and frequency of freezing and thawing of QC samples

67

Example of Inspection Observations

- The firm failed to demonstrate stability of the analyte stock solution . Experiments to demonstrate stock solution stability was not performed.
- The reference standard used for preparation of standard and QCs was from Lot D. The source of this lot is unknown. The firm cannot provide the purity and expiration date of Lot D.

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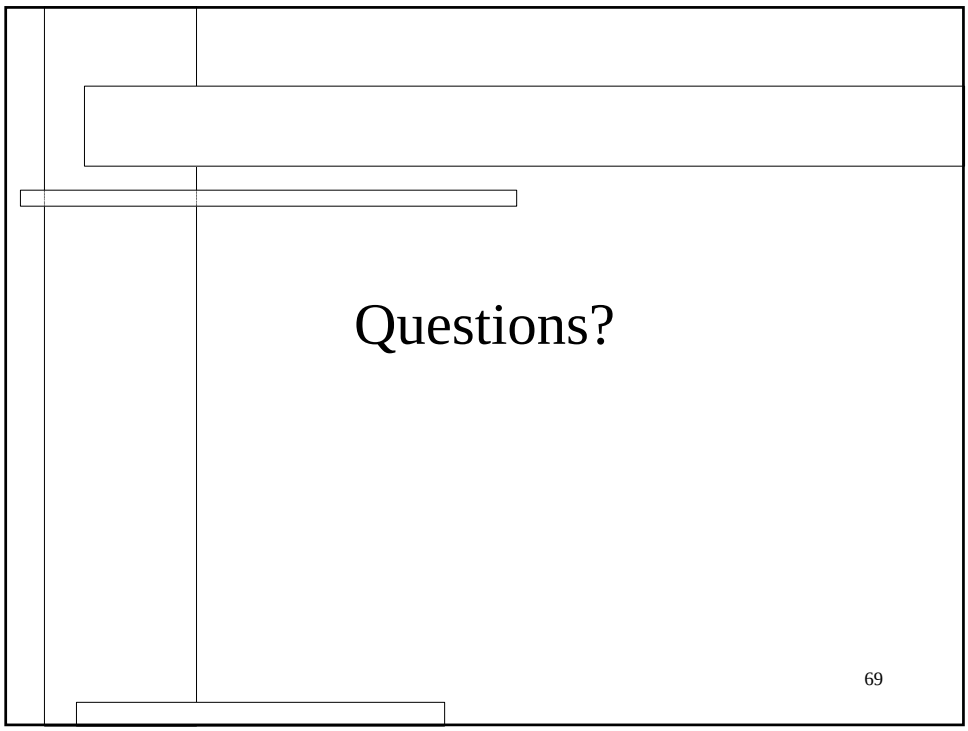
Questions?
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Part III.

Summary of Round Table Discussion

Summary of Round Table Discussion : Gaps and Challenges for Implementation, and Suggestion for Future Cooperation

A round table discussion at the closing of the "Advanced Workshop on GCP/ Clinical Research Inspection" provided an opportunity for open comments or suggestions from all facilitators and participants to identify gaps and challenges for implementation, and suggestions for future cooperation.

The comments from facilitators and participants are listed below

Gaps and Challenges for Implementation

- Adopted and implemented the same ICH Good Clinical Practice Guideline, but economies and country have different measures to regulate investigational drugs and their clinical trials.
- Limited numbers of trained inspectors
- The GCP Inspection of Clinical Trials do not yet exist in a few economies and are not fully-functional in some economies
- Most economies do not have GCP inspection experts, who could facilitate on the job training in their economies.

Suggestion for Future Cooperation

- The training course should continue every year or every other year to update and sustain knowledge, and provide experience sharing, and networking opportunities.
- The training and experience sharing opportunity could be a back to back meeting at APEC Life Sciences Innovation Forum. APEC should provide support, e.g. technical support, experts from competent drug regulatory agencies, and some financial support.
- Facilitators from developed economies, i.e. US FDA, agree to communicate with other economy's regulators when their inspectors come to inspect clinical trials abroad. This could be an opportunity for local inspector to observe or practice GCP inspection together with experienced inspectors. The requesting economies should write to US FDA to specify their contact persons.
- Suggested future topics of interests are
    - Updates on implementation and regulation of clinical trials

- Hand-on exercise on Bioequivalence Study Inspection
- Hand-on exercise of GCP inspection for clinical trials using electronic CRF

Part IV.

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Part V.

Questionnaires Survey Results

Questionnaire Survey Results

Project Code:	CTI36/2008
Project Title:	Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice (Phase 2)
Workshop	Advanced Workshop on GCP/ Clinical Research Inspection

Bangkok, Thailand, 2-6 March 2009

Part A for Participants

Number of respondents was 22 among 27 participants.

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

- The information given during the first and second day by Dr Lepay and Dr Yau is useful in the review of Basic GCP Inspection workshop and approach to Bioequivalence studies/Inspection. Practical Experience through the mock inspection experience help to reinforce the "how" to perform an inspection. It was really helpful to have mentors to guide the process.
- The training from both the basic and advanced workshops were form the reference to implement the GCP inspection program in my economy
- It is very helpful to my career. I had great chance to learn more concerte GCP inspection through the mock inspection
- This project will help us to build inspection that comply with GCP and provide training to our team in my economy
- This workshop is enable us to prepare an action plan which is needed to implement of GCP inspection according to presentation in the lecture and afterward it could also develop our institution.
- We can learn and share experience on GCP with colleague in APEC region
- We will improve the GCP inspection and its procedure
- Will improve the roles and responsibilities of regulatory authority in particular the harmonization of inspection activity

- Mock inspection exercise is very beneficial
- The patient, who participate in the trial are protected for possible harm that may be caused by investigational drug in clinical trial. In addition, the reliability, accuracy on clinical data generated by clinical trial in APEC are more trustworthy
- Bioequivalence study inspection program will promote the quality of generic drug
- We understand the scope of inspection better
- We learn GCP inspection skill from US FDA and Health Canada, but it is still too short that I can not see any progress at this moment

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

- Apart from the information sharing, the presentations and mock inspections, the exchange of information among the participating economies and facilitators (US FDA, Health Canada and the 3 industry representatives) have been obviously valuable to harmonize as well as to boost the capability for this regional agencies to improve the GCP inspection work or better understand the process and approach. Importantly, also the contacts gained at this workshop would be helpful as a resource when follow-up is required in this area
- The elements of preparation what to work during inspection and to make a report after an inspection
- The section on bioequivalence study really provide a further in depth how to do inspection for bioanalytical part
- Experience sharing between economies and country
- Though my economy has already done a lot of GCP inspection, but it is somewhat different from US FDA and Health Canada. I think especially we try to do foreign inspection, it is a good experience for me to learn from these mentors
- We learned more about 15 key elements of WHO GCP
- We learned skills GCP inspection step by step i.e. how to plan the inspection, how to inspect, what to be inspected and what to do after gathering the inspection and exhibits
- We learned the critical points in GCP and BE inspection and report.
- We learned the team work
- This workshop provided the hands-on mock inspection in different economy where having different culture and approach. However, I learned that there is no different in the implementation of GCP inspection program

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

- To establish in regulatory GCP inspection initiative in my economy
- To prepare and improve my economy's action plan for GCP inspection of both clinical research and bioequivalence study
- To develop the procedure and scheme for GCP inspection
- To train GCP inspection in my economy
- To review the current inspection manual and SOP
- To establish the GCP inspection team
- To share knowledge gained from this workshop and experience sharing session
- To help more clinical research center to be complied with GCP guideline
- The conduct of GCP inspection for clinical trial and bioequivalence study should be mandated by legal support

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

- As more clinical trials are increasingly being done in our region, the capacity building is very important, more training should be conducted to develop this area
- The present format of the project is good containing both theory and practical. Having a mentor system on the training is very helpful
- We need more practical workshop with more detail and more time for hands-on exercises
- Next training might provide more examples on observations from GCP inspection
- Next project may do mock inspection in other economies to see different economies' GCP practicing
- Further training on GCP inspection of electronic CRF and Bioequivalence study, and Pharmacogenomic guideline
- Next training should give more time for mock inspection at the trial site
- Next project may provide training for SOP of IEC/IRB
- The sharing of experience is important and useful
- Should maintain our network of inspectors
- When US FDA inspectors go to perform GCP inspection internationally, please allow the local GCP inspectors to observe or help at the inspection because it would be one of the effective way to learn by practicing with experienced inspector
- Next training may be Basic Principle of Good Laboratory Practice Inspection(GLP) and its inspection technique

- In my economy, the working group should be formed to plan the law and enforcement, human development and budget

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

- To pursue to set a GCP group in the APEC Life Sciences Innovation Forum or ASEAN pharmaceutical development group, where to develop GCP inspection in the region
- Encouraging APEC to sustain this and perpetuation of clinical trial/ GCP oversight networking beyond this workshop. For example, follow up workshop after (or before) some future APEC LSIF conference e.g. 2010 or another stand-alone GCP/ Inspection workshop in 2010 (or early 2011) as member economies follow-through with projected GCP inspection (implementation)
- To establish network among APEC in this area or at least bilateral collaboration with nearby economies
- Share information with inspector about GCP and other regulation linked
- To develop the regulatory system to ensure the protection of patient safety and promote best quality clinical trials in my economy

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

- [5] (good) : 17 (77%)
- [4] : 5 (23%)
- [3] : 0
- [2] : 0
- [1] (poor) : 0

Question (g):What is your assessment of the overall effectiveness of the project?

- The workshop has a high impact on the ability of the regional authorities to force a common understanding in this project
- The practical aspect of the inspection really provides further understanding as discussed in the theory part
- The workshop is very effective and well organized, whereby it provided us with the essential knowledge and great opportunity to share experiences both technical and regulatory issues
- This project provides a very constructive scheme in providing the basic knowledge, advanced knowledge, and practice in conducting GCP inspection

Question (h):Was the project content: (Check One):

- Just Right (20)
- Too Detailed (0)
- Not Detailed Enough (2)
- N/A(0)

Question (i): Please provide any additional comments. How to improve the project, if any?

- To be able to have more participants to join the workshop
- To prevail questionnaire at the beginning of the workshop
- It is not easy to fill out this questionnaires
- To provide more time for on site mock inspection exercise e.g. 3 days
- To establish inspection network among APEC economies
- To add the topic of electronic system validation and inspection
- To provide on-site mock inspection exercise for Bioequivalence study

Part B for Facilitators/Speakers/Mentors

Number of respondents was 7 among 7 speakers.

(a): Do you think the project achieved its objectives? What were the project's results/achievements?

- The project achieved its objectives
  - Review of basic workshop (GCP Inspection) material
  - Updates from participating economies on GCP Inspection
  - Introduction to Bioequivalence / BEQ Inspection
  - Full mock small group inspection exercise
- The comments from the participants regarding the lectures and site visits were very positive and all expressed that they learned a lot about bioequivalence inspection program
- Interaction from GCP regulators and sponsor personel from economies and country
- Agencies with little or no experience in regulatory inspection conduct gain knowledge from more experienced regulators
- The mock inspection exercise was completed. Hopefully participants have a good understanding of inspection process
- Experiences have been shared.
- Closed links between agencies are being forced which must be a good thing

- Presentation material and delivering of them was excellent

(b): Were the attendees the most appropriate target group?

- The attendees were the most appropriate target group
- Broad representative of many APEC economies and their regulators involved in clinical trial oversight
- They are all knowledgeable about principles of clinical trials, compliance, and GCP

(c): What is your assessment of the overall effectiveness of the project?

- Highly effective for
    - Information exchange
    - Education on current clinical trial oversight issue
    - Collaborative training by regulators and industry
- The hands-on training an inspection technique is the most effective approach to somebody keen to start as an inspector to learn the "nuts & bolts" of the trade. The keen interest of the participants confirms this assessment.
- It was an excellent initiative. I have gain valuable experience from attendance here this week
- Opportunities for industry auditors and regulatory inspectors to discuss and indeed perform train on inspection are rare, if unknown. I would be very keen to see more activity of this type
- The overall project was well organized and well planned.
- The participants were well represented

(d): Was there any room for improving the project? If so, how?

- Time allotted could be 1 day longer for hands-on : Clinical Trial and Bioequivalence activities
- Follow-up is needed, i.e. in 12-24 month, economies participating in this workshop should be able to show their progress (identified inspectors, inspection SOPs in place, site inspections conducted, and then another hands-on workshop would be beneficial whereas the mentors act as observers rather than trainers
- Prehaps more time to prepare write up the inspection activity. I had a group of 4 inspectors who had never been to a site and found myself having not only to cover off the basis of an audit/ inspection but also some very basic GCP aspect. Many more time would have given me the opportunity to do training more thoroughly
- More time for inspection, report writing, and reporting

(e): Any other suggestions?

- Encouraging APEC to sustain this and perpetuation of clinical trial/ GCP oversight networking beyond this workshop. For example, follow up workshop after (or before) some future APEC LSIF conference e.g. 2010 or another stand-alone GCP/ Inspection workshop in 2010 (or early 2011) as member economies follow-through with projected GCP inspection (implementation)
- Economies could ask commercial sponsors to conduct at least an audit on their territories and then have inspectors to join the sponsor auditors for training
- Some etiquette training for new inspectors to ensure skills of diplomacy and courtesy are observed which asking questions of investigator site and monitoring staff.