

Advanced Workshop :

Review of Drug Development in Clinical Trials

2 - 6 February 2009, Bangkok

REPORT

Produced for
Asia-Pacific Economic Cooperation Secretariat
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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 It means that if the product has shown life threatening adverse effects, it would be withdrawn from the market regardless of how much the company invested in research, development or even marketing of the product.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 : Review of Drug Development in Clinical Trials is the first workshop conducted under the APEC Project CTI36/2008T. But its curriculum was designed to cover advanced topics after the "Preliminary Workshop" that was conducted on 17-21 March 2008 under the prior APEC Project CTI24/2007T.

It has been more than 6 months for the planning stage. Health Canada designed the first draft agenda by information taken from the preliminary workshop. Consultants from Pharmaceutical and Medical Devices Agency, Novartis (as Industry representative), and Thai Food and Drug Administration later finalized the agenda. Speakers had worked well together via lots of email exchanges and teleconference calls to prepare all materials (i.e. lectures, presentations, examples, case studies, and exercises) for the workshop.

Thai Food and Drug Administration hosted the advanced workshop in Bangkok on 2-6 February 2009. 4 speakers and 26 participants are from 12 different APEC economies and countries i.e. Brunei, Canada, Chile, Indonesia, Japan, Malaysia, Peru, Philippines, Saudi Arabia, Singapore, Chinese Taipei, Thailand. The facilitators are from both public and private sectors i.e. Health Canada, Pharmaceutical and Medical Devices Agency(PMDA), and Novartis (Thailand). The participants are all drug regulatory agencies' officials.

The workshop provided training presentations, case studies, exercises and discussion opportunities according to regulatory clinical trial assessment. The main topics were Assessment of Chemistry and Manufacturing (Quality), Review Principles of Dose Selection, First in Human and Higher Risk Trials, Novel Designs in Clinical Trials, Ethics in Clinical Trials, Concept of Continuous Safety through the Lifecycle of a Product.

The participants of this workshop also had opportunities to present and exchange their economy and country updates on clinical trial regulations, 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 Siam City Hotel, Bangkok

2-6 February 2009

Dr Viner, Dr Stevens, Dr Sato, and Dr Sudhichai,

Distinguished participants,

Ladies and Gentlemen:

It gives me a great pleasure to welcome all of you and chair the Opening Ceremony this morning to the "Advanced Workshop: Review of Drug Development in Clinical Trials" jointly organized by Asia Pacific Economic Co-operation and Food and Drug Administration, Thailand.

The significance of Drug Clinical Trials and Capacity Building for Drug Regulatory Agencies are well noticed by several international networks including ASEAN or Association of South East Asian Nations, APEC or Asia Pacific Economic Cooperation, and ICH Global Cooperation Group. This project has been endorsed by ASEAN Working Group on Technical Cooperation in Pharmaceutical (AWGTCP), APEC Life Sciences Innovation Forum (LSIF) and ICH Global Cooperation Group (GCG) since the year 2002, 2006 and 2007, respectively.

By the listed international cooperation, indeed, we have received technical, financial, and moral supports. Please allow me to recall the last year achievement of hosting 2 training workshops in Thailand, those are "Preliminary Workshop : Review of Drug Development in Clinical Trials" and "Basic Workshop on GCP/ Clinical Research Inspection".

The accomplishments of both mentioned courses have brought to the 2nd project endorsement by APEC in later of the year 2008. Therefore, Thai FDA again is able to organize the 2nd or advanced phase of the training courses, which include the advanced course of clinical trial assessment and advanced course of clinical trial inspection.

Today's workshop would include numbers of advanced topics regarding the drug development in clinical trials and their assessments to ensure quality and safety of the

clinical trials and the investigational drugs themselves. This workshop has been designed to be practical with lectures, examples and exercises to provide skills, encourage participation and exchange information.

Today's workshop is attended by 4 speakers representing both leading Drug Regulatory Agencies and Industries, those are Health Canada, Pharmaceutical and Medical Device Agency (JAPAN), and Novartis, and officers from Drug Regulatory Authorities of 10 different economies and country including Brunei, Chile, Indonesia, Malaysia, Peru, Philippines, Saudi Arabia, Singapore, Chinese Taipei, and Thailand. Therefore, this workshop will provide us not only essential knowledge but also a great opportunity to share experiences both technical and regulatory issues

I would like to take this opportunity to express my sincere thanks to the organizers and in particular our honorable speakers. All of them have been working with us since the beginning of the planning stage and they are still here today for all of us, even though they are both very busy with their responsibilities at their agencies. We truly appreciate your dedication. Again, this training program could not have been made possible without APEC, ICH, ASEAN, Health Canada, PMDA, and Novartis , who foresee the importance of Clinical Trial Assessment. I hope that everyone would take the results of this program to develop our regulatory system to ensure the quality and safety of clinical trials and investigational products.

Finally, this is an opportune time for me to declare the official opening of the "Advanced Workshop: Review of Drug Development in Clinical Trials" and I wish all 5 fruitful days of interesting and beneficial program and also that you have a pleasant stay in Bangkok.

I warmly welcome you again.

Speakers' Biographical Sketches

(1) Junko Sato, Ph.D.

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Pharmaceuticals and Medical Devices
Agency (**PMDA**)
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Junko Sato is a Review Director in Office of New Drug I, Pharmaceuticals and Medical Devices Agency (PMDA). She received her B.Sc. (1990) in pharmacy from Kyoritsu University of Pharmacy and her Ph.D. (1997) from Jikei University, School of Medicine. From 1990-8, she was an instructor in Jikei University. She researched the mechanism of drug adverse events, especially in antimicrobial agent area.

She is a councilor of the Japanese Society of Chemotherapy, Japanese Association for Infectious Disease, Japanese Society of Environmental Infections Japan Society for Surgical Infection and The Japanese Society of Clinical Pharmacology and Therapeutics. She is also a diplomat of Antimicrobial Agents, Clinical Trial Supervisor, in the Japanese Society of Chemotherapy.

She joined Pharmaceutical and Medical Devices Evaluation Center (PMDEC) in 1998. She visited FDA as a guest reviewer to study the US drug regulatory system from September 2002 to March 2003. She is a member of ICH-E2E Expert Working Group, CIOMS VII, ICH-E2F Expert Working Group. Her specialty is infectious disease. She also works in National Hospital Organization Tokyo Medical Center as an Infection Control Doctor, in 3rd Department of Surgery, Toho University School of Medicine as an assistant professor, in Graduate School of Infection Control Sciences as an assistant professor.

She is a member of editorial board of Japanese Journal of Chemotherapy, Japanese Society of Environmental Infections, Journal of Japan Society for Surgical Infection. She is also a member of committee of PK/PD analysis, committee of antimicrobial agents susceptibility surveillance, etc.

(2) Norman Viner, M.D.

Chief, Clinical Trial Division
Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
Biologics and Genetics Therapies Directorate
Health Products and Foods Branch, Health Canada
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CANADA
Email : Norman_Viner@hc-sc.gc.ca

Dr. Norman Viner is Chief of the Clinical Trials Division, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB) in the Biologic and Genetic Therapies Directorate (BGTD), Health Canada, where he manages a team of reviewers who are responsible for reviewing the clinical aspects of the applications made to the Centre. This includes the applications involving Biotherapeutic Products, Therapeutic Vaccines, Gene Therapies and Radiopharmaceuticals. These reviews utilize the principles of risk benefit analysis in applying the Canadian Food and Drug Regulations to the clinical trial applications which fall under the jurisdiction of this directorate.

He graduated from the University of Ottawa Medical School in 1981. Prior to joining the Public Service, he was in full time general practice in the Ottawa area for over 15 years. He remains on active staff at the Queensway Carleton Hospital in Ottawa and continues to practice geriatric medicine part-time.

In 1996, he conceived a potential smoking cessation therapy. He ran a pilot study at McMaster University, which involved the design, manufacturing and use of a prototype novel pharmaceutical product. He has published several patents and a clinical research paper related to this effort.

(3) Will Stevens, Ph.D.

Chief, Plasma Derivatives Division
Centre for Biologics Evaluation
Biologics and Genetic Therapies Directorate, Health Canada
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CANADA
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Email : will_stevens@hc-sc.gc.ca

Will Stevens obtained his Ph. D. in protein biochemistry from Queen's University. Prior to arriving at Health Canada he worked as a researcher at the National Research Council of Canada's Biotechnology Research Institute in Pharmaceutical Biotechnology. Since 2000 he has worked for the Biologic and Genetic Therapies Directorate (BGTD) of Health Canada in various roles related to Pre-Market Assessment, On-Site Evaluation, and Lot Release for Biologics. Currently he is responsible for the Plasma Derivatives Division in the Centre for Biologics Evaluation.

(4) Sudhichai Chokekijchai, M.D.

Chief Scientific Officer
Novartis (Thailand) Limited
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Khet Klongtoey
THAILAND
Phone: +66 2 685 0764
Email : sudhichai.chokekijchai@novartis.com

Dr Sudhichai obtained his medical degree from Faculty of Medicine at Siriraj Hospital, Mahidol University since 1986. He completed his Internal Medicine residency at Rajvithi Hospital since 1991 and his general fellowship on HIV Drug Research at the National Cancer Institute (USA) since 1996. He has numbers of researches and publications in the area of HIV Drug Research and Development.

Before he first pursued his career with pharmaceutical business, he had spent 6 years as a medical staff of Allergy and Immunology Unit of Pramongkutklao Hospital and Medical College. He had worked as the Medical Director of leading pharmaceutical companies in Thailand, i.e. Bristol-Myers Squibb (Thailand) Ltd., Eli-Lilly Asia Inc.(Thailand), and AstraZeneca (Thailand) Ltd. His current position is the Chief Scientific Officer of Novartis (Thailand) Limited.

Part II.
PRESENTATIONS

Disclaimers

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

Workshop on "Advanced workshop : Review of Drug Development in
Clinical Trials"
BANGKOK, THAILAND
2-6 February 2009

Country Report

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

By:
Hajah Nor Izdiyana Haji Ibrahim
Pharmaceutical Chemist
Drug Administration Section
Dept. of Pharmaceutical Services

3/25/2009 1

OVERVIEW

- Background
- Regulatory Infrastructure or Authority
- Current GCP Laws & Practices
- Requirements for Ethics

3/25/2009 2

BACKGROUND

DEPARTMENT OF PHARMACEUTICAL SERVICES (DPS)
 MINISTRY OF HEALTH
RESPONSIBLE FOR

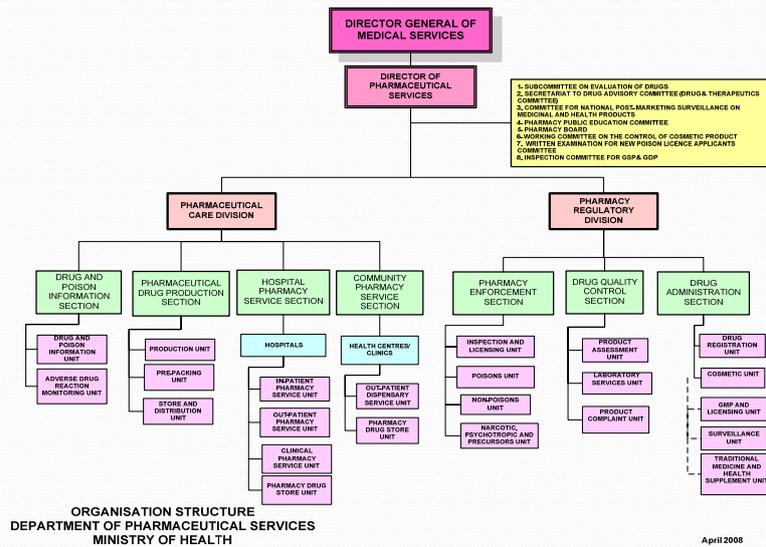
Implementation of Drug Policies and other related policies pertaining to the Department of Pharmaceutical Services

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

3/25/2009

3

REGULATORY INFRASTRUCTURE – Organisation Chart



3/25/2009

4

- Current GCP Laws & Practices

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

3/25/2009

5

- Legislation

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

3/25/2009

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FUTURE LEGISLATION

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

3/25/2009

7

CURRENT STATUS ON CLINICAL TRIAL

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

3/25/2009

8

REQUIREMENTS FOR ETHICS - COMMITTEES

- Assurance 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). The 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.

3/25/2009

9

- GUIDELINES

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

3/25/2009

10



 Health Canada Santé Canada *Your health and safety...our priority* *Votre santé et votre sécurité... notre priorité*

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Information Sharing Session

Follow-up from the Preliminary Workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

Canada

 Health Canada Santé Canada *Your health and safety...our priority* *Votre santé et votre sécurité... notre priorité*

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

Canada



Health Products and Food Branch

Update for Canada

- *Standards for REB*
- *Progressive Licensing*
 - *Integrating pre and post-market into ongoing benefit/risk considerations and assessment. Where appropriate cooperative risk-management*
 - *Challenges of moving things along from both the bureaucratic side and political*
 - *New Act and review/ modernization of regulations (formerly Bill C-51)*
- *Pharmacogenomics Guideline*
 - *Adopting ICH E-15 (Nomenclature and Coding for Genomics)*
 - *Active involvement in ICH E-16: Currently Step 1 document. Subject: filing data for acceptance of genomic markers*
 - *First workshop on Biomarkers in Canada (run by CMOD: Critical markers of Disease a non-profit academic consortium between NIH and the Montreal Heart Institute (implications for genomics [disease and drug response] and surrogate endpoints*

4

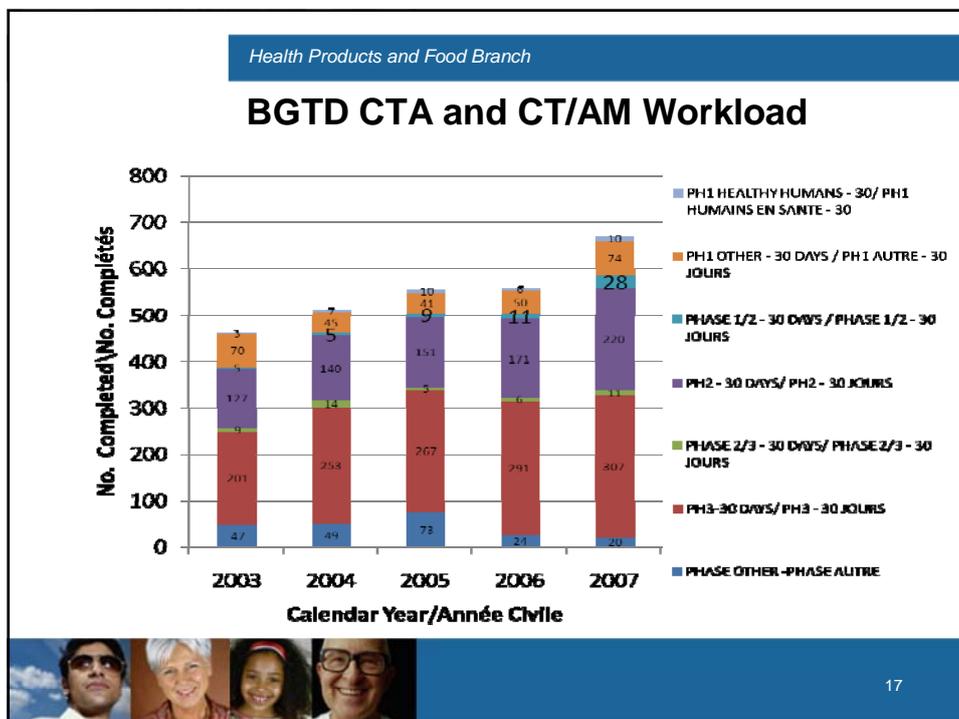
Health Products and Food Branch

Clinical Trials in BGTD

- Consistent increase in the number of applications since 2003 up to 2008
- Majority of trials are in Phase 2 or 3 developmental stage
- **Many withdrawals**
 - Minimal number of applications receive rejection letters (Non-Satisfactory Notices - NSN)
- Most clinical trials are for biotherapeutic products



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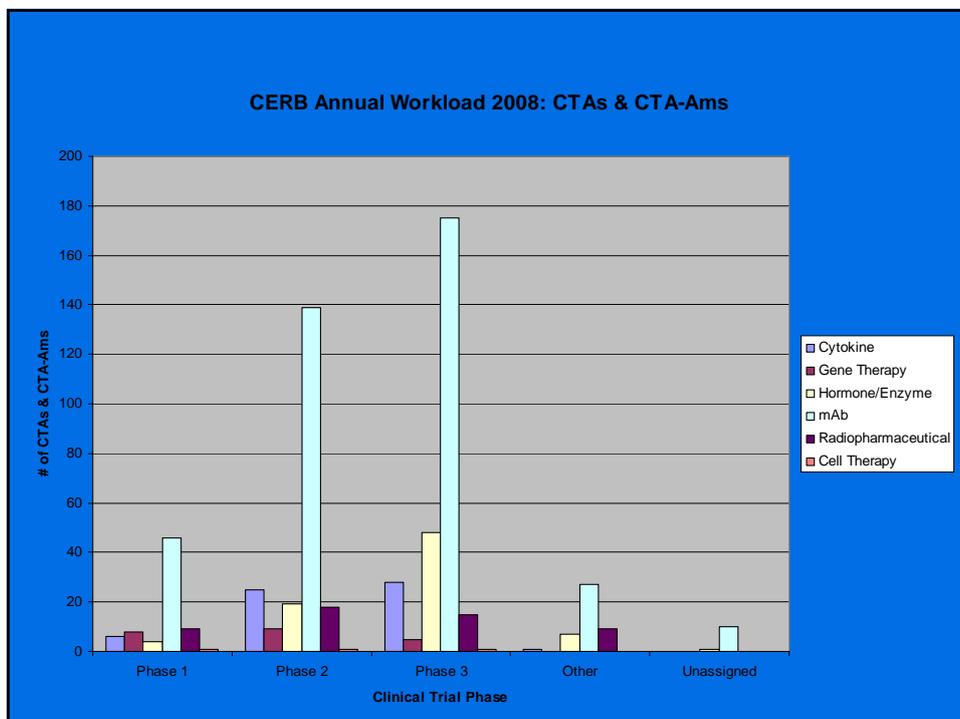
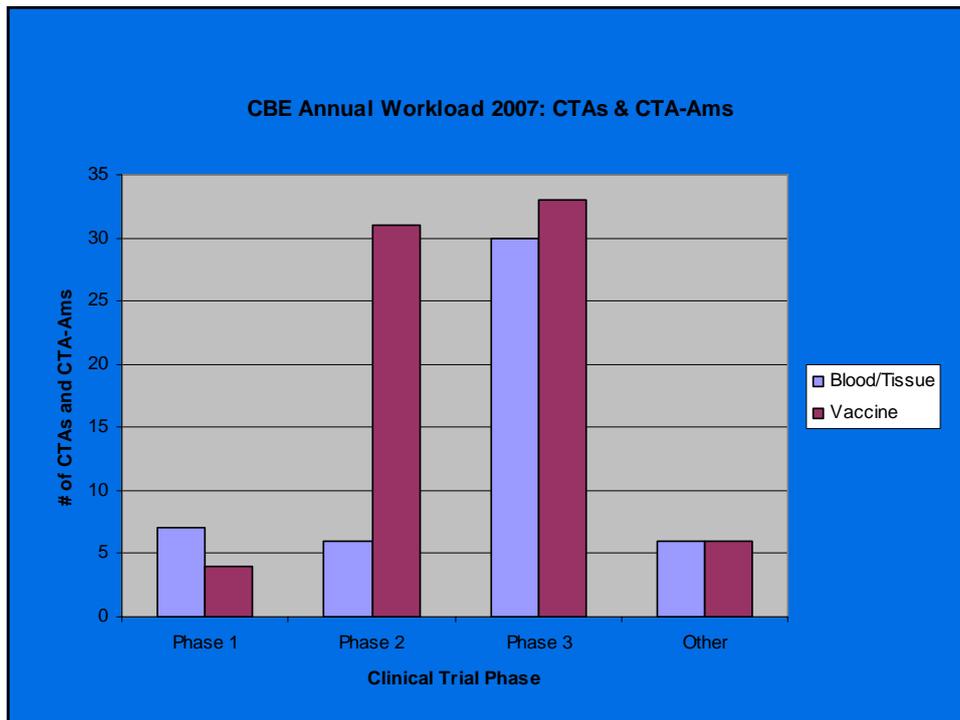


CTAs Received by Product Line - 2007

	Phase 1	Phase 2	Phase 3	Other	TOTAL
Cytokines	3	9	12	0	24
Gene Therapy	2	5	3	0	10
Hormones & Enzymes	3	15	30	3	51
Monoclonal Antibodies	23	90	81	5	199
Radiopharmaceuticals	13	15	5	2	35
Cell Therapy	0	0	0	0	0
Blood Products	1	3	10	2	16
Vaccines	2	17	20	1	40
TOTAL	<u>47</u>	<u>154</u>	<u>161</u>	<u>13</u>	<u>375</u>

CTAs Received by Product Line - 2008

	Phase 1	Phase 2	Phase 3	Other	TOTAL
Cytokines	4	8	11	1	24
Gene Therapy	2	3	1	0	6
Hormones & Enzymes	4	6	24	2	36
Monoclonal Antibodies	15	54	44	3	116
Radiopharmaceuticals	5	12	10	0	27
Cell Therapy	1	1	2	0	4
Blood Products	1	4	4	7	16
Vaccines	2	6	9	6	23
TOTAL	<u>34</u>	<u>94</u>	<u>105</u>	<u>19</u>	<u>252</u>



Health Products and Food Branch

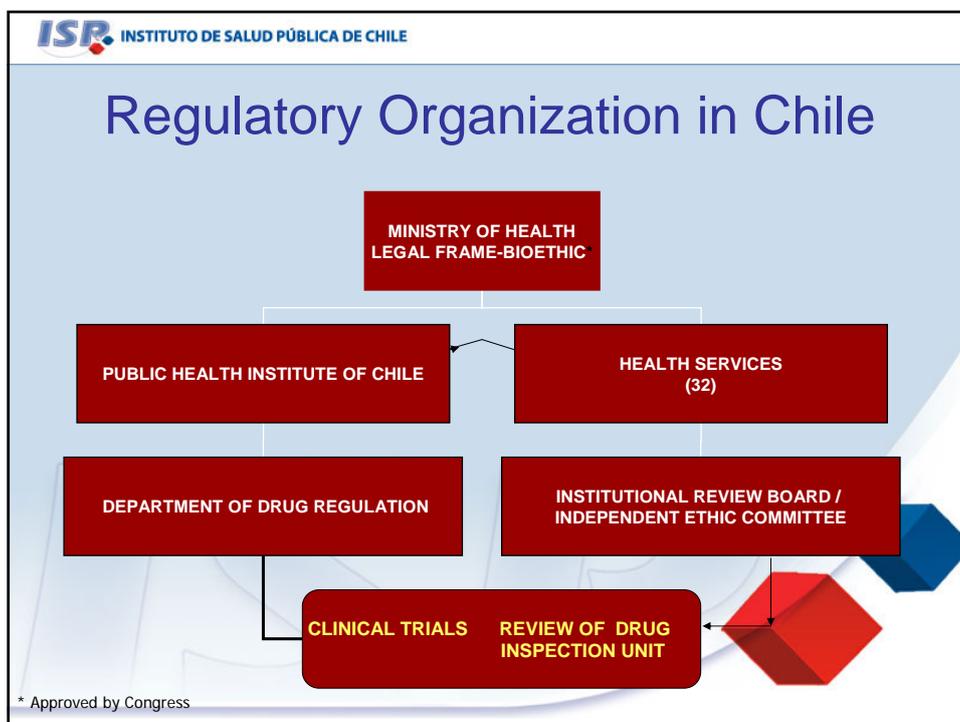
Progress

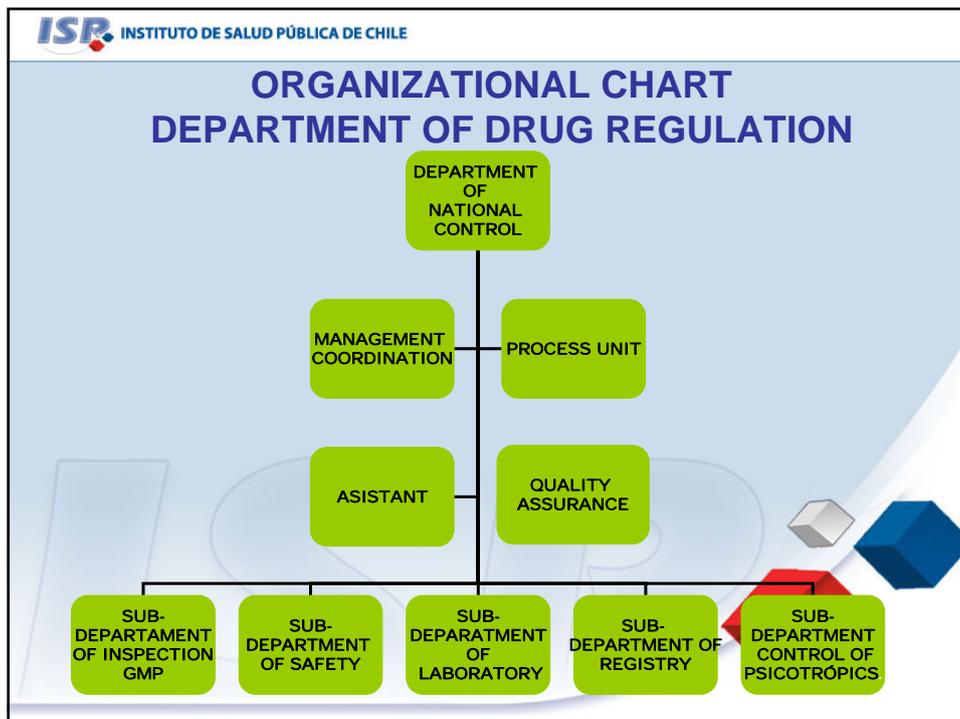
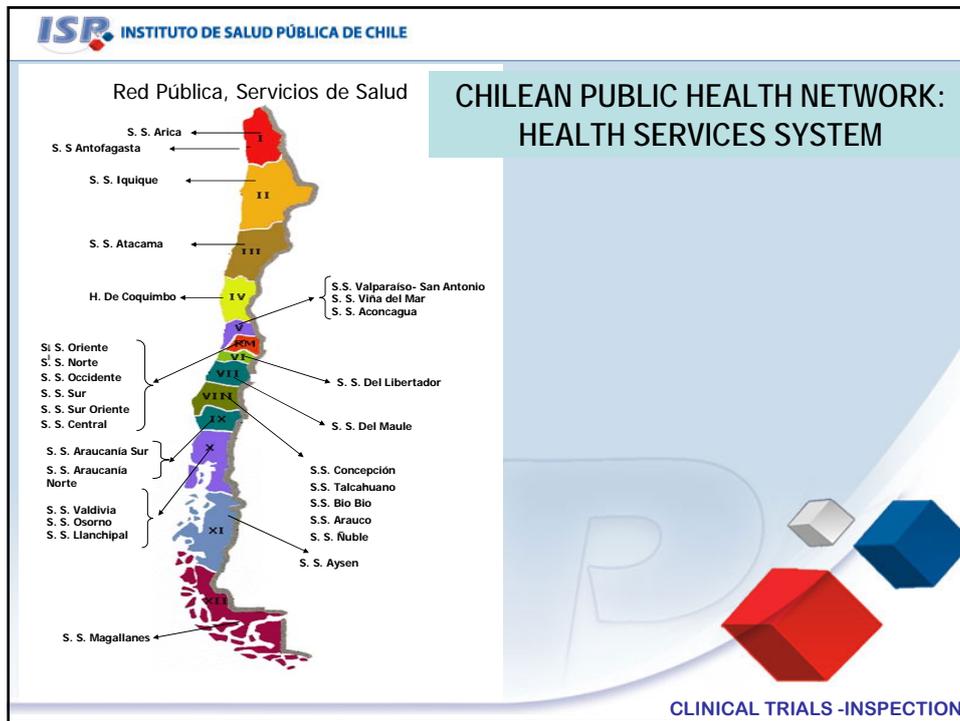
- New CT Review Division in CBE
 - 3 CT units in 2 Directorates
- Despite lack of modernization of our Regulations
- Silo effect of 3 separate review organizations
- Roles and Responsibilities for integrating a Life Cycle Approach
 - with organizations not designed with this purpose in mind
- Risk Management Plans
- **Depends on the willingness of people to collaborate**
- Poses Challenges that we are managing and overcoming!



11







ISR 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.”

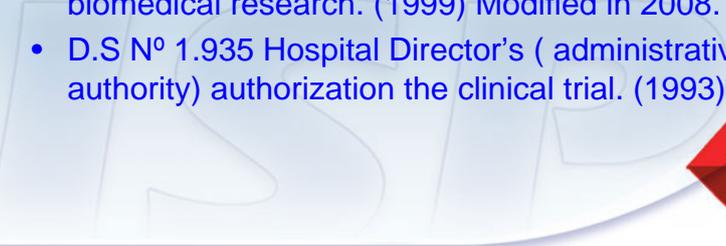


CLINICAL TRIALS

ISR INSTITUTO DE SALUD PÚBLICA DE CHILE

Laws/Regulation in Chile

- Law N° 20.120 Scientific investigation (2006)
- DS. N°1876 regulatory requirements of pharmaceutical product.(1995 – 2005). Modified in 2008.
- N° 57 normative of clinical trial.(2001)
- D.S N° 494 .Authorized ethics committees that review biomedical research. (1999) Modified in 2008.
- D.S N° 1.935 Hospital Director's (administrative authority) authorization the clinical trial. (1993)



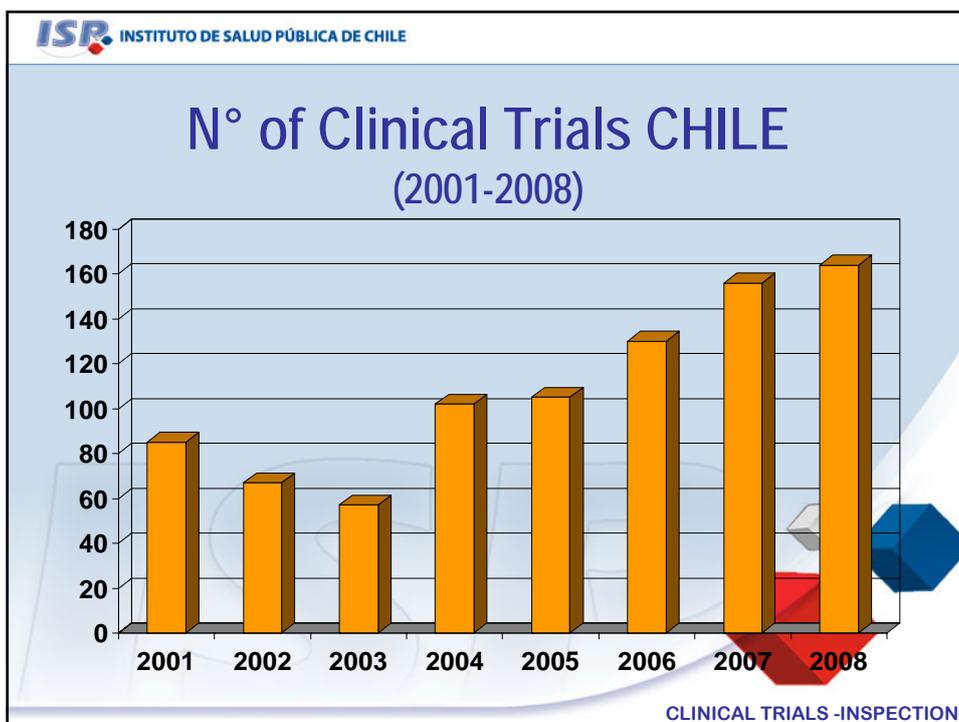
CLINICAL TRIALS

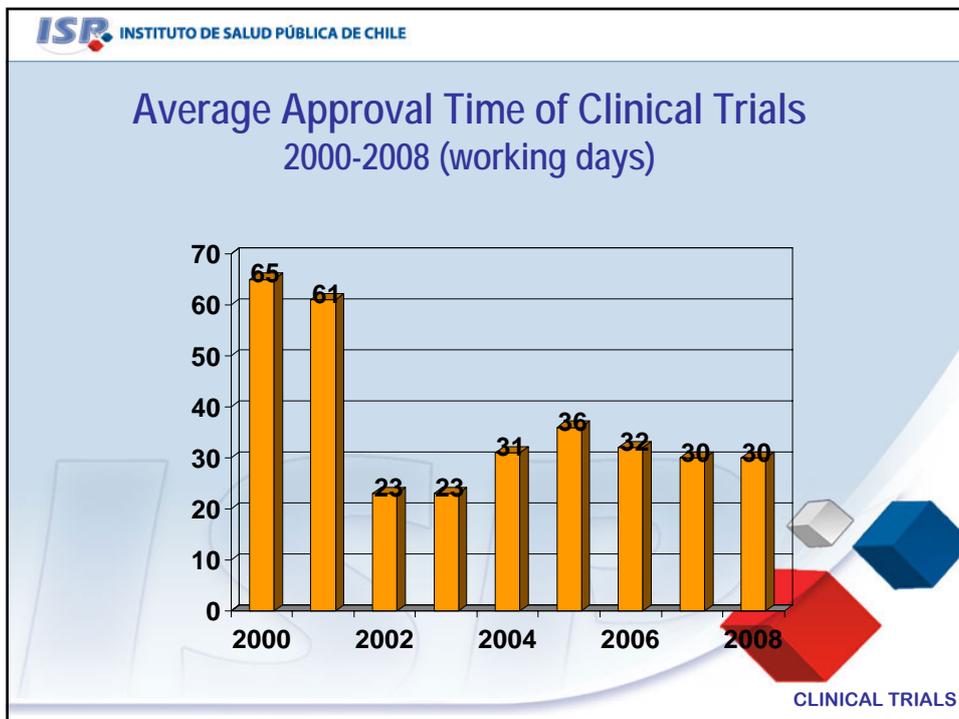
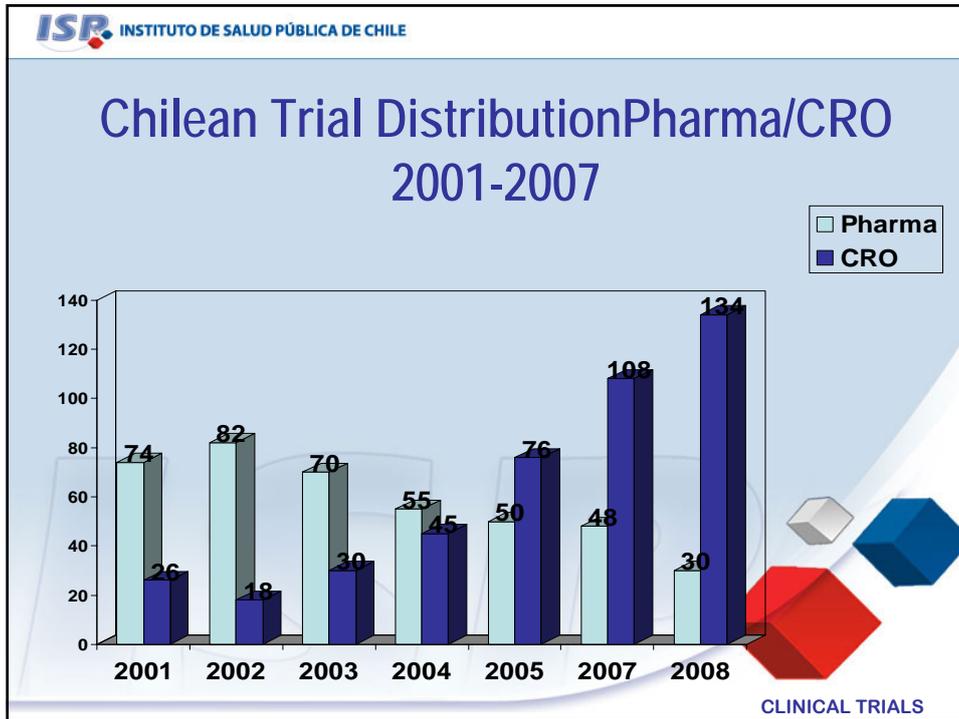
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Law/Regulation in Chile

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

CLINICAL TRIALS



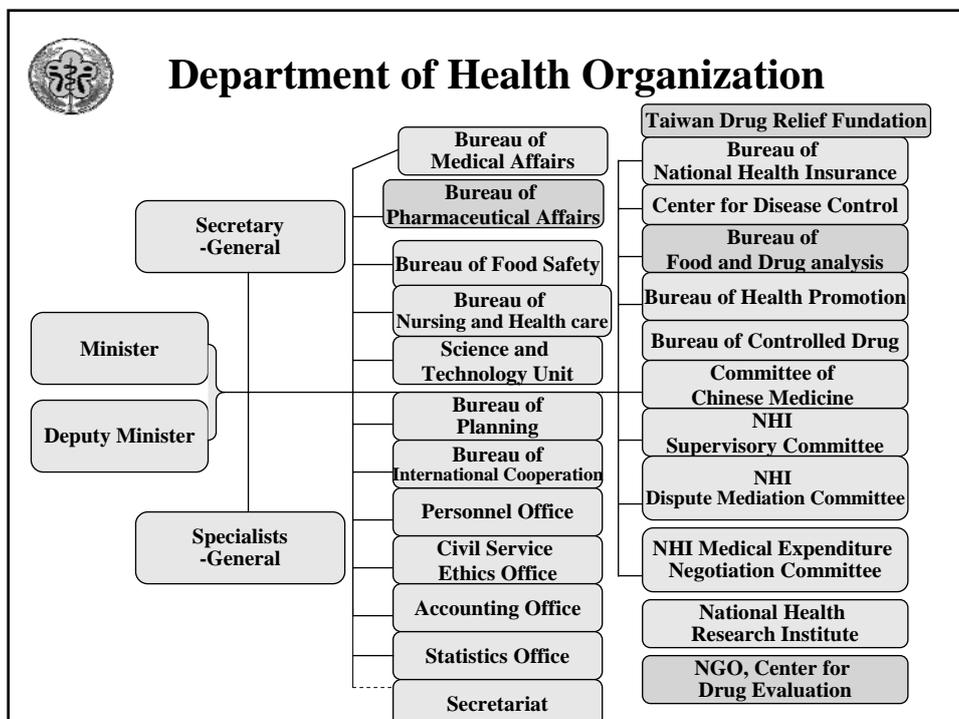


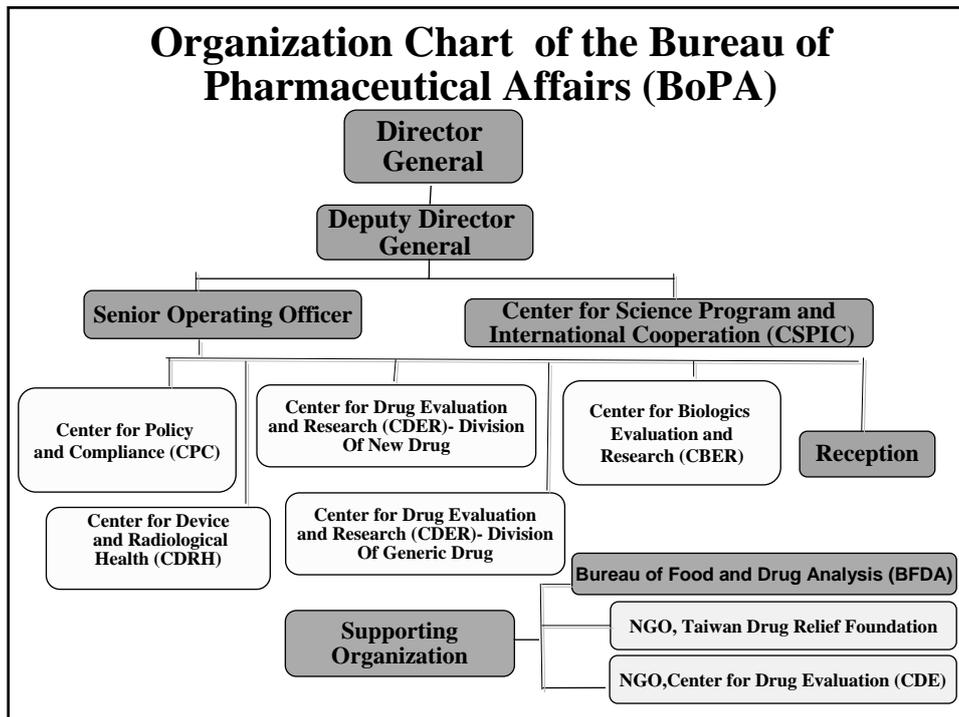


Status of Clinical Trial in Chinese Taipei



Lien-Cheng Chang
 Bureau of Pharmaceutical Affairs
 Department of Health, Chinese Taipei
 2-6 February 2009





Roles for Pharmaceutical Regulatory Authorities

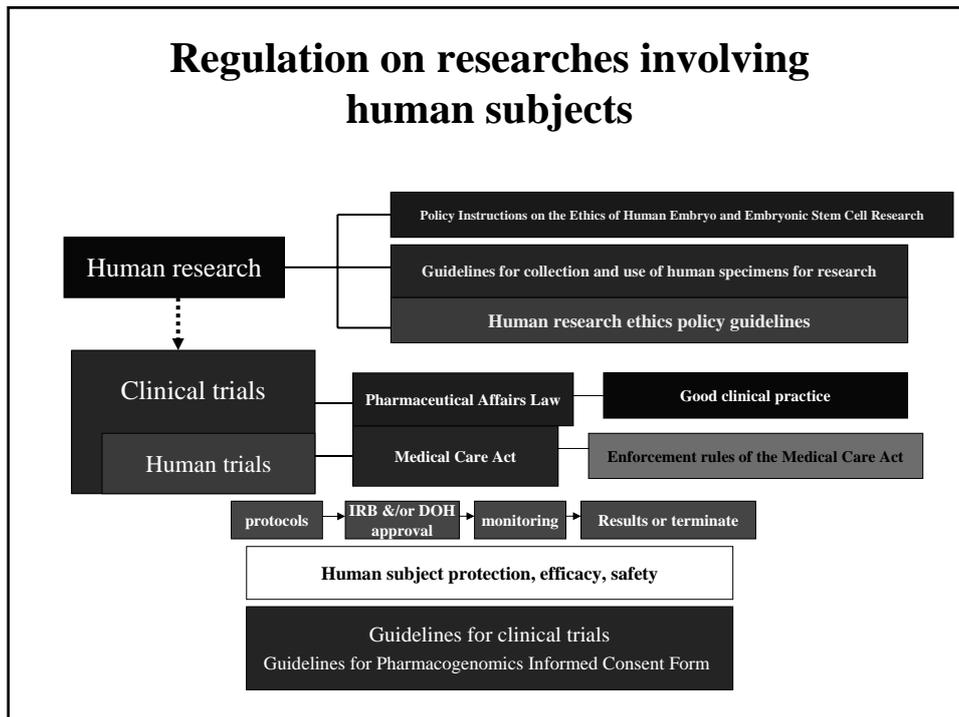
- Balance between Public Health Protection & Promotion
- Protecting Public Health
 - Quality, safety and efficacy
 - Evidence-based review system
 - Risk Management
- Promoting Public Health
 - Facilitate access of new drug
 - Facilitate new drug and new medical device development
 - International harmonization

Pharmaceutical Research Monitoring and Human Subject Protections

- ✓ Human Subject Protections
 - Ethical Review of Clinical Trials and other Researches involving Human Subjects.
 - Guidelines and check-list of IRB surveys were established in 2004.
 - IRB surveys have been implemented in 2005 and 2007.
- ✓ Protocol Review/Science Evidence Base
- ✓ Compliance with Good Clinical Practice
- ✓ Cultivating clinical trial/research professionals-via training and rewarding

Human Subject Protections

- Apply at every stage of clinical research
- ✓ Preclinical/laboratory studies
- ✓ Study review and oversight
- ✓ Conduct of the clinical study
- Applies to all involved with clinical research, including the clinical investigator, sponsor/monitor, study staff, IRB, DOH, etc.

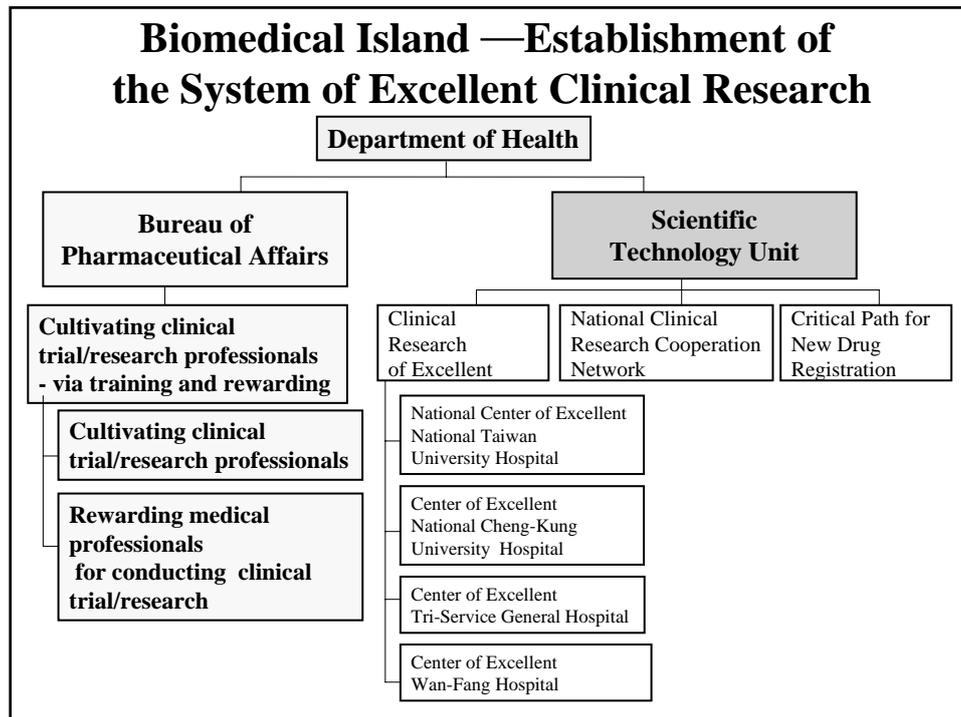


Conformity to international regulations on protection of human subjects

- 「 Investigation Project on Institutional Review Boards at Medical Institutions 」 (announced in 2005)
- Status of SIDCER certifying domestic IRB
 - SIDCER conduct the first IRB certification in the APEC region in 2005

Year	APEC certifications	Taiwan certification
2005	3	2
2006	7	4
2007	23	11

SIDCER: Strategic Initiative for Developing Capacity in Ethical Review



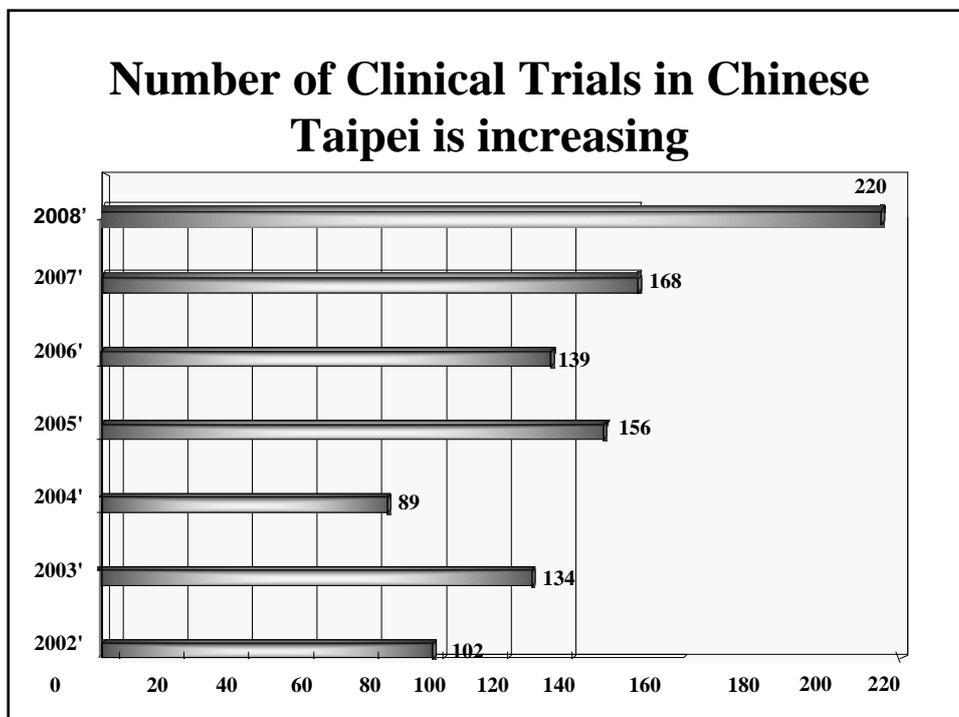
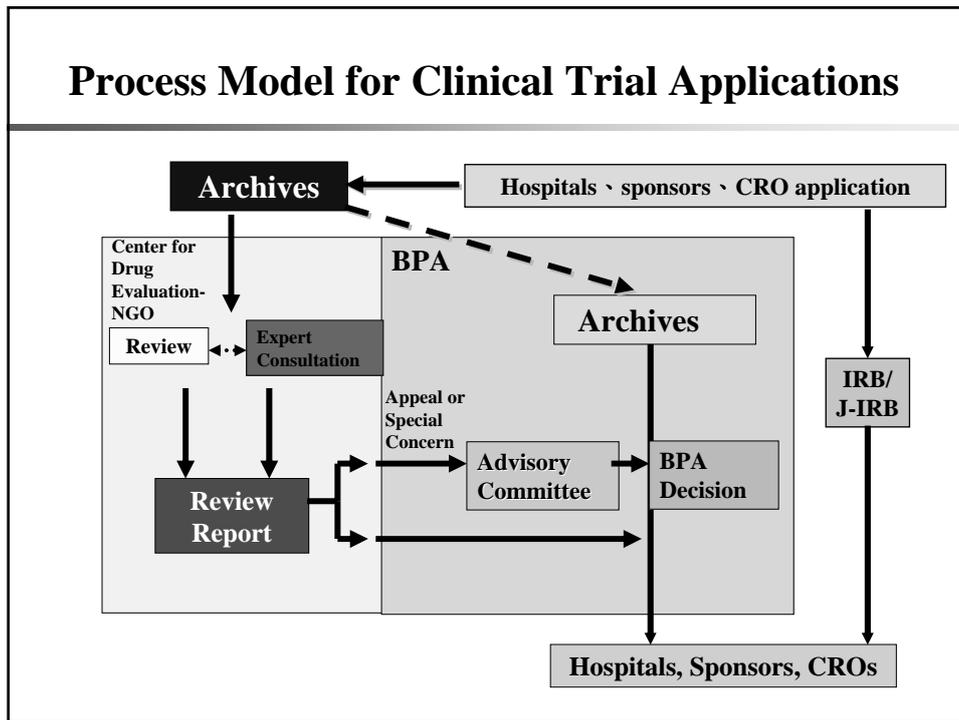
**Cultivating clinical trial/research professionals
 - via training and rewarding**

1. Cultivating clinical trial/research professionals

- to raise the knowledge of personnel involved in clinical trials/researches via
 - (1) Workshops on drug clinical trial/research design
 - (2) Workshops on medical device clinical trial/research design
 - (3) Conference on regulations of medical device clinical trial/research

2. Rewarding medical professionals for conducting clinical trial/research

- provide medical professionals with incentives to conduct clinical trial/research
 - (1) Physicians
 - (2) Pharmacists
 - (3) Nurses
 - (4) Statisticians



Points to Consider in New Drug Review

■ Safety and Effectiveness

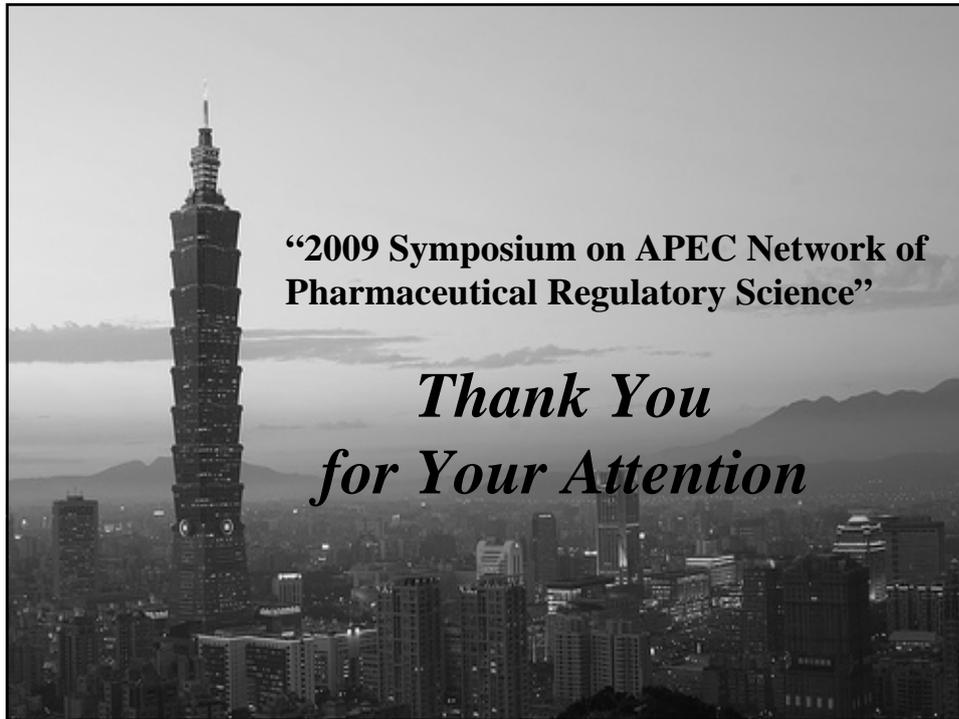
- Preclinical animal tests (pharmacology and toxicology)
- Pharmacokinetics
- Bioavailability (BA) / Bioequivalence(BE)
- Bridging study evaluation
- Clinical trials

■ Quality

- API and drug product characteristics
- Chemistry, Manufacturing & Control
- Pharmaceutical stability test
- cGMP

International Cooperation

- Regulation conformity to international standards
- Set up Mechanism for Exchange of Letters and Mutual Recognitions
- Existing Achievements:
 - Drug:
 - APEC ISTWG (Industrial Science and Technology Working Group)
project: APEC Network on Pharmaceutical Regulatory Science
 - APEC LSIF (Life Sciences Innovation Forum)
project: APEC Regulatory Science Symposium of CPP
 - ICH (International Conference on Harmonization): ICG GCG (Global Cooperation Group) Participants





CLINICAL TRIALS (CT) IN INDONESIA

Advance Workshop :
Review of Drug Development
in Clinical Trials

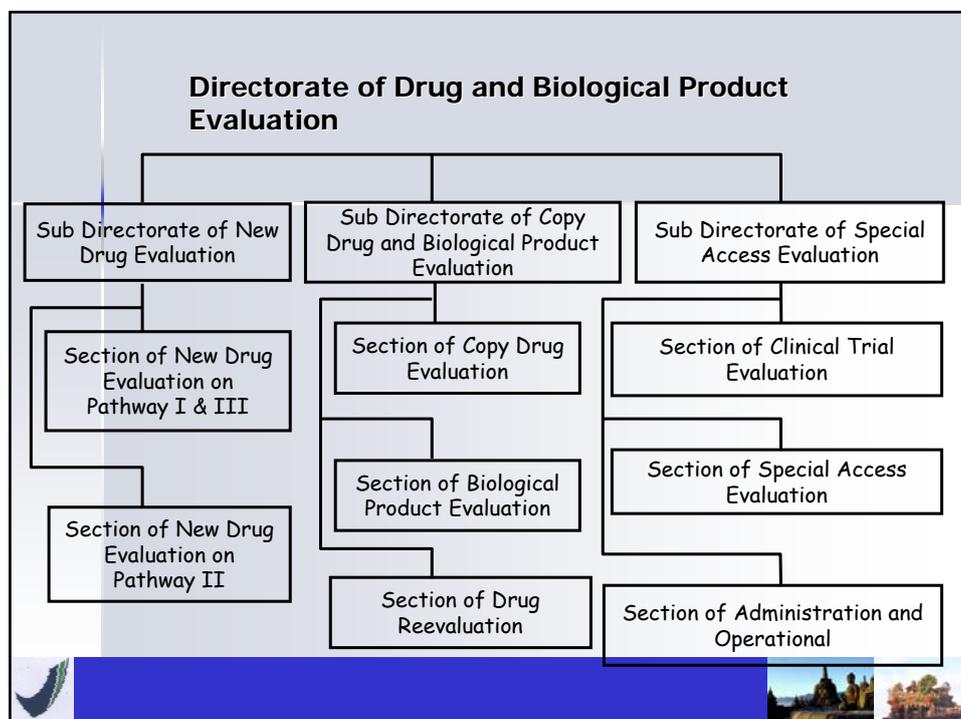
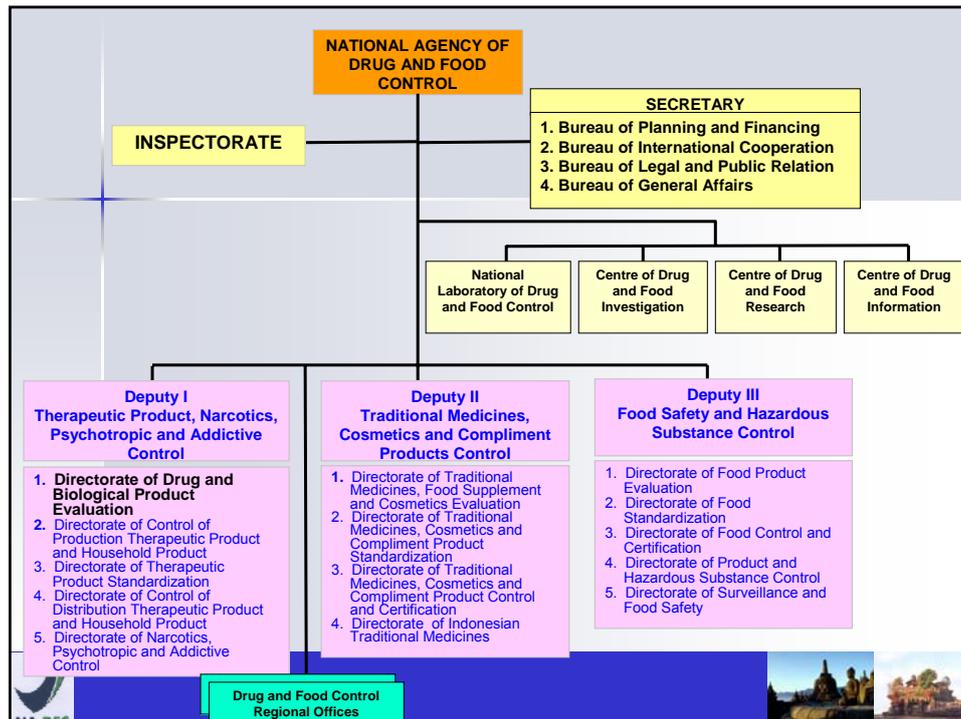
Bangkok, 2 – 6 February 2009,



INTRODUCTION : INDONESIAN COUNTRY PROFILE

- Indonesia is the largest archipelago in the world, stretching for more than 5,000 kms across the equator, estimated 17,508 islands (about 6,000 are inhabited)
- The estimated population is approximately 238 Mi with ann pop growth rate 1,4% and life expectancy at birth 65,92 years (male) & 69,9 years (female)
- GDP/GDP per capita : US \$ 935 billion / US \$ 3,800
- Total Pharmaceutical market value: ~ US \$ 2.6 billion
- Health care (HC) system:
 - 85 health Research Institute
 - > 1215 Hospitals (0,6 bed / 1000 pop)
 - Health Research Budget US \$ 5 Mi





REGULATORY FRAMEWORK OF CLINICAL TRIAL :

Objectives : CT in accordance with GCP to enable sound benefit/risk assessment

- Protect CT subjects, particularly on Safety issues
- Ensure merit of scientific research.
- Ensure consistency CT assessment
- Ensure credibility of data for reg.subms'n
- Maintain sponsor, stakeholder, public trust



Scope of Regulatory Authority for Clinical Trial

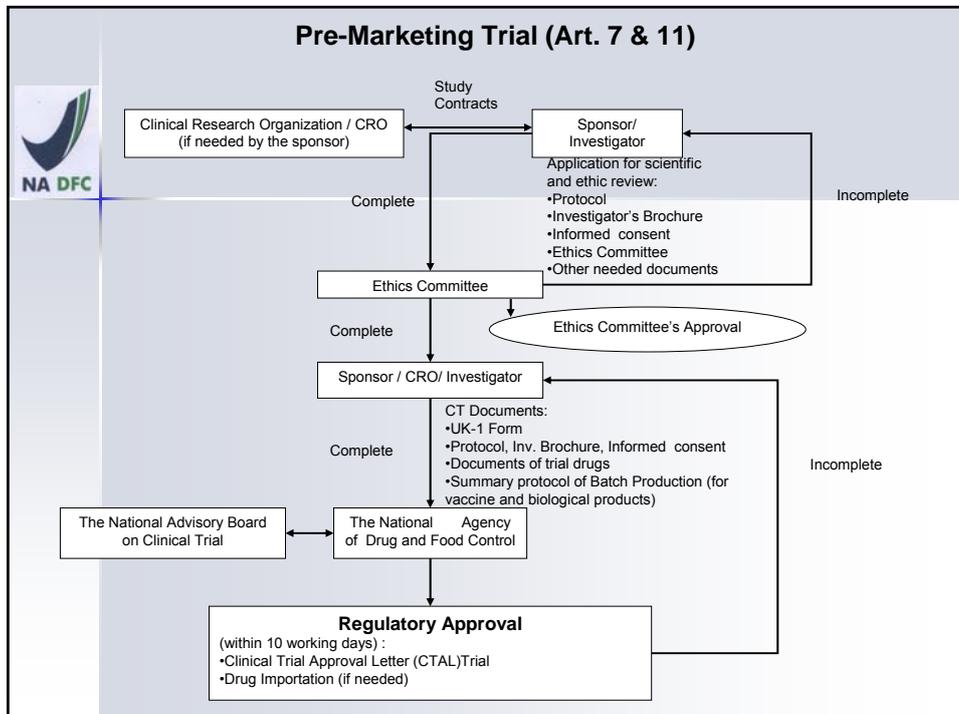
CT Authorization :

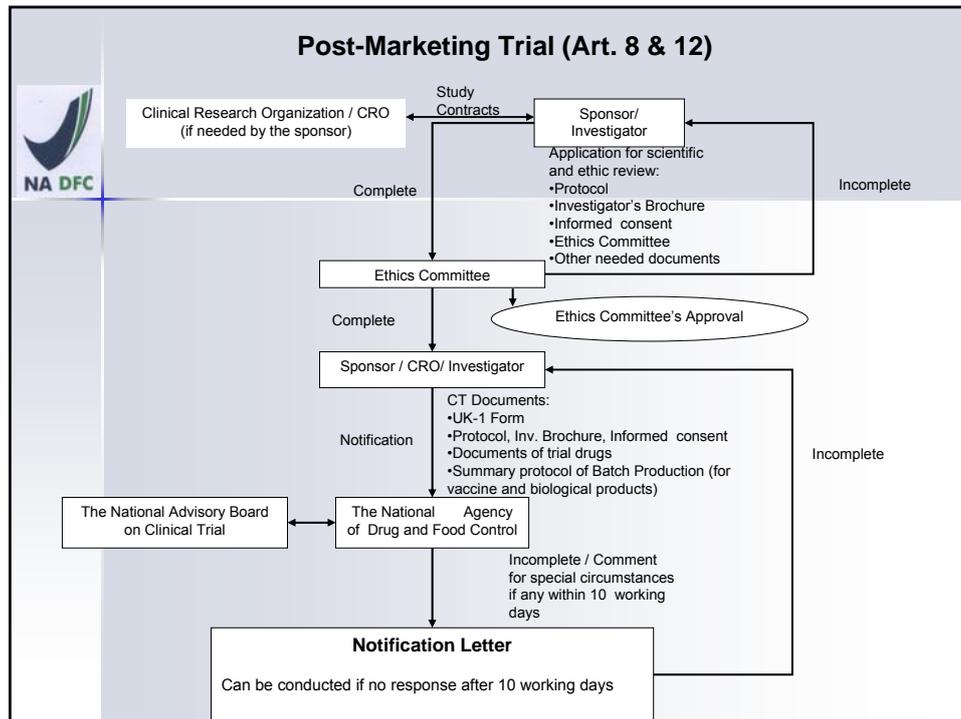
- Established since 2001
- Law : Health Law, 1992
Consumer Protection Law 1999
- Decree : - NADFC Decree on Procedures for Clinical Trial (CT) No. 02002/SK/KBPOM, February 2001
- NADFC Decree on Procedures for Bioequivalence Trial No. HK.00.05.3.1818, 29 March 2005
- Guideline : Indonesian Guideline 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



SOME AREAS OF REGULATION IN THE INDONESIAN GUIDELINE ON GCP

- Type CT (Art. 2)
- Institution (Art. 4)
- Application for the conduct of CT (Art. 7-9)
- Regulatory approval for the conduct of CT (Art. 11-12) → CT authorization
- Reporting and Reports (Art. 13-15)
- CT termination (Art. 16 & 17)
- GCP inspection (Art. 18 a)
- CT product/drugs procurement (Art. 20 & 21)





Requirements for Ethics

Ethics Committee :

- Should be independent
- Ethical clearance :
 - List of attendance, signed and dated
 - Version and date of protocol/informed consent and its amendments which are approved

Application for scientific and/or ethic review:

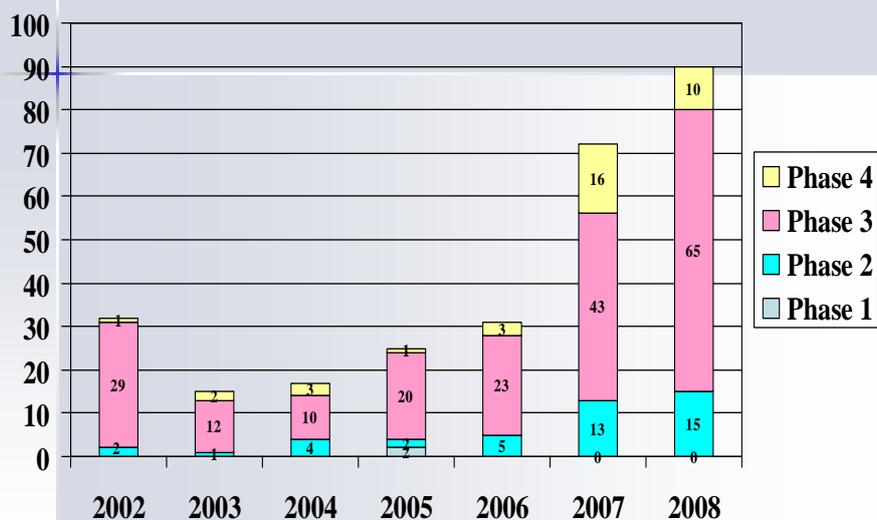
- Protocol
- Investigator's Brochure
- Informed consent
- Other needed documents

Strategic for Review of Clinical Trial

- Standardization of Review Process
 - Format of review report (template, checklist)
 - Earlier writing of review report → to identify critical/major issues in early stage
 - Frequent communication with an applicant in review process → to make common understanding
- Transparency in review process → to avoid inconsistent decision making
 - To standardize general review policy
 - "IND like system" → evaluation of CT protocol by team including external expert NADFC's opinion for development of protocol in consultation
- Predictability in review process



CT APPLICATION and APPROVAL IN INDONESIA*



* Not including Bioequivalence Studies



Update in PMDA

Junko Sato

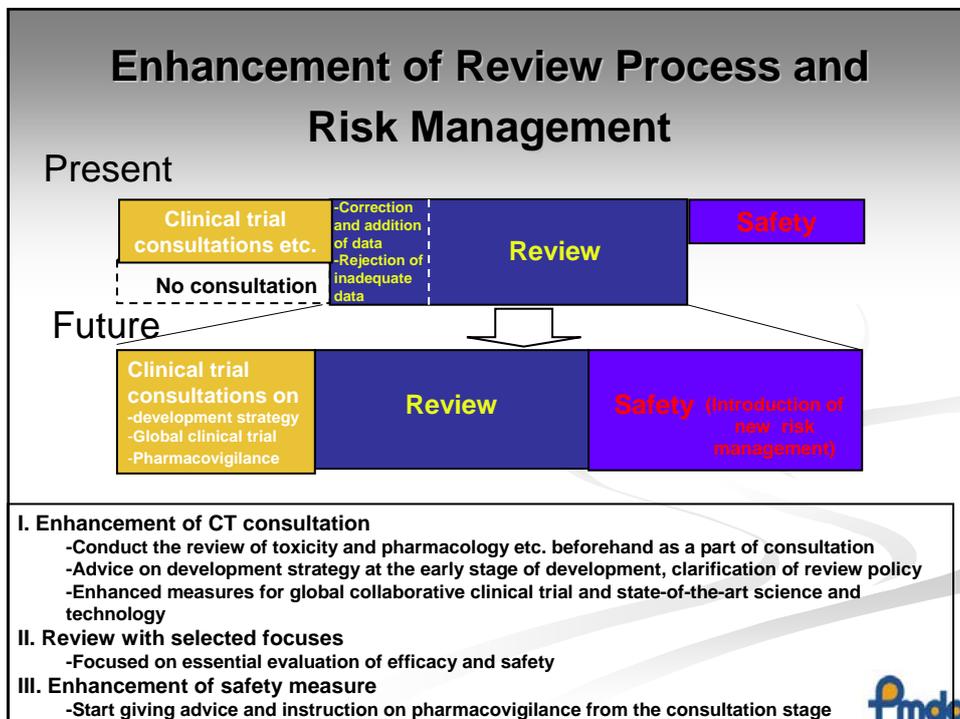
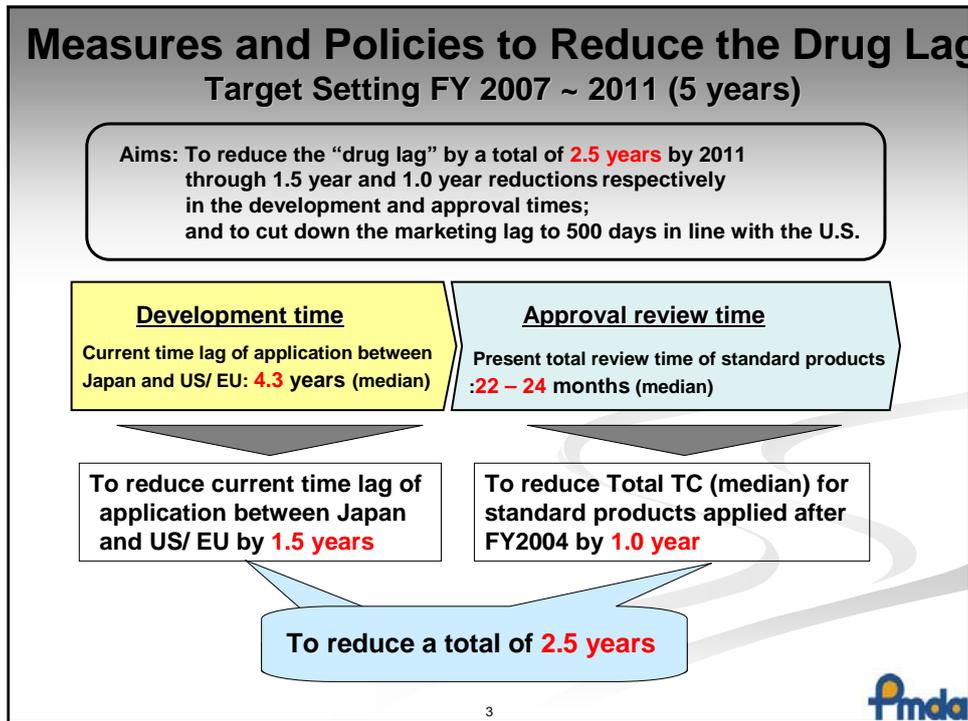
Pharmaceuticals and Medical Devices Agency
(PMDA)



Outline

- To shorten and disappear drug lag
- Publication of our philosophy
- Improvement of English website





Introduction of Risk Management System - Product Management -

- **Purpose of RM System**
 - PMDA will collect, compile, evaluate and manage all the safety information on new drugs from development to post approval stages to give guidance and advice to companies on PMS at early stage and in a timely manner.

- **PMDA RM System will help the life cycle management of drugs in safety aspect**
 - Identification safety specification from development stage
 - Guidance and advice on designing post-approval surveys, studies and other activities at review stage
 - Evaluation and advice on outcome and problems of post-approval surveys, studies and other activities etc

Tentatively called 'Product Management'



Possible Benefits of New Risk Management System

- **Efficient preparation of effective PMS plan**
- **Consistent safety management throughout lifecycle both in PMDA and companies**
- **Preventing withdrawal of new drugs (at early stage)**
- **Completion of lifecycle of a drug**
- **Protection of patients especially at early stage of marketing**



Philosophy of PMDA

PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

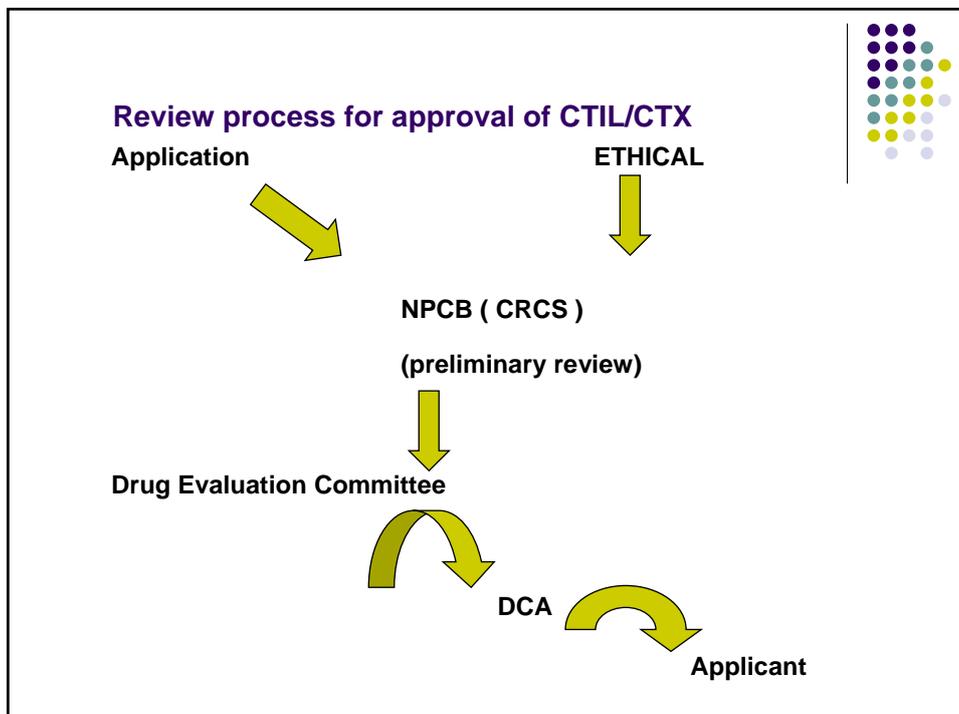
- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.
- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.
- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.
- We play an active role within the international community by promoting international harmonization.
- We conduct services in a way that is trusted by the public based on our experiences from the past.



Improvement of English website

- Most of documents were posted in only Japanese on PMDA website.
- Increasing documents written in English
 - Important notifications
 - PMDA review policy
 - Review reports
 - First approval in the world





Best Practices



- Review Process
- Ethical Approval
- CTIL/CTX only issued after both the DCA and IEC given approval.

Control of Drugs and Cosmetics Regulations 1984 (Revised 2006)



Regulation 29. Directions

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

(I) clinical trials

Updates on CTIL/CTX Guideline



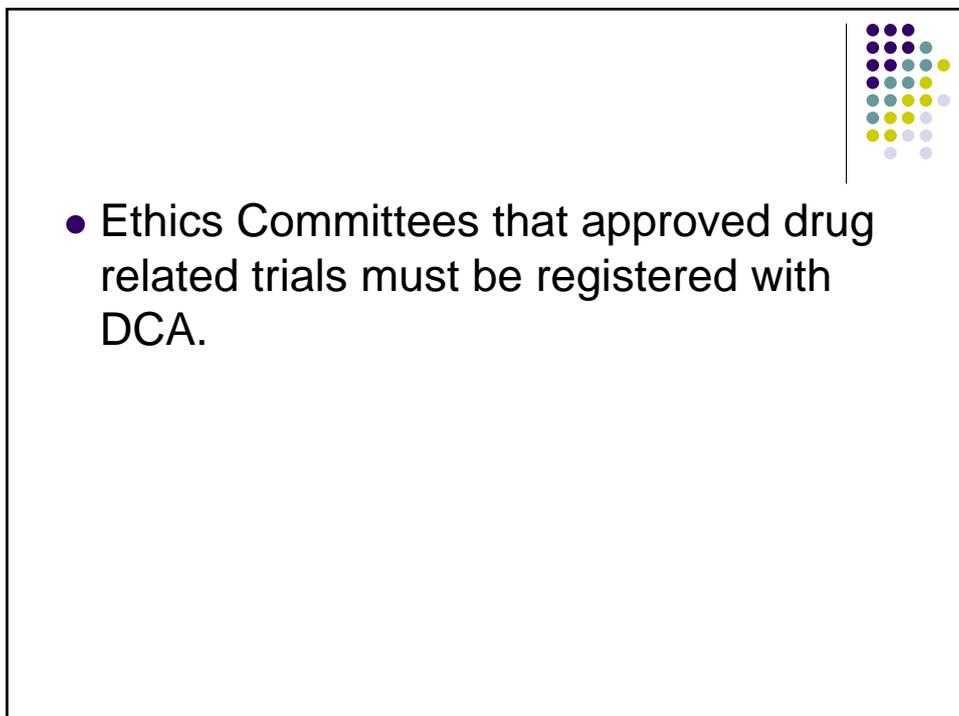
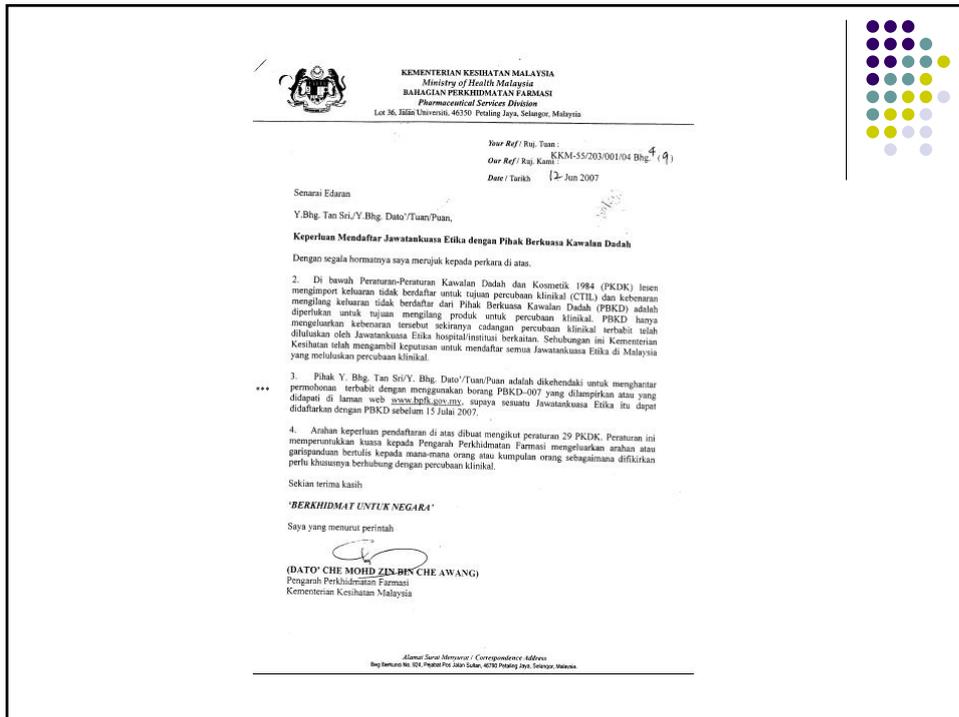
- Guidelines for Application of CTIL and CTX in Malaysia will be updated to include :
 - SAE Reporting will be based on ICH E2A
 - Additional label requirement i.e. to include source of gelatine use (porcine/bovine).
 - Annex C (Investigator's Brochure) – the information on preclinical studies need to be done according to the OECD GLP template.
 - To include the new definition of 'product' according to **Control of Drugs and Cosmetics Regulations 1984 (Revised 2006) Regulation 2**

Plans for 2009



- All drug related clinical trials that applies for CTIL/CTX must be registered with the National Medical Research Registry (NMRR).
- All drug related clinical trials that do not required CTIL/CTX need to apply for Clinical Trial Authorization and registered with NMRR.

ADVANCED WORKSHOP : REVIEW OF DRUG DEVELOPMENT IN CLINICAL TRIALS



Compliance



- Effective monitoring on the implementation of GCP
 - Inspection Program have been developed
 - Inspection on Ethics Committee and Bioequivalence Centres will be conducted in 2009

- All non-clinical studies for pharmaceutical, veterinary and cosmetics need to be done under GLP Laboratories (OECD GLP)



Thank You
For Your Kind Attention



www.bpfk.gov.my



Ministerio de Salud
 Personas que atendemos Personas

Clinical Trials

Regulations in Perú

Hans Vásquez, MD
 National Direction of Drugs and Medical Device (DIGEMID)
 Ministry of Health, Peru

Thailand, February 2009
 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.

PERÚ: DISTRIBUCIÓN RELATIVA DE LA POBLACIÓN CENSADA, SEGÚN DEPARTAMENTO, 2007 (Porcentaje)

Departamento	Porcentaje
Lima	39,8
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
Ancash	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
Aperímac	1,5
Amazonas	1,4
Tarma	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

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 (or 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 necessary: inusual or difficult trials
Frecuently coordination with email and telephone

Clinical Trials submitted

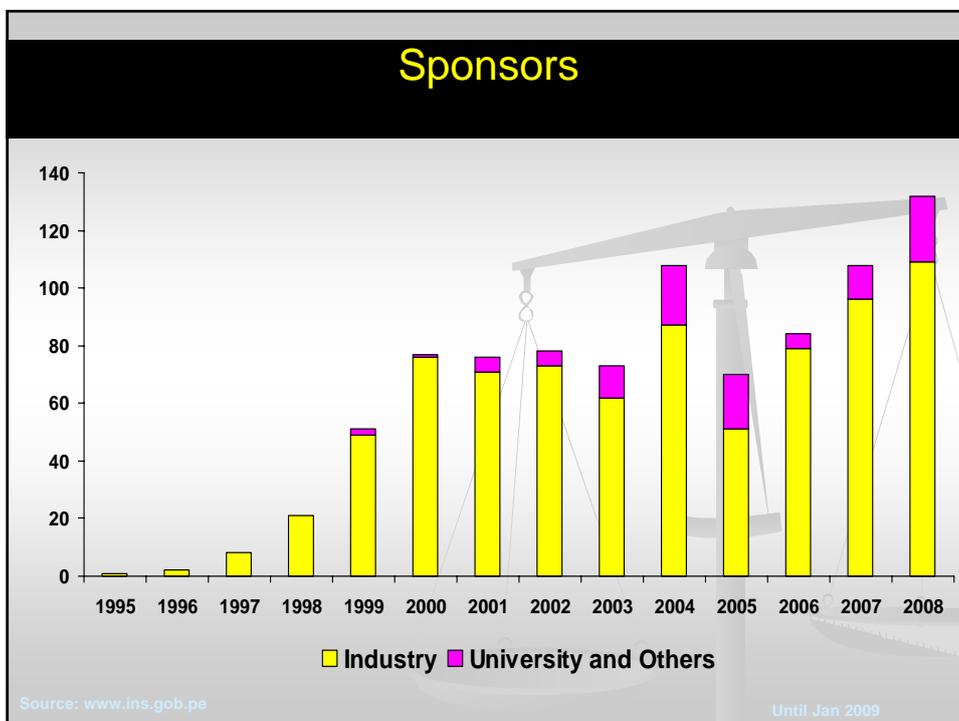
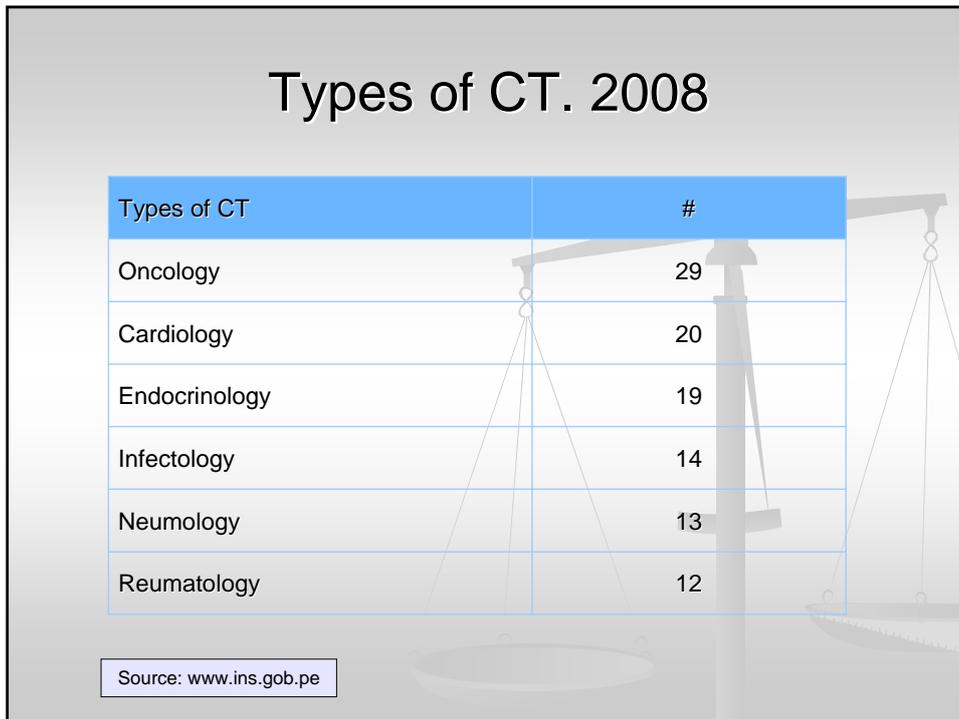
Year	Number of CT submitted
2006	84
2007	123
2008	176

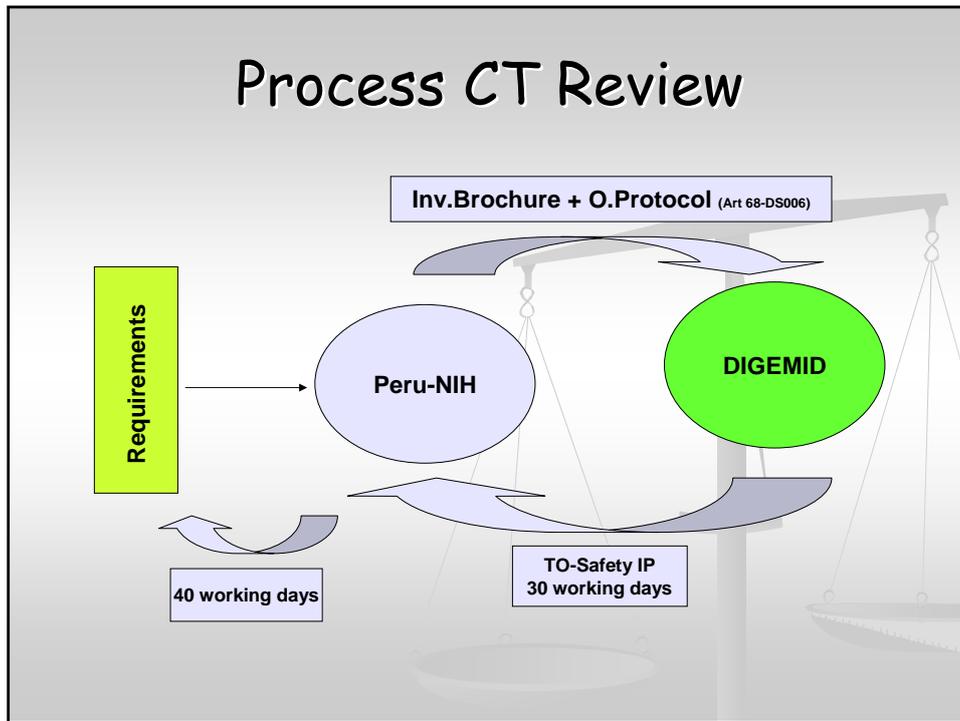
Source: www.ins.gob.pe

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







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Magandang Umaga
Sawasdee Ka
Buenos Dias
GOOD MORNING



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**Country Report on Clinical Trial
Evaluation**
Philippines
Regina S. Obligacion
Pia Angelique D.M. Priagola



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- Republic Act 3720 :
Food, Drugs, Devices and Cosmetics Act
(as amended by Executive Order 1750)

*states that it is the policy of the state to
ensure safety, efficacy and quality of
drug supply to protect the health of the
people.*



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Drug Regulatory Authority
Bureau of Food and Drugs (BFAD)
under the Department of Health

- is mandated by Republic Act 3720 *to
ensure safety, efficacy and quality of drug
supply to protect the health of the people.*



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Clinical Trials Regulation

- Administrative Order No. 47A s.2001

Subject:

Rules and regulations on the registration, including approval and conduct of clinical trials, and lot or batch release certification of vaccines and biological products
(section III. Approval Process and Conduct of Clinical Trials)



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General Standards and Policies

- **1.1 Investigational, new or established biologic products: clinical trial protocol approval by BFAD**
- **1.2 Protocol approval shall be on per phase of the clinical trial per product basis**
- **1.3 Full disclosure of all pertinent documentation and information regarding product, subjects and disease process, study endpoints, clinical trial sites, existing resources and infrastructure at the proposed trial sites and other field site information, such as location, personnel, resources, equipment and facilities**
- **1.4 Strict adherence to the codes of GCP, GLP and GMP**
- **1.5 Same specifications, preparation and composition as the batches to be registered and commercially produced in the future**



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Clinical Trials Regulation

**(Administrative Order No. 47A s.2001
Sec. III. Approval Process and Conduct of Clinical
Trials)**

- 1. General Standards and Policies**
- 2. Procedures for Application**
- 3. Obligations of the Sponsor or Applicant to the
BFAD**
- 4. Termination of the Study**
- 5. Appeal**
- 6. Schedule of Fees**



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2. Procedure for Application

- 2.1 File letter of application addressed to
BFAD Director with documents specified
in Checklist of Requirements**
- 2.2 Review of Completeness of Documents
and Requirements**
- 2.3 Evaluation of Documents**
- 2.4 Action on the Application (Approval, Notice of
Deficiencies or Denial)**



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Major points to be considered
2.3 Evaluation of Documents

- a. disease or disease process
- b. compliance with GMP and GLP
- c. compliance to the code of GCP
- d. therapeutic/prophylactic value of product
- e. track record of competence of the investigators, sponsors and monitor
- f. Clinical endpoints
- g. Site of clinical trials
- h. Appropriateness of the IEC or IERB in place



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Major points to be considered (continued)
2.3 Evaluation of Documents

- i. Comprehensiveness and structure of the protocol
- j. Appropriateness of statistical analysis
- k. Objective of the study
- l. Number and suitability of the subjects
- m. Resources and Infrastructure
- n. Result of previous clinical trial
- o. Experience of other countries conducting similar trials, if any
- p. Reports from the WHO and other NRA



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3. Obligations of the Sponsor or Applicant

- 3.1 Prompt submission of incident report prepared and signed by the principal investigator**
- 3.2 Prompt submission of deviation report prepared and signed by the principal investigator**
- 3.3 Prompt submission of an interim report after the completion of the actual clinical trial**



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3. Obligations of the Sponsor or Applicant (continued)

- 3.4 Prompt submission of any information or findings on similar studies from other countries that may have bearing on the health of subjects**
- 3.5 Prompt notification of any amendments to the approved clinical trial protocols**
- 3.6 prompt notification of any changes in key personnel (such as the monitor and principal investigator, and associates) of the on-going clinical study**



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4. Termination of the Study

- At any time, the BFAD may terminate all clinical trials that have failed to comply with the codes of GCP, GLP, cGMP, or after careful evaluation of the incident report, deviation report, AEFI report, and information and findings from other NRAs and international bodies, like the WHO



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5. Appeal

Applications which were not approved may be appealed to the Secretary of Health



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6. Schedule of Fees

- The applicant shall be guided by the latest Bureau Circular on the schedule of fees.
 - Evaluation of Protocol for Monitored Release / Post Marketing Surveillance, Php 2,500
 - Evaluation of Protocol for Clinical Study (Phases I, II, III), Php 2,500
 - Amendment of protocol, Php 2,500



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Administrative Order No.67 s.1989 **(Subject: Revised Rules and Regulations on** **Registration of Pharmaceutical Products)**

Clinical study requirements for New Drugs

1. Results of animal and Phase I,II and III clinical studies (+ Phase IV done abroad if product is imported)
2. Phase IV Clinical Trial (local) commences upon issuance of Certificate of Product Registration



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ASEAN Common Technical Document (ACTD)

Part I. Administrative Data
Part II. Quality
Part III. Non clinical
Part IV. Clinical Document

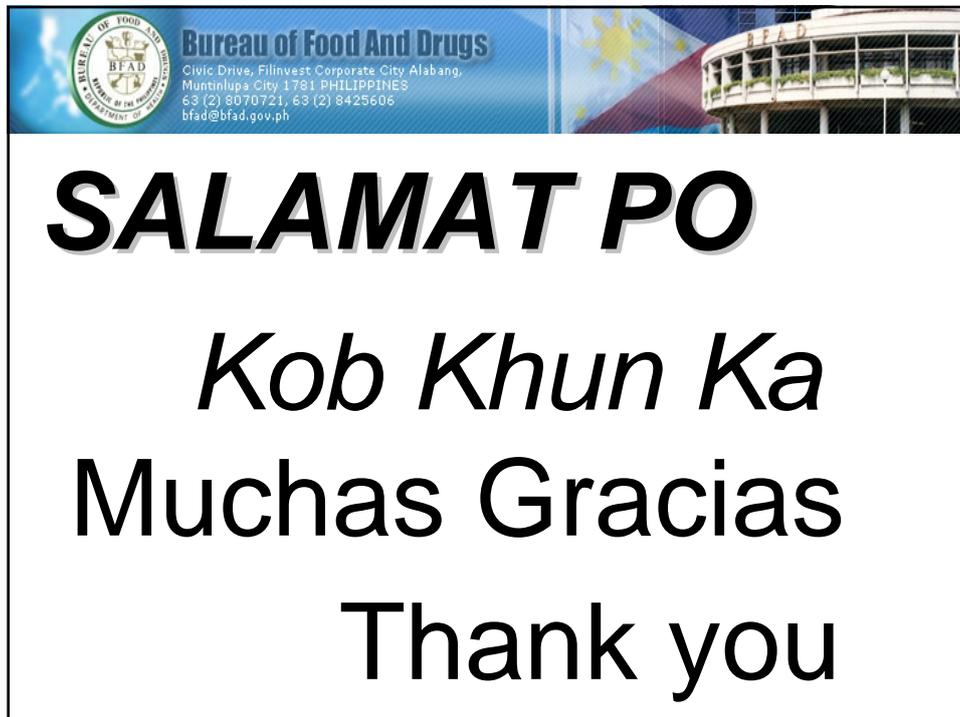


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ACTD Part IV Clinical Document

- Based on the ICH Guidelines

[FINAL VERSION OF ACTR-CLINICAL DATA.pdf](#)





**Review of Drug Development in Clinical Trials:
SINGAPORE**

2 Feb 2009, Bangkok

**Clinical Trials Branch
Health Products Regulation Group
HEALTH SCIENCES AUTHORITY
SINGAPORE**

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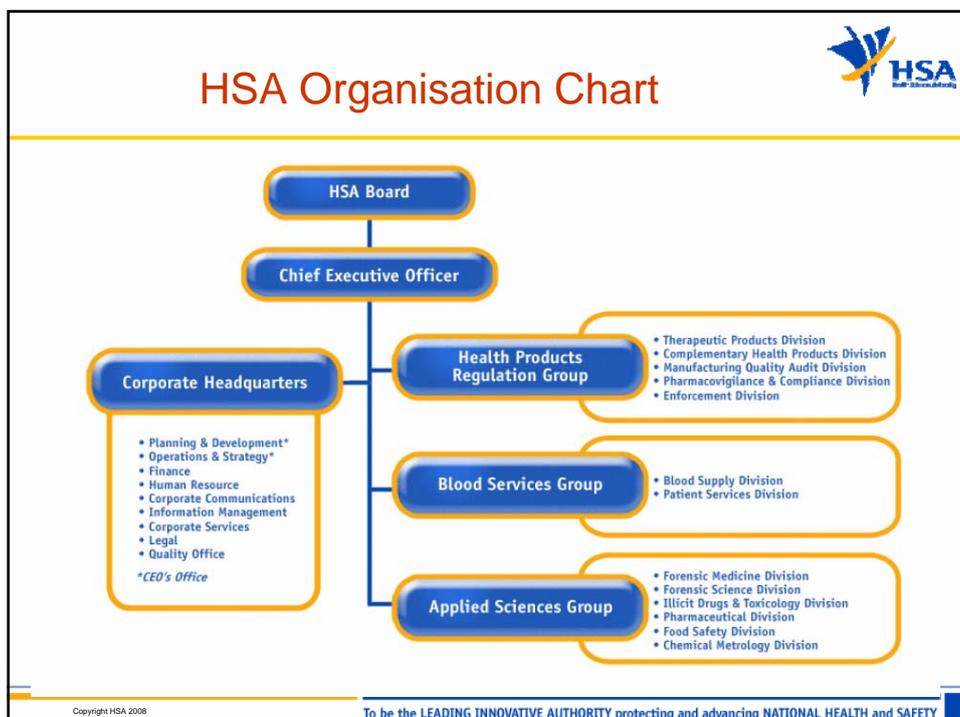
PRESENTATION OUTLINE

- Regulatory Infrastructure: An Update
- Strategies for Review of Clinical Trials
- Ethics Requirements



Regulatory Infrastructure: An Update

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Clinical Trials Oversight – Regulatory Basis 

Legislation for oversight of clinical drug trials:

- Medicines Act (Chapter 176, Sec 18 and 74)
- Medicines (Clinical Trials) Regulations
- Singapore Guideline for Good Clinical Practice (SG-GCP, adapted from ICH E6 on GCP)
- All clinical drug trials conducted locally have to comply with these standards

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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

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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.

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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.

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Best Practices / Strategies for
Review of Clinical Trials

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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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Regulatory Perspective / Practices 

- Compliance / reference to international regulatory standards or guidelines
- Active promotion of Good Clinical Practice
- Regulatory Dialogues
 - Early consultation for planned applications on novel compounds
 - Feedback on regulatory processes

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Regulatory Perspective / Practices 

- Continually enhancing capabilities to manage emerging technologies and therapies
- Use of IT systems
 - Online submission of applications (PRISM)
 - Electronic storage of trial documents and reports
- Triaging of applications
 - Risk stratification strategy
 - Optimisation of limited resources

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Regulatory Perspectives / Practices

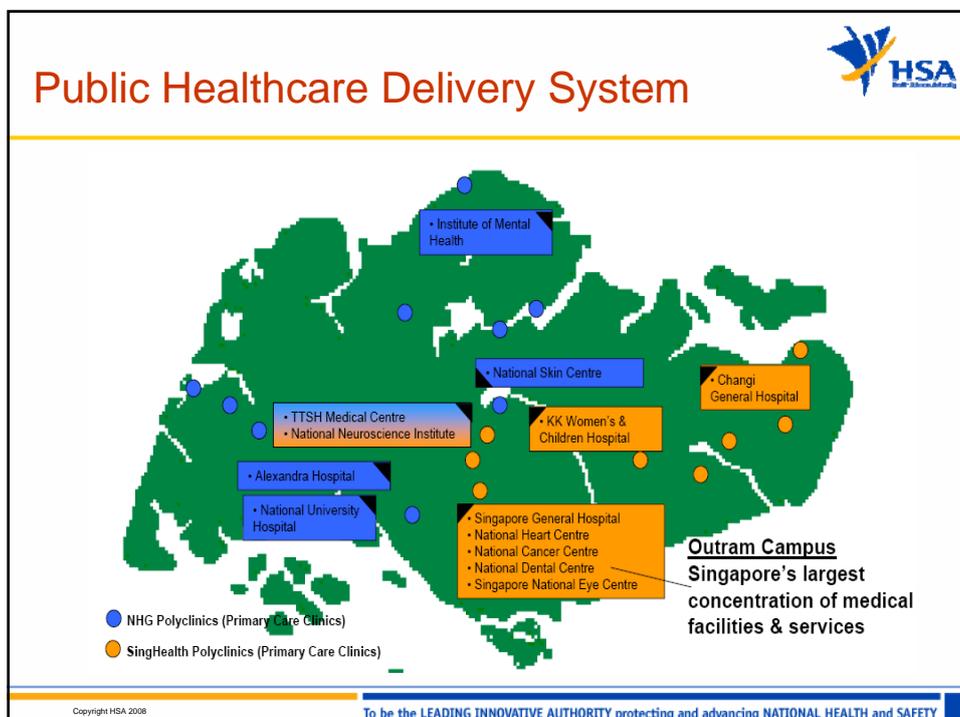
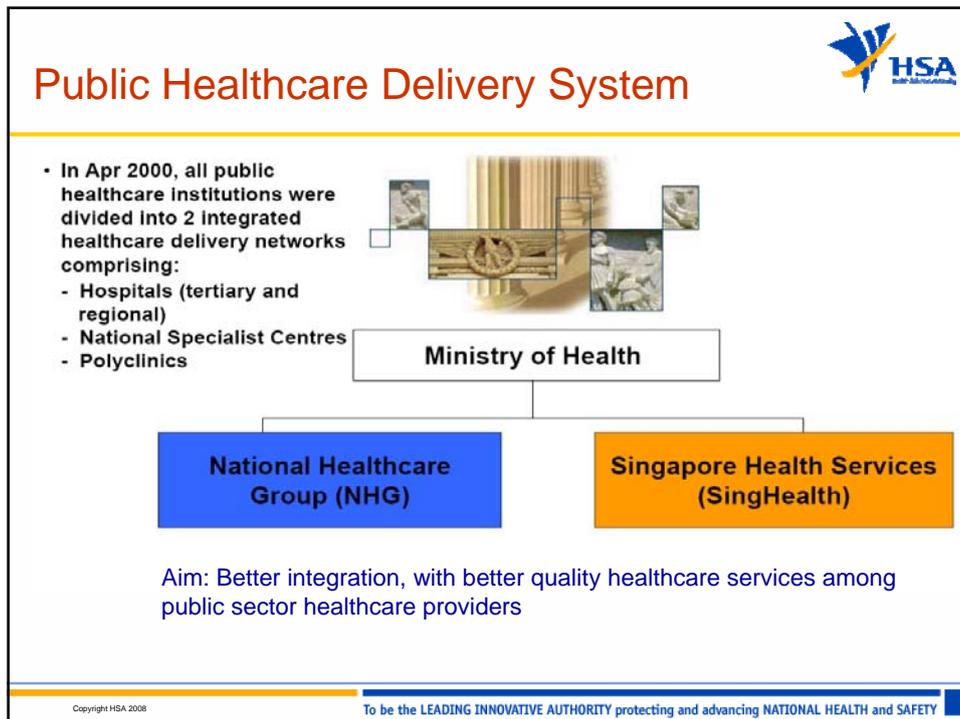
- Robustness and consistency ensured through
 - Common template for evaluation reports
 - Peer reviews within evaluation teams
 - Cross-functional reviews
 - External scientific experts' opinion sought where necessary
 - Advice from Medical Clinical Research Committee (MCRC)

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Ethics Requirements

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Research Ethics Review Committees

SingHealth 

Institutional Review Boards (7 IRBs)

- Review, approve and monitor trials at institution level

National Healthcare Group 

Domain Specific Review Board (DSRB)

- Functions like a central IRB for all 6 NHG institutions (reviews trials under its respective scientific domain)
- Accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)

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Research Ethics Review Committees

National Healthcare Group 

DOMAIN SPECIFIC REVIEW BOARDS

<p>Domain A</p> <ul style="list-style-type: none"> • Ophthalmology • Psychiatry • Neurology/Neurosurgery • Genetics • Geriatric Medicine 	<p>Domain B</p> <ul style="list-style-type: none"> • Oncology • Haematology • Pathology • Paediatrics • Respiratory Medicine 	<p>Domain C</p> <ul style="list-style-type: none"> • Cardiovascular Science • Pharmacology • Emergency Medicine • Endocrinology • Diagnostic Imaging
<p>Domain D</p> <ul style="list-style-type: none"> • Obs / Gynaecology • Anaesthesia • Surgery • ENT • Dentistry • Sports & Rehab Medicine • Allied Health 	<p>Domain E</p> <ul style="list-style-type: none"> • Infectious Disease • Gastroenterology • Renal Medicine • Rheumatology/Immunology • Dermatology 	

With effect from 01 April 2008.

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Ethics requirements

- Common application form for SingHealth IRB(s) and DSRB
- Parallel submission to HSA & IRB(s), but both regulatory and ethics approval must be obtained by sponsor before initiation of a trial
 - Sponsor declaration at the point of CTC application
 - CTC condition
 - To be stipulated in revised CT regulations (proposed)

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Summary and Conclusion

- Ongoing review of clinical trial regulatory framework and infrastructure
- Proposed revised clinical trial regulations under the Health Products Act
- Continuous review and improvement of clinical trial review processes
- Research ethics committees an important stakeholder
- Goal: Science-based, risk-based, efficient regulatory system

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Thailand Update

by
Yuppadee JAVROONGRIT, Ph.D.
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Drug Control Division, TFDA, MOPH, Thailand

Advance workshop: Review of Drug Development in Clinical Trials
Siam City Hotel, Bangkok, Thailand
02-06 February 2009

Advance WS: Review of Drug Dev. in CT



Outline:

- **Regulatory Infrastructure /Authority**
- **Best Practice - *Strategy for Review***
- **Requirement for Ethics**

Advance WS: Review of Drug Dev. in CT



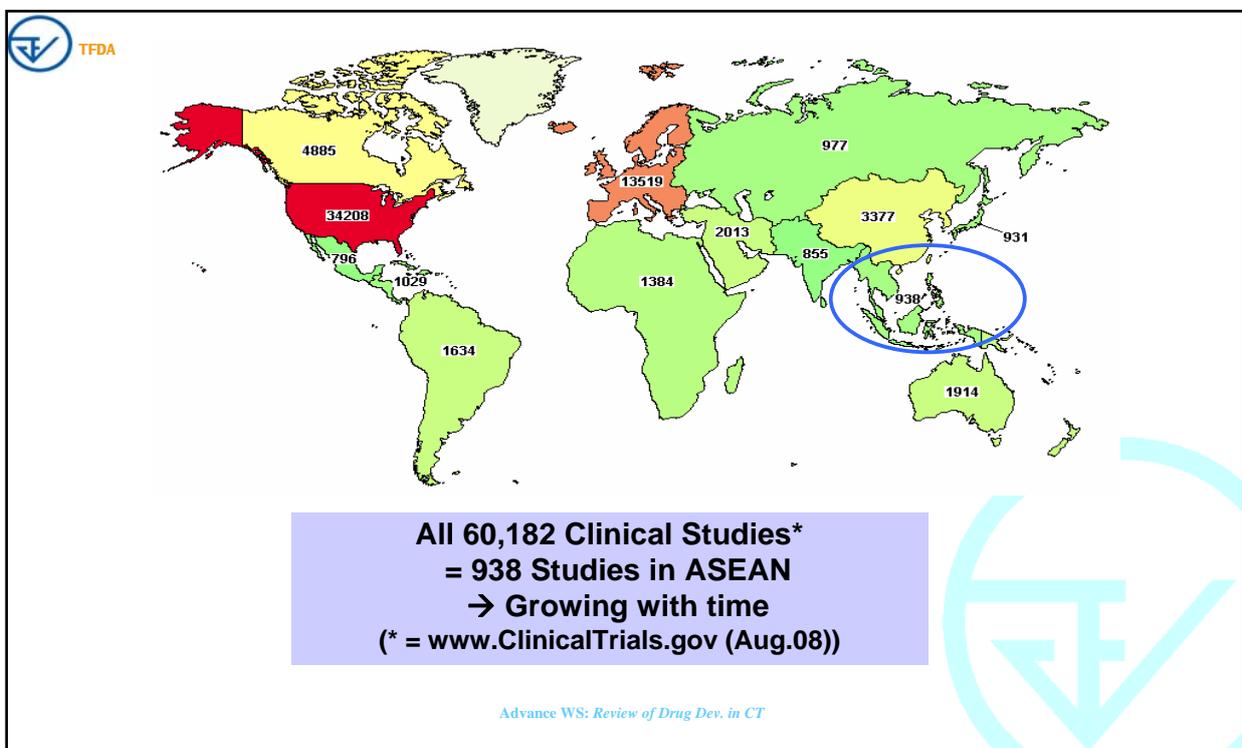
 **Regulatory Infrastructure/Authority**

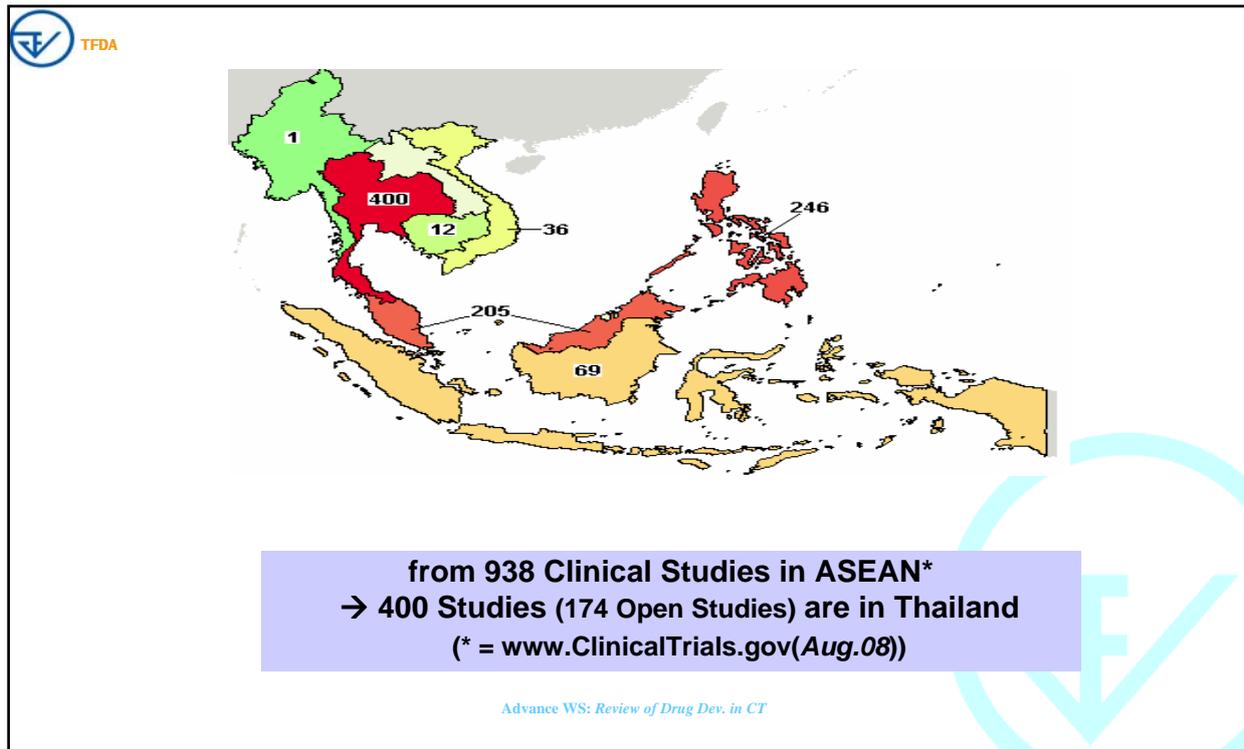
The Drives

- **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**

Outline:
- Regulatory Infrastructure/Authority
- Best Practice - Strategy for Review
- Requirement for Ethics

Advance WS: Review of Drug Dev. in CT





Regulatory Infrastructure/Authority

The Opportunity

- Training Visit – *Health Canada*
- Training Course – *US FDA-CDER*
- Visiting Trip – *KFDA, EMEA*
- Training Workshop
 - APEC-LSIF “Review of Drug Development in Clinical Trials”
 - Industry “Drug Development” by Astra Zeneca

Outline:
- Regulatory Infrastructure/Authority
- Best Practice - Strategy for Review
- Requirement for Ethics

Advance WS: Review of Drug Dev. in CT



Regulatory Infrastructure/Authority

The Update after Preliminary WS

- **Amendment the Regulation ...**
 - requesting “document on Standards & Drug Development”
 - enhancing “Responsibility of Applicant”
 - adopting “relevant Standards – GCP, GLP, GMP”
- **Coming activities...**
 - scientific review on Clinical Trial Application
 - GCP Inspection
 - monitor Reports on Unexpected&SADRs of CT’s Material/Drug
 - implementing Quality System
 - working on Good Review Practice

Outline:

- Regulatory Infrastructure/Authority
- Best Practice - Strategy for Review
- Requirement for Ethics

Advance WS: Review of Drug Dev. in CT



Best Practice – Strategy for Review

The Update after Preliminary WS

- **The Principle & Target...**
 - transparency, consistency, efficiency, and quality
- **Strategy...**
 - developing Template & SOP for the review
 - studying additional relevant Technical (ICH-S&E gld., ...)
 - strengthening Internal Reviewers
 - forming the network with External Experts

Outline:

- Regulatory Infrastructure/Authority
- Best Practice - Strategy for Review
- Requirement for Ethics

Advance WS: Review of Drug Dev. in CT





Requirement for Ethics

The Update *after Preliminary WS*

- **a new Regulation - *EC's Recognition***
- **The Requirement...**
 - **approval, on ethical, by recognized EC**
 - **recognized EC shall...**
 - **compliance to the "GCP"**
 - **monitor all approved Trials**
 - **handle the Subject's Safety**
- **Well recognized system - *FWA, SIDCER***

Outline:

- Regulatory Infrastructure/Authority
- Best Practice - *Strategy for Review*
- Requirement for Ethics

Advance WS: Review of Drug Dev. in CT



Wish ...

Advance WS

“Review of Drug Development in Clinical Trials”



Help complete the “Review’s attempt”

Advance WS: Review of Drug Dev. in CT





Update of the Regulation of Clinical Trials in Saudi Arabia

*Abdulmohsen H. AL Rohaimi,
DDS, APC, MSc, Ph.D*

Director of Research and Publication

February 2 – 6, 2009

Advance workshop of clinical trails

Riyadh - kSA

KFMC

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority



SFDA

Objectives of my talk

- To give update about regulation of clinical trails in Saudi Arabia
- Regulations & guidelines
- Current initiatives
- What are the challenges in the initiative of clinical regulations?

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Saudi Food & Drug Authority



SFDA

An insight of clinical trails in Saudi Arabia

- **Types of Clinical trials** : Most of Clinical Trials are :- Phase III
 - IIT (Investigator Initiative Trial)

Places of Clinical Trials In Saudi Arabia

- Tertiary Hospitals :e.g. King Faisal Specialist Hospital & Research Center
- King Abdulaziz City for Science & Technology

The Current Efforts for clinical trails regulation in Saudi Arabia

Past

MOH : The Central Committee For Research Ethics

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

- **National committee For Research Ethics**

- - informed consent : predictable side effects and risk
 - protect research subject from unethical risk

Nowadays - soon

- 1- all clinical trails must register with Saudi Food and Drug Authority
- 2- all clinical trail site will be inspected by saudi arabai

SFDA Guidelines

Protection of Trial Subjects Guidelines

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

Clinical trails regulation - continue

- International committee was established to build clinical trail system for SFDA.
- First draft was prepared in 28-10-2008
- The regulation was adapted from UK regulation
- It forms from 9 parts

Main Clinical Trails Requirements by SFDA

Trial protocol.

- Investigator Brochure & CV
- Subject Recruitment Procedure
- Consent forms
- Available safety Data
- Ethical Committee Approval
- Forms for clinical trail application

Trend & Plan - SFDA

- **Sponsor & CRO approval**
Develop system for :
 - internal Auditing
- **provide Training**
- **Enhance clinical trail development and increase in a Numbers but with no effect on :**
 - **the Quality & Speed of the Trial**
 - **transfer of New highly technology to country**

Primary registry

- *Content*
20 items – minimum requirement by WHO
- *Administrative and governance – NON PROFIT*

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Challenges

- Few experts in CRO approval process
- Few experts in GCP inspection

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Helping the people of Canada maintain and improve their health
Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Advanced Workshop Overview

Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

Canada

Thank You

APEC
Linnus Teo Siow Yen

Health Canada
Mike Ward and Dr's (Agnes Klein MD, Celia Lourenco, Will Stevens)

ICH

Novartis
Susan D'Amico, Dr. Namrata Bahadur, Dr. Sudhichai Chokekijchai

PMDA
Dr. Junko Sato

Thai FDA
Akanid Wapeewuttikorn



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Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009



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Workshop - General Approach

- To be as practical as possible
- Lots of time for interaction
- Please give us feedback as we go so we can adjust to help meet your needs
- Exercises that simulate CT review challenges
- Both Industry's and the Regulator's perspective.
- On behalf of the 'the faculty' please feel free to ask questions and bring your own experiences to bear so that we can all learn from each other.



5

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It seems to me what is called for is an exquisite balance between two conflicting needs: the most skeptical scrutiny of all hypotheses that are served up to us and at the same time a great openness to new ideas.

If you are only skeptical, then no new ideas make it through to you. On the other hand, if you are open to the point of gullibility and have not an ounce of skeptical sense in you, then you cannot distinguish useful ideas from the worthless ones.

~ Carl Sagan ~



6

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Day 1

- Today's program begins with an "Information Sharing Session"
- Review of the Preliminary workshop
 - as a warm up/ refresher.
- The day ends with a session on the "What is Involved in Setting-up a Review Operation" or setting up the "Business"



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Day 2

- Will focus on Quality considerations - Dr. Stevens
- Biologic and Genetic Therapies Directorate's (BGTD) sister organization the Centre for Biologic Evaluation (CBE)
 - Responsible for blood and vaccines



8

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Day 3

- Dose Selection – Dr. Sato
- FIH – Dr. Chokekijchai
- The Critique of High Risk Clinical Trials – Dr Viner
 - Many examples
 - Exercises
 - Review Literature Articles
 - Mix of Small Groups and Plenary Sessions



9

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Day 4

- Lighter Day
- Novel Clinical Trial Design - Dr. Chokekijchai
- Ethics lecture and article – Dr. Viner
- Pharmacovigilance – Dr. Sato



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Day 5

- Wrap up with some practical exercises
- Stroke study dreamed up by a neurologist in BGTD's CT division
- Novartis has prepared what sounds like a very interesting session with a 'made-up' infectious disease and proposed therapy
- Panel discussion



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Acronyms / Terminology

Review of Drug Development in Clinical Trials

ADR	Adverse Drug Reaction
ADME	Absorption Distribution Metabolism Excretion
ASR	Annual Safety Report
CA	Competent Authorities
CIOMS	Council for International Organizations of Medical Sciences
CTs	Clinical Trials
DMC	Data Monitoring Committee (see DSMB)
DSMB	Data Safety Monitoring Board (see DMC)
DSUR	Development Safety Update Reports
EC	Ethics Committees
EFPIA	European Federation of Pharmaceutical Industries Associations
EFTA	European Free Trade Association (represented by Swissmedic)
EMA	European Medicines Agency
EU	European Union
EUDRA	European Union Drug Regulatory Authorities
FIH	First in Human
FIM	First in Man
FDA	Food and Drug Association
GCP	Good Clinical Practice
GCG	Global Cooperation Group (ICH)
GMP	Good Manufacturing Practice
HA	Health Authority
HED	Human Dose Equivalent
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use
ICU	Intensive Care Unit
IFPMA	The International Federation of Pharmaceutical Manufacturers and Associations

IMP	Investigational Medicinal Product
IRB	Institutional Review Board (see REB)
JMPA	Japan Pharmaceutical Manufacturers Association
MABEL	Minimum Anticipated Biological Effect Level
MAH	Market Authorization Holders (Sponsors)
MD	Multiple Dose
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare products Regulatory Agency, UK
NHRV	Normal Healthy Research Volunteers
MRSD	Maximum Recommended Starting Dose
MS	Member State
MSD	Maximum Safe Starting Dose
NCA	National Competent Authorities
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PhRMA	Pharmaceutical Research and Manufacturers of America
PI	Principal Investigator
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PoC	Proof of Concept
PSUR	Periodic Safety Update Report
REB	Research Ethics Board (see IRB)
SAE	Serious Adverse Event
SD	Single Dose
SUSAR	Suspected and Unexpected Serious Adverse Reactions
WHO	World Health Organization

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Preliminary Course *Refresher*



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009



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Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009





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If you don't read the newspaper, you are uninformed; if you do read the newspaper, you are misinformed.

~ MARK TWAIN ~
(Samuel Langhorne Clemens)

4

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Refresher Topics

- ICH
- Global Factors
- CT Oversight
- ICF
- Good Regulatory Practices
- Drug Development
- Bioequivalence
- Lifecycle Approach
- Pharmacogenomics
- Elements in CT Assessment



5

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ICH

- Progress in the Global Cooperation Group (GCG) promoting knowledge of ICH guidelines
- Learning from each other in a climate of trust and cooperation, can greatly increase the strength of all harmonization efforts
- Helps to moves us to toward efficient and effective regulatory systems and increased availability of safe, efficacious pharmaceuticals of high quality on a global level



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Global Factors on R&D

- Multinational clinical trials
- Harmonization
- Decreased number of blockbuster drugs
- Personalized medicine, pharmacogenomics
- Exponential rise in generics
- Rising costs and emerging markets
- In choosing to place a clinical trial, companies will look for countries with the appropriate laws, along with the required population, disease prevalence, health care system, qualified investigators and staff, with high standards of professional integrity and ethics



7

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CT Oversight

- Origins
- Roles and Responsibilities
- Good Regulatory Practices
- Regulations and Guidelines



8

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Origins of CT Oversight

Lessons from the Past

- Tuskegee Syphilis Experiment (1932 – 1972)
- WWII experiments
- Thalidomide disaster (early 60's)
- Diethylstilbestrol and vaginal cancer in female offspring (1971)
- Gene therapy trials (2003)
- 20 healthy volunteers infected with tuberculosis in bioequivalence drug trial (2006)
- TGN1412: 6 healthy men in critical condition (2006)

Summary

- Lessons learned from the past and present
- International movement for the protection of human rights and research volunteers
- Incorporation of human rights principles into regulations
- Research in humans must be conducted with the highest level of scientific and ethical standards
- There is public trust in the regulator, and as regulators, we have a duty to protect
- In moving forward: life-cycle of drug product, pharmacogenomics



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CTs: Roles and Responsibilities

Major Groups involved in CTs

- Regulator
- Sponsor
- Institutions/Clinical Trial Sites
- Qualified Investigators (QI) & Staff
- Research Ethics Boards
- Clinical trial subjects or legal guardians
- Data safety Monitoring Board (DSMB)
- Contract Research Organization (CRO)
- Site Management Organization (SMO)

Summary

- Regulator has the legal authority, therefore, has responsibility and accountability
- All have legal and ethical responsibilities and accountabilities
- By signing the consent form, subjects do not forfeit their legal rights



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Informed Consent

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



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Consent in Vulnerable Populations

(Defined in E6 - GCP and relevant to E7 - Geriatrics and E11 - Pediatrics)

- Those not capable of consenting (minors or incapacitated)
 - Consent given by a legal representative
 - Subjects should be informed to the extent compatible with the understanding
- Those unable to read or make their mark
 - Use an Impartial witness
- In Emergency situations
 - When not possible to get consent from a legal representative or impartial witness, the subject can be enrolled if provisions for such are stipulated in the protocol



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Vulnerable Subjects

- Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.
- Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.



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Impartial Witness

A person, who is independent of the trial,
who cannot be unfairly influenced by people involved with the trial,
who attends the informed consent process if the subject or the
subject's legally acceptable representative cannot read, and
who reads the informed consent form and any other written
information supplied to the subject.



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Good Regulatory Practices

- Develop regulations that are flexible
- Use risk management principles
- Be consistent in guidance and decision-making
- Be efficient in information and records management
- Measure and maintain performance and transparency
- Be reachable and reach out to stakeholders
- Be aware of changing regional and global factors in R&D and access to drugs



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Risk Management Principles

- Science-based risk management, with risk-based decision-making
- Precautionary principle: "absence of full scientific certainty shall not be used as a reason to postpone decisions when faced with the threat of serious or irreversible harm"
- Proactive – take initiative to address and prevent public health & safety concerns:
 - Safety of Canadian blood system
 - Bovine spongiform encephalopathy / Creutzfeldt-Jakob disease
 - Pandemic influenza
- Know own strengths and weaknesses:
 - Consult with experts on complex scientific, medical, or regulatory issues
 - Implement and make use of scientific advisory committees



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Consistency (both in Guidance and Decisions)

- Adopt international guidelines when appropriate
- Develop SOPs:
 - Good guidance practices
 - Good review practices
- Develop and implement guidelines to address regional issues
- Be aware of drivers, such as globalization



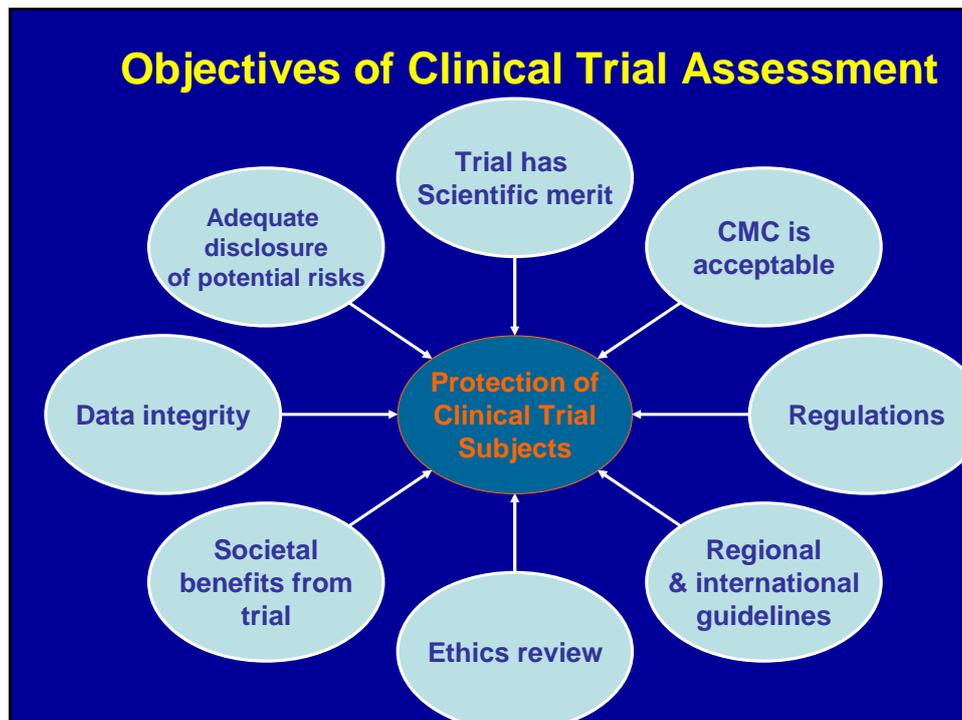
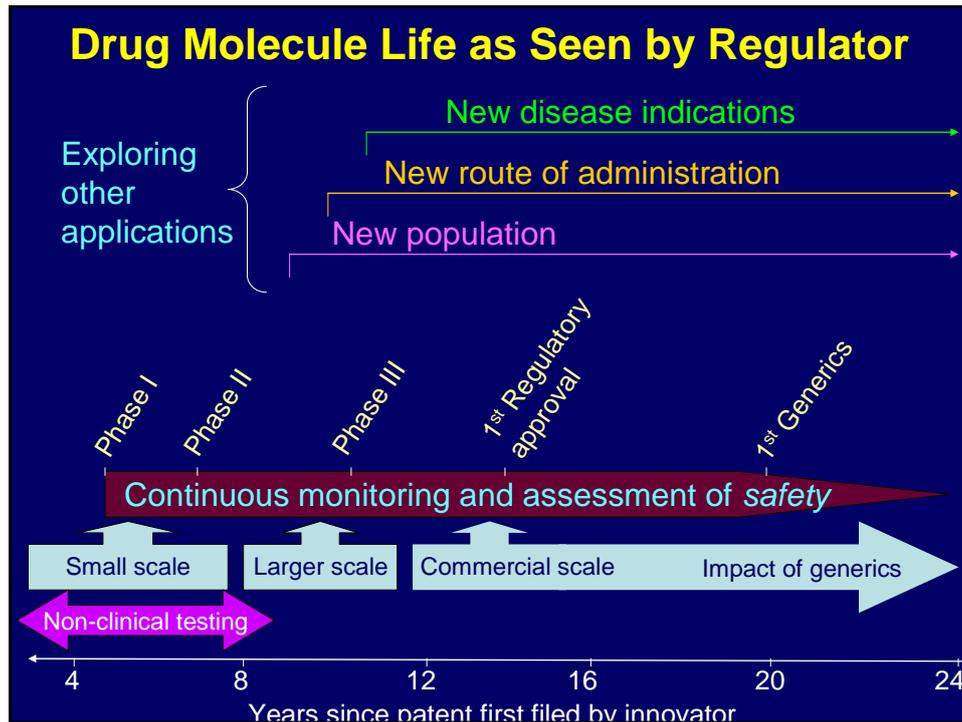
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Drug Development

- Phases of clinical trials
- Life of drug as seen by the regulator
- Common drug targets and future directions
- Current and future challenges and drivers for the regulator



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Regulations and Guidelines (for C&M and Non-clinical data)

At the clinical trial stage:

- Do not require that sponsors follow ICH guidelines
- Do not inspect manufacturing sites against the Annex 2 of the GMP
- Expect that sponsors work towards meeting the guidelines by improving the manufacturing and control of the drug substance and drug product as the product progresses through clinical development
- Guidelines are applied at the marketing stage
- Generally require that sponsors follow all applicable ICH guidelines for the non-clinical program



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Arriving at the Regulatory Decision

- Approach the CT application with *Safety* as the foundation
- Use a systematic, step-by-step approach, integrating all information submitted in the CT application and other information that is available publicly
- Quality is linked to clinical and clinical is linked to quality
- Identify any major gaps, and seek resolution through discussion with the sponsor
- On a case-by-case basis, there can be flexibility in data requirements as long as safety is preserved
- Ensure that the decision is science/evidence-based

For a Positive Regulatory Decision

- **Both** CMC and clinical components comply with:
 - Regulatory requirements
 - Quality standards, as applicable
 - Acceptable risk mitigation measures in quality and clinical aspects
 - Commitments requested by regulator



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Clinical Trial Assessment (at the different phases of development)

- Regulator and Applicant or Sponsor must identify
- What information has been collected
- What are the unclear issues
- Lack of Data
 - Good reason for Increasing the # of Asian Studies
- Economic
- Motivation high for both patients and investigators
- Less ethnic differences within Asia
- From Canadian/global perspective increase ethnic data improves safety especially in multicultural societies



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Continuous Assessment of Risk - Benefit

- Assessing benefit / risk involves:
 - Analysis of unmet medical need and disease characteristics
 - Analysis of data accumulated through product development
- Both the regulator and the sponsor should assess benefit / risk continuously



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Benefit / Risk

Spectrum of Proof of Concept (PoC)

- Target
- Mechanism
- Efficacy
- Commercialization

Translational Medicine approach with 2 phases:

Exploratory Phase

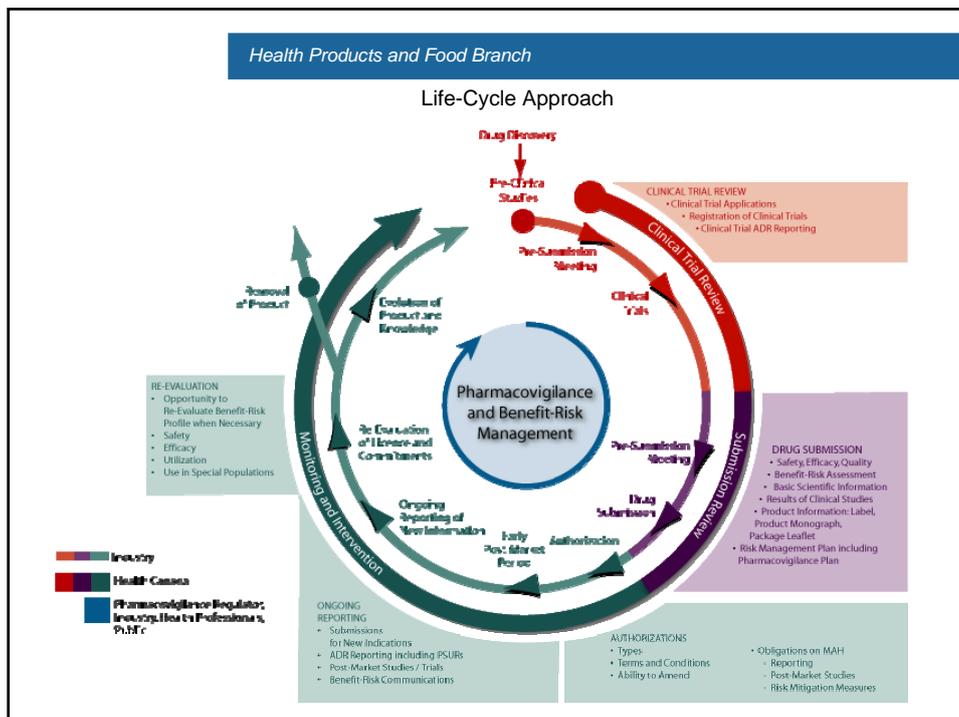
- FIM: SD safety and tolerability in Healthy volunteers
- PoC (may require SD and MD in patients in preparation of)
- Validation

Confirmatory Phase

- Human ADME, multiple PK studies (bioavailability, special populations, drug-drug interactions), mechanistic (biomarker, imaging studies), phototox, Abuse liability studies.



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Bioequivalence Studies

- Objective & characteristics
- Study designs
- Essential components in the review



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Objective & Characteristics

Objective

- To test the formulation of a subsequent-entry pharmaceutical product as compared to a reference

Characteristics

- Healthy adult volunteers
- Canadian reference product or product that is marketed in US, EU, Australia, or Switzerland
- Single or total daily dose does not exceed that specified in the labelling of the reference drug product
- The study does not include the simultaneous administration of a radioactive labelled and unlabelled drug product



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Study Designs

- Single dose with a two period cross-over design
- Conducted in fasted and fed state (if indicated to be taken with food)
- Three and four-period cross-over for modified-release formulations
- Some studies involve parallel group designs
- Steady-state studies for formulations likely to accumulate (e.g., delayed release drug products)



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Quality Review

- Information on Canadian Reference Product or Non-Canadian Reference Product
- Drug substance:
 - Attestations (GMP, ICH organic solvents, TSE/BSE)
 - Batch analyses
- Drug product:
 - Composition of dosage form
 - Attestation (non-medicinal ingredients consistent with reference product, prohibited excipients, GMP)
 - Batch analyses
 - Excipients of human or animal origin (information may be submitted later, but 2 days prior to starting the study)



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Clinical Review

- Use a Reviewer's check-list
- Dose as labelled
 - Consider titration and tapering at end of dosing ("critical dose" drugs - abrupt discontinuation can lead to withdrawal symptoms)
- Wash-out period
 - Should consist of at least 10 terminal elimination half-lives; should not exceed 3 to 4 weeks
- Sample size usually >12 and depends on the estimated intra-subject variability
- Eligibility criteria
 - Should take into consideration the contraindications, warnings and precautions for the drug
 - TB screening for drugs with immunosuppressant properties (medical history and skin test)
- Pregnancy testing if females of child-bearing potential included; acceptable contraceptive methods defined
- Total blood volume collected should not exceed 500 mL within a 4 week period
- Intravenous catheter for multiple blood draws in early time points
- Risks related to the drug are listed in the informed consent form and acceptable contraceptive methods defined



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Summary Bioequivalence Studies

- Choice of Comparator is important
 - Not all studies for local registration
 - Canada allows use of non-local reference product from another ICH region, Australia, or Switzerland
- Health Canada has several guidance documents on the requirements for registration
- Review of comparative bioavailability studies focuses on safety



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Pharmacogenomics (PGx)

Pharmacogenomics is the identification and study of genes and their corresponding products which influence individual variation in the efficacy and/or toxicity of therapeutic products, and the application of genomic information to help inform therapeutic product development and/or clinical application. This may include:

- Choosing the most appropriate therapeutic product for a patient;
- Selecting optimal dose; and/or
- Identifying those at risk for unexpected or more frequent adverse drug reactions



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Informed Consent and PGx

Very important in all following scenarios:

- PGx testing carried out within the context of the main clinical trial
- PGx testing as a sub-study that is not linked, but may be indirectly related to the main clinical trial
- For future use (banking) as in exploratory studies

The informed consent form should explain:

- That PGx testing will be conducted and the purpose of such testing (i.e., how the PGx data will be used)
- The sample and data coding strategy, and the storage, destruction, and security measures used for sample and data preservation to ensure confidentiality to the extent possible
- The rights of the subject with regards to the PGx testing and the study overall



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PGx Regulatory Guidance

- FDA: Guidance for Industry - Pharmacogenomic Data Submissions
- EMEA: Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling
- ICH Topic E15: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories
 - To ensure consistency in the terminology used by the different regions
- Japan
- Health Canada Guidance: Submission of Pharmacogenomic Information



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Examples of PGx

Drug Metabolism

- CYP2C19 and CYP2D6 Variants – Poor vs extensive metabolizers
- N-acetyltransferase - slow and fast acetylators
- Deficiency of dihydropyrimidine dehydrogenase (DPD) activity - *Capecitabine*
- Glucose- phosphate dehydrogenase (G6PD) deficiency - *Rasburicase*
- Thiopurine methyltransferase deficiency or lower activity - *Azathioprine*
- Homozygous UGT1A*28 allele - *Irinotecan*

Drug Target

- C-KIT expression in GIST - Imatinib
- CCR5 -Chemokine C-C motif receptor on human T-cell - Maraviroc
- EGFR expression - Erlotinib, Cetuximab, Vectibix
- Her2/neu expression – Trastuzumab, Herceptin
- Philadelphia (Ph1) chromosome – Busulfan
- ApoE4 carriers– Vasculitis – Alzheimer's Rx Anti-Amyloid Antibody



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PGx Summary

- PGx is not a new topic but facilitated by new tools
- Several Guidance documents have been developed by different regions
- We are now seeing CTAs with a PGx component
- Co-approval of an ITA for the PGx test may be required
- Informed consent is one of the most important aspects of PGx testing



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Essential Elements in Clinical Trial Assessment

Sufficient evidence

Sufficient evidence signifies a positive benefit-to-risk ratio based on the sum of the following:

- Acceptable Quality (CMC) for the phase of development
- Acceptable supporting nonclinical and clinical data (as applicable) for the phase of development
- Acceptable protocol and informed consent form for the proposed trial
- Maintenance of the positive benefit/risk ratio during the conduct of the trial through safety monitoring of the trial as well as other ongoing trials with the drug ('product life-cycle' approach)



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Regulations Development

When developing regulations, consider:

- What are the disease areas of interest (what can your population offer)?
- What can your health care system offer?
- What is the status of investigator/institution-driven research in your country?
- What frameworks are in place for ethical review of human research and protection of clinical trial subjects?
- What are sponsors looking for in your country?

Prepare your regulatory framework, and scientific expertise accordingly



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Regulatory Frameworks

- Regulations must aim to protect clinical trial subjects and enable sound benefit / risk assessment, without unduly restricting research and access
- Regulatory requirements should take into consideration the global context
- Globalization: adopt international guidelines where possible
- Address regional-specific issues by developing region-specific guidelines
- Guidance documents on process, format, and content, of clinical trial applications should be available



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Good Review Practices - Overview

- Regulatory expertise
- Scientific expertise
- Time management
- Documentation
- Systematic approach to review
- Review of subsequent information
 - Life cycle approach



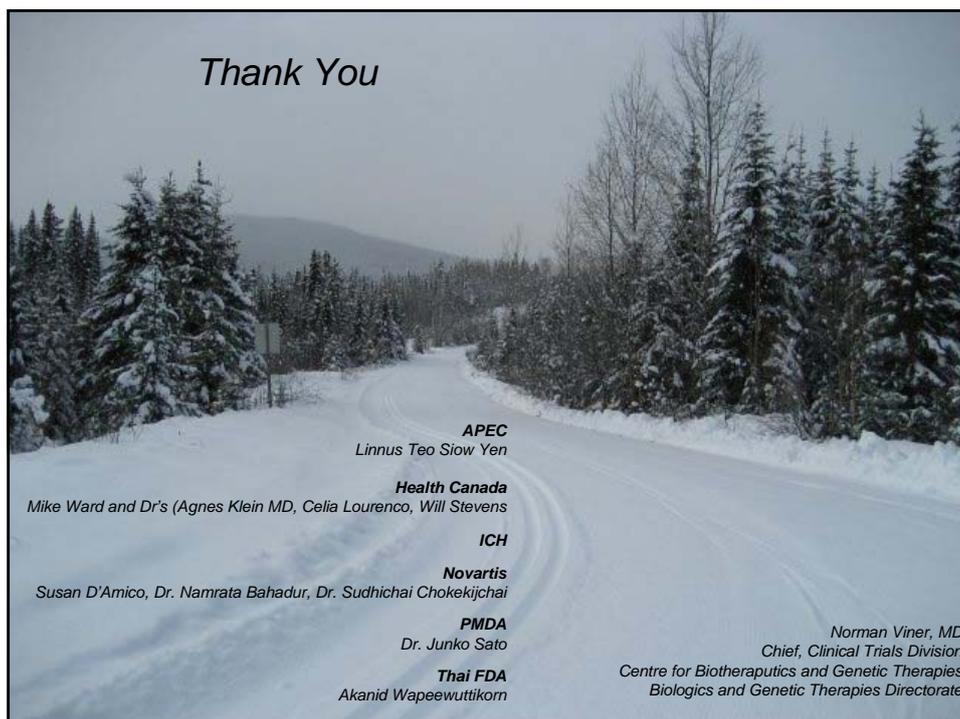
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Challenges

- A small group of clinical reviewers have to cover a broad knowledge base on different disease areas
 - Has the potential to lead to ill-informed decisions: “ignorance of ignorance”
- Always approach a review with a perspective of safety
 - Regulatory requirements must be met
 - Challenge sponsors if there is inconsistency with international guidelines
- Do not review in isolation



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Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Review Operation

“Setting Up the Business”



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

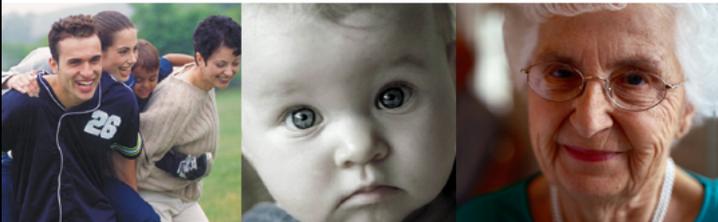
Canada

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Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

Canada

Health Products and Food Branch

Topics to Discuss

- Context
- Canadian Perspectives on Staffing CT Review Group
- Challenges
- summary



3

Health Products and Food Branch

Health Canada: Branches and Agencies

Ministers and Officers

- Minister of Health
- Deputy Minister
- Associate Deputy Minister
- Chief Public Health Officer

Branches, Offices and Bureaus

- Audit and Accountability Bureau
- Chief Financial Officer Branch
- Corporate Services Branch
- Departmental Secretariat
- First Nations & Inuit Health Branch
- Health Policy Branch
- Health Products & Food Branch**
 - Clinical Trials

Agencies

- Healthy Environments & Consumer Safety Branch
- Legal Services
- Office of the Chief Dental Officer
- Pest Management Regulatory Agency
- Public Affairs, Consultation and Regions Branch
 - Regions

Agencies

- Canadian Institutes of Health Research
- Hazardous Materials Information Review Commission
- Patented Medicines Prices Review Board
- Public Health Agency of Canada



4



APEC LSIF PROJECT “Capacity
Building For Drug Regulatory Agencies
on Clinical Trial and Good Clinical
Practice (Phase 2)”

Health Products and Food Branch

Health Products and Food Branch (HPFB)

Directorates and Offices

- **Biologics and Genetic Therapies Directorate**
 - Clinical Trials x 2
- Food Directorate
- Health Products and Food Branch Inspectorate
- Marketed Health Products Directorate
- Natural Health Products Directorate
- Office of Consumer and Public Involvement
- Office of Management and Program Services
- Office of Nutrition Policy and Promotion
- Departmental Biotechnology Office
- Office of the Assistant Deputy Minister
- Policy, Planning and International Affairs Directorate
- Regional Operations
- **Therapeutic Products Directorate**
 - Clinical Trials
- Veterinary Drugs Directorate



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Health Products and Food Branch

Regulatory Framework

- Business set up should match the Regulations and compliment the review process
- Screening – for completeness
- Assigning to a Review – Manager's 'triage' role
- Initial Review
- Information/clarification = communication with the sponsor
- Timelines for each step
- Final decision
 - No objection
 - Voluntary withdrawal
 - Not satisfactory letter
 - ability to resubmit **without prejudice**



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Health Products and Food Branch

He who studies medicine without
books sails an uncharted sea, but
He who studies medicine without
patients does not go to sea at all.

~ **Sir William Osler, 1st Baronet**



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Health Products and Food Branch

Competencies of staff

- Including manager
- Clinical perspective is imperative
- Mix of expertise – to match the submissions
 - Minimum PhD or MD
- Mix in BGTD
 - Licensed Physicians (part time – tele-workers): Neurologist, Internist, Gastroenterologist, General practitioner
 - Full time staff: Veterinary Toxicologist, Molecular biologist, unlicensed physicians; Romania x 2, China, Guatemala, Armenia and soon (hopefully) an Argentinean Pediatrics Endocrinologist



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Health Products and Food Branch

Clinical perspective is imperative

- Although the majority of CTs come from industry for the purpose of drug registration
- Others that can and should get captured by Competent Authorities' Regulations include:
 - Academic
 - Clinical Trial Networks, eg.
 - National Cancer Institute (NCI/C)
 - Children's Oncology Group (COG)
 - National Surgical Adjuvant Breast and Bowel Project (NSABP)
 - Eastern Clinical Oncology Group (ECOG), etc.



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Health Products and Food Branch

Flexibility in the Work Place

Working from Alternate Locations:

- Agreements
- Issues of working off site with deadlines

Fostering a collaborative approach

- Culture of trust
- Respect
 - Safety in numbers

"none of us is as smart as all of us"



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Health Products and Food Branch

Three Clinical Trial Groups in Health Canada

HC's Clinical Trial set up – iterative process, was one big organization split apart and then has grown organically.

Pharmaceuticals: Therapeutic Products Directorate (TPD)

- chemically synthesized or derived
- small molecules
 - OCT

Biologics: Biologic and Genetic Therapies Directorate (BGTD)

- vaccines, hormones, animal/cell derived molecules, blood products
- complex compounds
 - CBE - CTD
 - CERB - CTD

Post Market (MHPD)

- over lap with safety issues for products still in CT
- (with licensed indications)



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Health Products and Food Branch

BGTD Organization

Regulatory Affairs Directorate (RAD)
part of BGTD's Centre for Policy and Regulatory Affairs

- **BQ-RAD** (Biotherapeutics, Quality)
- **BTOV-RAD** (Blood, Tissue, Organs and Vaccines)

**Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutics
CERB-CTD**

- 9.9 FTEs including a manager

Centre for Biologic Evaluation CBE-CTD

- 2.8 FTEs



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Health Products and Food Branch

Frequent Interaction between CT Review Groups

- **smaller biologic molecules can be manufactured synthetically**
 - eg hormones, antigens/adjuvants for use in/as vaccines
- **target same indications**
 - eg. VEGF/EGFR inhibitors, immunosuppressants
- **Grouping of products**
 - Heparins moving towards being classified as a blood product
 - Oligonucleotides: should they be reclassified as biologics (Gene Therapy) despite being chemically synthesized?
- **Harder to define therapeutic approaches**
 - eg. Genetically altered Oncolytic Viruses: blend of therapeutic vaccine, gene therapy and viral therapy



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Health Products and Food Branch

Quality (CMC) Review of Clinical Trials

- Different models are in place for Pharmaceutical Drugs and Biologics at Health Canada:
- For Pharmaceuticals, review of the Quality information provided for Clinical Trial drugs is carried out by a dedicated group in the Office of Clinical Trials. This allows for more focussed expectations and interactions between Clinical and Quality reviewers and centralized management of review activity
- For Biologics, Review of the Quality information is carried out by review staff also responsible for review of New Drug Submissions and post market Changes, organized along Product lines. This allows for more product-specific expertise, and linking expectations and information from clinical development through to licensure



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Background of Quality Reviewers

- Typically Quality reviewers have graduate degrees in a relevant area of science pertinent to the products regulated, and an understanding of the methods of manufacture and analytical testing applied.
- Depending on the product area this could mean various streams of chemistry (analytical, organic, pharmaceutical), biology, biochemistry, molecular biology, immunology, virology, physiology, pharmacology etc.
- Most of our review staff come from either academic or pharmaceutical manufacturing backgrounds



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Regulatory Framework

- Business set up should match the Regulations and compliment the review process
 - Requires clear regulatory Mandate and Authority for Decision-making
 - Regulations should be supported by clear Guidances and Policies (your own or adopted) available to all stakeholders that describe:
 - Regulatory expectations (interpretation of regulation)
 - Information requirements (guidance or templates)
 - Decision Making Process
 - Consequences of Decisions
 - Regulations should also be supported by some mechanism for enforcement of compliance and adequate resourcing



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Health Products and Food Branch

Quality System

- Goal: Clear consistent and predictable decision-making
 - Outcomes and timelines
- A set of documentation of internal processes and procedures that describe and define roles, responsibilities and performance expectations around key business activities
 - Screening – for completeness
 - Assigning to a Reviewer – Manager's 'triage' role
 - Initial Review
 - Information/clarification = communication with the sponsor
 - Decision-making and communication of decision
- Supporting these should be job descriptions, a hiring process, systems for information storage and retrieval, and defined managerial responsibility for the processes and their outcomes.

Improvement is an iterative process, and there needs to be a clear means to identify, track and address gaps



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Health Products and Food Branch

Challenges

Resource Issues:

- **Small # of reviewers, not organized by Indication or Disease area**
 - BGTD clinical reviewers have to cover a broad knowledge base on different disease areas, which has the potential to lead to ill-informed decisions:
 - “Need to know what you don’t know”
- **reviewers have a very short time frame to arrive at a review decision and an increasing workload with a relatively stable # of reviewers and screeners**

Increasing Complexity of Trials:

- **Increased complexity in science, types of products, and treatment of disease (e.g., gene therapies, product combinations, nanotechnologies)**



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Health Products and Food Branch

More Challenges

Lack of clarity over regulations

Interpretation of the regulations = Opportunity for flexibility

- Can be greatest challenge in dealing with staff
- Need consistent strategy in managing differences of opinion with review staff.
- Take the time to listen and effectively communicate
 - Best investment one can make in insuring the 'business' runs smoothly!!!



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Health Products and Food Branch

Efficiency in Information and Records Management

- Develop and implement tools to manage documents and information submitted by sponsors
 - Maintain accurate records with a numbering system for sponsor/drug and submissions
 - Clinical trial applications, amendments and notifications
 - ADR database for integration and analysis
 - Submission allocation database
 - Clinical trial inspection database
- System to manage other information such as general enquiries
- Ensure security and maintain confidentiality of records



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Health Products and Food Branch

Measure and Maintain Performance and Transparency

- Measure workload and performance at periodic intervals (e.g., quarterly)
- Use information on workload and performance to develop/revise business plans
- Publish performance measures periodically (e.g., annually)
 - Number of clinical trials, protocol amendments, notifications, ADRs, types of trials, etc.
 - Submission processing and review times



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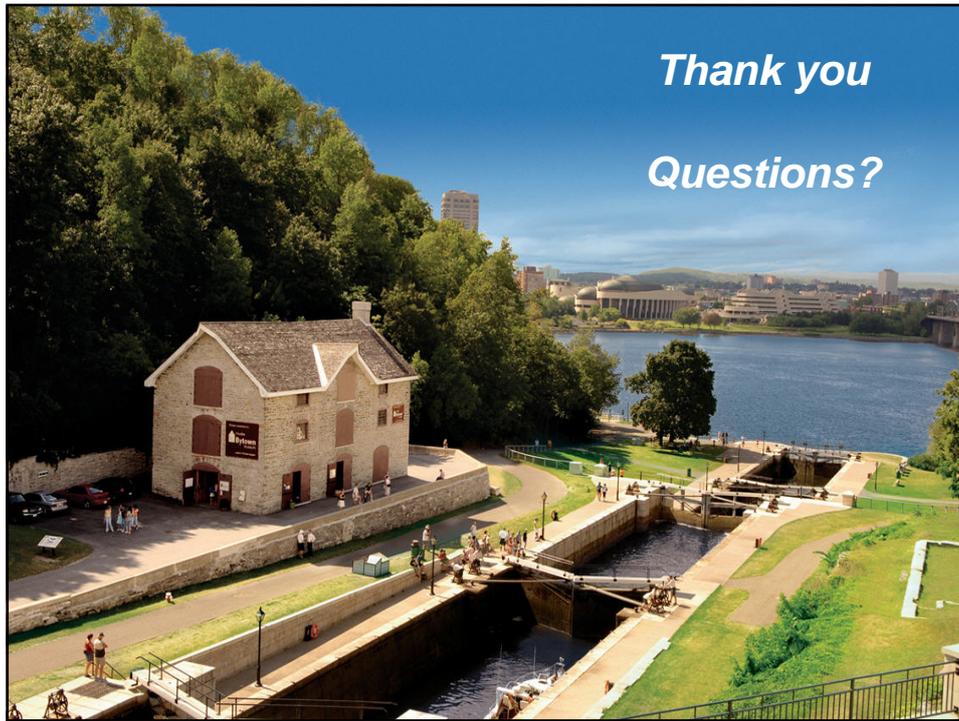
Health Products and Food Branch

Communicate Effectively

- Provide opportunities for dialogue with sponsors and stakeholders formally and informally (being mindful)
 - Pre-clinical Trial Meetings
 - Telephone Conferencing
 - Informal email enquiries
- Provide an Appeal Process
- Consult with all stakeholders before implementing or adopting new regulations, policies, and guidelines
- Communicate horizontally within organization
- Seek lessons learned through impact analyses



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Your health and safety... our priority. *Votre santé et votre sécurité... notre priorité.*

Expectations for Data to Support Clinical Trial Drugs

Presentation to:
APEC Advanced Workshop on Review of Drug Development in Clinical Trials
Bangkok Thailand Feb 2-6 2009

**Willem Stevens Ph.D., Chief
Plasma Derivatives Division
Centre for Biologics Evaluation
Biologics & Genetic Therapies Directorate**



Overview

- Focus of Quality review for Clinical Trial Drugs
- Challenges presented by Clinical Trial materials
- Context for Review
- Summary of Quality (CMC) requirements & data expectations through Drug Development



Focus

Safety:

Ensure that participants in Clinical Trials are not placed at undue risk arising from unsatisfactory manufacture or control of Clinical Trial Drugs.



Challenge

- Production and control of investigational drugs involves added complexity in comparison to marketed drugs due to:
 - limited experience in the production of the investigational drug
 - lack of full validation of manufacturing process and analytical methods
 - incomplete knowledge of the potency and toxicity of the product
 - incomplete knowledge about the stability of the product
 - increased risk of product cross-contamination and mix up when using non-dedicated facilities and equipment and with packaging blinded materials



Context for Review

- What is the intended use, patient population, size of trial?
- What is the phase of trial and stage of development of the drug?
- What is already known about the product?
 - Previous trials
 - Drug development
- Is product type/class known to have specific quality concerns (e.g. problematic impurities, previous safety issues)
- What is the level of experience of the manufacturer and the degree of their involvement in drug development?
- Is there enough data present to assess the safety of the drug from a Quality (CMC) standpoint and is the data supportive?



Quality Expectations: Drug Substance





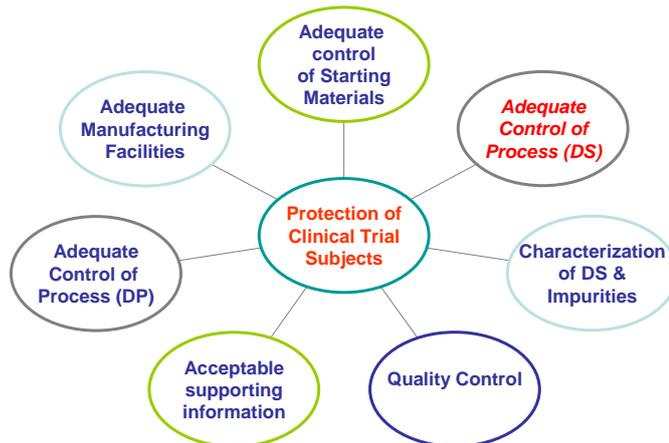
- ### Control of Starting Materials
- Is there adequate data to support starting materials and excipients as suitable for intended use?
 - Specifications/ Certificates of Analysis provided for non-compendial starting materials.
 - Adequate data to support suitability of animal-derived or biological starting materials (*e.g.* certification of compliance with EP Monograph 5.2.8).
 - For novel excipients is there adequate information about manufacture, control and link to acceptable pre-clinical study data?
- 

Control of Starting Materials (Biologics)

- Depending on product type, additional information may be required to support safety of complex starting materials such as cell lines, human or animal tissues or body fluids including additional characterization, screening or testing data.
 - Donor selection criteria, screening tests for plasma (or urine)
 - Descriptions of source and origin of animal derived materials or tissues
 - For products of prokaryotic or eukaryotic cell culture, derivation of cell stocks (ICH Q5D)
 - Testing for endogenous or adventitious pathogens for cell lines (ICH Q5A)
 - In some cases, excipients, adjuvants or process aids might need to be evaluated as products themselves (e.g. albumin excipient, MAbs used for purification, novel vaccine adjuvants)



Quality (CMC) Requirements



Manufacturing Process (DS)

- Given the stage of development for the product, is there an adequate description of the manufacturing process? Level of detail and in-process control should increase through product development
- Are starting materials, reagents, catalysts identified and consistent with other information supplied?
- For Phase II/Phase III materials is there a process narrative & does it agree with flow diagram and defined process scale?
- For Phase III materials, are critical steps identified and appropriate in-process controls in place, are specifications in place for isolated intermediates?
- For Phase III materials is there an adequate description of process development and a discussion of evolution of the process to the current one?



Manufacturing Process (Biologics DS)

- Is there a process narrative and flow diagram describing the manufacturing process and its control, including definition of scale and any blending or pooling?
- Are critical process intermediates identified with summary of quality control and storage parameters for any isolated intermediates?
- Any existing process validation/ evaluation should be summarized (this is expected to progress through development).
- Steps to control adventitious agents should be described and summary data provided.
- A brief summary of process development and comparison of material derived from various processes where the changes have been significant (this is expected to progress through development).





- ### Characterization (DS)
- Are the basic physicochemical properties of the Active ingredient defined quantitatively?
 - Is there a potential for polymorphism... if so is there data supporting properties of forms present?
 - If solubility is limited, is particle size distribution addressed and controlled?
 - For pharmaceutical Active Ingredients, is there enough data to confirm intended structure based on synthetic route?
 - For existing drugs this could be achieved through spectral comparison with a suitable reference.
 - Where isomeric forms can or do exist is this addressed?
 - Are possible isomers that can arise from the manufacturing process discussed, and summary data available to indicate their physical, chemical and biological properties?
 - It should be specified if a specific stereoisomer or a mixture of stereoisomers will be used/have been used in previous studies, and a rationale for this decision provided.
 - For complex actives (e.g. peptides) absolute structure may not be feasible and purification and control of purity take on more importance
-
- A row of four small images: a nurse examining a child, a laboratory flask, a couple smiling, and a person holding a pill.

Characterization (Biologics DS)

- In most cases for biologics, the active substance will be a “family” of closely related species reflecting the desired product and product-related substances.
- Is there adequate data in place to support primary and higher order structure and biological activity?
 - Typically multiple methods will be required to address structure and activity.
- Is there adequate data in place to describe presence or absence of expected post-translational modifications?
- Is the purity established and adequate for the intended use?

Guidance on methods in ICH Q6B



Impurities

- Based on route of synthesis or extraction and available characterization are potential or actual impurities adequately addressed?
 - Product related (intermediates, by-products, metabolites)
 - Process related (solvents, reagents, catalysts)
- For Phase I expect structure (or identifier) and origin
- For Phase II expect Limit of Detection & Quantification and actual impurity levels to be established (ICH Q3A, Q3C)



Impurities (Biologics)

- Are potential impurities arising from the expression or extraction process or the purification and/or potential degradation of the desired product adequately addressed?
 - Product Related (variants, related species, glycoforms, truncated species, multimers, aggregates)
 - Process Related (host cell DNA, Host cell protein (or unrelated proteins), affinity ligands, residual solvents)
- Are levels of impurities in batches produced to date described (for batches used in non-clinical studies and clinical trial where available)?



Adventitious Agents (Biologics)

- Are adequate measures implemented to control endogenous and adventitious agents (ICH Q5A, Q5D, Q6B)?
 - For non-viral agents (bacteria, mycoplasma, fungi) are measures in place to test, evaluate and eliminate risks during production?
 - Where relevant, is information available on measures in place to address risks from prions (EU Guide on TSE agents)?
 - For viral agents, are controls at the level of starting materials in place and testing conducted during appropriate stages of production?
- Are the results from viral clearance studies present and adequately discussed?
- Where applicable is there a calculation of estimated particles/dose?





- ### Specifications (Pharmaceutical DS)
- For Phase I while a specification is not necessary, expect the results for the batch(es) to be used to be provided.
 - Expect at least an interim specification for Phase II drug substances with appropriate tests and acceptance criteria based on the nature of the drug substance, and that reasonable limits for impurities and residual solvents have been established.
 - Acceptance criteria should be based on manufacturing experience, stability data and safety considerations. These are expected to be firmed up as development proceeds towards commercial process and scale.
 - By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6A).
- 

Methods (Pharmaceutical DS)

- For Phase II and III trial applications, is there a brief description of any non-compendial analytical methods used? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6A)? Complete validation is not usually necessary at Phase II but expected at Phase III.



Batch Analysis (Pharmaceutical DS)

- Has a description of batches produced and the results of their testing been provided? For Phase I and II trials expect that analytical results for the batch to be used in the proposed clinical trial are provided.
- For Phase II if data from specific batches to be used in the proposed protocol are not supplied is there data from representative batches (produced by the same method of manufacture, equipment, specifications, and container closure and at a similar scale) and a commitment to provide data for the specific lot(s) prior to dosing?
- For Phase III, if specifications and analytical methods are well supported, representative batch analysis data may be sufficient.



Specifications (Biologic DS)

- For Phase I and II drug substances has an interim specification been provided with appropriate tests and acceptance criteria based on the nature of the drug substance, with reasonable limits for impurities?
- Is testing carried out at the appropriate stage of manufacture? Some tests (e.g. for adventitious virus) might be more appropriate at earlier stages of production.
- Acceptance criteria should be based on manufacturing experience, stability data and safety considerations. These are expected to be firmed up as development proceeds towards commercial process and scale.
- By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6B).



Methods (Biologic DS)

- Is there a brief description of any non-compendial analytical methods used? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6B)? Movement towards full validation is expected by Phase III.
- Is there an adequate description/characterization of the reference material(s) used?

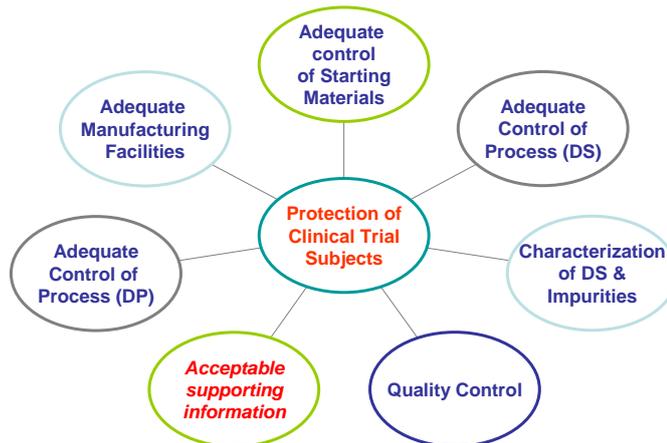


Batch Analysis (Biologics DS)

- Has a description of batches produced to date and the results of their testing been provided and discussed?
- For Clinical Trials of biologics expect that the analytical results for the batch to be used in the proposed clinical trial are provided.
- For lengthier protocols, have a Fax-back process providing a certification that the batch to be used met the specification in the Clinical Trial Application, and/or justification for any parameters that were not met.



Quality (CMC) Requirements



Stability (DS)

- Is there data in place to support the practices (e.g. storage, shipping and handling) in place at the time of filing the Clinical Trial Application?
- Was the data available collected on material representative of the intended material for the proposed trial (process, equipment, facility, container closure)?
- Is the data provided current (are there planned test points that could have been provided but weren't)?
- Are any gaps covered by commitments to evaluate stability on an ongoing basis?
- As development proceeds expect the amount of data to increase towards that necessary to cover the intended commercial practice



Plenary Discussion: Drug Substance

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Quality Expectations: Drug Product



Control of Starting Materials

- Is there adequate data to support starting materials and excipients as suitable for intended use?
 - Specifications/ Certificates of Analysis provided for non-compendial starting materials.
 - Adequate data to support suitability of animal-derived or biological starting materials (*e.g.* certification of compliance with EP Monograph 5.2.8).
 - For novel excipients is there adequate information about manufacture, control and link to acceptable pre-clinical study data?



Control of Starting Materials (Biologics)

- Depending on product type, additional information may be required to support safety of complex starting materials such as cell lines, human or animal tissues or body fluids including additional characterization, screening or testing data.
 - Donor selection criteria, screening tests for plasma (or urine)
 - Descriptions of source and origin of animal derived materials or tissues
 - For products of prokaryotic or eukaryotic cell culture, derivation of cell stocks (ICH Q5D)
 - Testing for endogenous or adventitious pathogens for cell lines (ICH Q5A)
 - In some cases, excipients, adjuvants or process aids might need to be evaluated as products themselves (*e.g.* albumin excipient, MAbs used for purification, novel vaccine adjuvants)





- ### Batch Definition
- Is there a description of the dosage form, it's composition (including all components used in the manufacture regardless if they appear in the final product)?
 - Are overages clearly indicated and the batch scale defined?
 - Does the batch scale described in the process narrative match the batch formula provided?
 - If there is a placebo form it should also be defined and it's composition provided.
- 

Pharmaceutical Development

- As development of formulation and manufacturing process proceeds expect some changes in formulation and process optimization. Is there a comparison of the current formulation (or process) with earlier iterations? Do these changes impact the relevance of earlier studies (e.g. stability)?
- Is there an assessment of the potential impact of changes on extrapolation of results from pre-clinical earlier clinical trials to the proposed trial?
- Is there data to support compatibility of the various components?
- The scientific rationale for the approach taken should be provided



Pharmaceutical Development (Biologics)

- For Biologics, the comparability of the test material during a development program should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made.
 - Comparability can be evaluated on the basis of biochemical and biological characterisation (i.e., identity, purity, stability, and potency)
 - In some cases additional studies may be needed (i.e., pharmacokinetics, pharmacodynamics and/or safety)
- Overall, the goal is to demonstrate that improvements in processes lead to improvements in product quality while preserving or improving safety



Manufacturing Process (DP)

- Given the stage of development for the product, is there an adequate description of the manufacturing process? Level of detail and in-process control should increase through product development.
- For Sterile products is a complete narrative of the manufacturing process and details of the sterilization procedure provided?
- For Phase II/Phase III materials is there a process narrative & does it agree with flow diagram and defined process scale?
- Are any non-standard or novel manufacturing processes or technologies described in adequate detail?
- For Phase III materials, are critical steps identified and appropriate in-process controls in place, are specifications in place for intermediate tests, and isolated intermediates?
- For Phase III materials is there an adequate description of the process development and a discussion of evolution of the process?



Manufacturing process (Biologic DP)

- Is there a process narrative and flow diagram describing the manufacturing process and its control, including any blending or pooling of Drug Substance to make a Drug Product batch?
- Any existing process validation/ evaluation should be summarized (this is expected to progress through development).
- Are any steps to control adventitious agents described and summary data provided?
- Is there a brief summary of process development and a comparison of material derived from various processes where the changes have been significant (this is expected to progress through development)?





- ### Specifications (Pharmaceutical DP)
- For Phase I if a specification is not provided, are the results for the batch(es) to be used to be provided?
 - Is at least an interim specification in place for Phase II drugs with appropriate tests based on the nature of the drug substance and dosage form?
 - Are acceptance criteria reasonable based on manufacturing experience, stability data and safety considerations? These are expected to be firmed up as development proceeds towards commercial process and scale.
 - By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6A) and reflect the additional manufacturing experience and available stability information.
- 

Methods (Pharmaceutical DP)

- For Phase II and III trial applications, is there a brief description of any non-compendial analytical methods used that aren't already described for the Drug Substance? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6A)? Complete validation is not usually necessary at Phase II but expected at Phase III.



Batch Analysis (Pharmaceutical DP)

- Has a description of batches produced and the results of their testing been provided? For Phase I and II trials expect that analytical results for the batch to be used in the proposed clinical trial are provided.
- For Phase II if data from specific batches to be used in the proposed protocol are not supplied is there data from representative batches (produced by the same method of manufacture, equipment, specifications, and container closure and at a similar scale) and a commitment to provide data for the specific lot(s) prior to dosing?
- For Phase III, if specifications and analytical methods are well supported representative batch analysis data may be sufficient.
- Discussion of the results should include ranges and trends observed, and numerical data should be provided for quantitative tests.



Specifications (Biologic DP)

- For Phase I and II drugs has an interim specification been provided with appropriate tests and acceptance criteria based on the nature of the drug and it's intended use?
- Is testing carried out at the appropriate stage of manufacture? Some tests might be more appropriate at intermediate steps rather than on the final container (e.g. residual solvent/detergent used for viral reduction).
- Are acceptance criteria based on manufacturing experience, stability data and safety considerations? These are expected to be firmed up as development proceeds towards commercial process and scale.
- By Phase III expectations are that specifications should reflect those intended for the marketing application (ICH Q6B).



Methods (Biologic DP)

- Is there a brief description of any non-compendial analytical methods used that wasn't provided for the Drug Substance? Detailed descriptions of analytical procedures are not needed unless there is some question of the feasibility or suitability of the method.
- Is there adequate summary data (specificity, range, accuracy, precision, Limit of Detection, Limit of Quantitation) to support intended use of analytical methods (ICH Q6B)? Movement towards full validation is expected by Phase III.
- Is there an adequate description/characterization of the reference material(s) used?



Batch Analysis (Biologics DP)

- Has a description of batches produced to date and the results of their testing been provided and discussed?
- For Clinical Trials of biologics expect that the analytical results for batches to be used in the proposed clinical trial are provided.
- For lengthier protocols, have a Fax-back process providing a certification that the batch to be used met the specification in the Clinical Trial Application, and/or justification for any parameters that were not met.



Quality (CMC) Requirements



Container Closure System

- Is there a description of all those components that contact product, help ensure stability or sterility, are used for drug delivery, support drug quality during transport?
- Is there data to support compatibility?
- For sterile products, is there a description of the preparation of sterile packaging components?



Stability

- Is there data in place to support the continued acceptability of the product for the duration of the trial?
- If full data isn't available, is there a commitment to monitor actual clinical batches (or representative batches) throughout the duration of the trial and a summary of the testing to be performed and the test stations?
- Is accelerated stability data provided?
- For drug products that are reconstituted or diluted, is there data to support the proposed in-use period?
- Should be using principles in ICH Q1A-E (Pharmaceuticals) and Q5C (Biologics)



Comparator Products (Pharmaceutical)

- Are comparator products to be used in the trial identified (proprietary name DP, common name DS, manufacturer, country of origin (market status) ,dosage form. strength)?
- Prefer comparator obtained from domestic market.
- Full Quality information required for comparators not obtained in EU, US, Australia or Switzerland.
- If comparator is modified (e.g. milling, encapsulation of tablets), data to support lack of impact on pharmaceutical properties (e.g. comparative dissolution). For sterile dosage forms that are repackaged, need evidence for maintenance of sterility.



Comparator Products (Biological)

- Where comparator products are not obtained from the domestic method either require evidence to establish equivalence of product with the Canadian version of the product, or full Quality data.

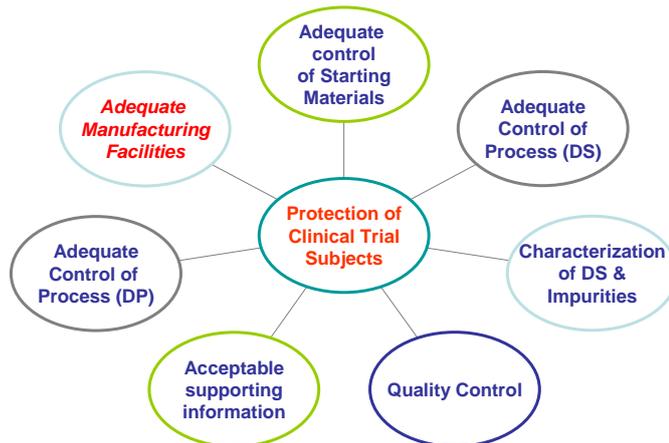


Diluents

- For reconstituted dosage forms, is there evidence supporting compatibility with the proposed diluent(s)?
- Is there a cross-reference or letter of access for diluents supplied with the Clinical Trial Drug?
- For non-commercial diluents provided manufactured by or for the clinical trial sponsor for reconstitution or suspension of clinical trial drugs, a separate drug product section should be completed.



Quality (CMC) Requirements



Facilities Considerations

- For Pharmaceutical Clinical Trial Applications expect an attestation that the facilities used to manufacture the drug in dosage form meet GMP (PIC/S Annex for Clinical Trial Drugs)
- For Biologics expect:
 - a descriptive summary of the facilities and the product contact equipment used (both for Drug Substance and Product)
 - for shared facilities and equipment, procedures or measures in place to prevent contamination or cross contamination (both for Drug Substance and Product)

Annex to the GMP Guidelines for Schedule D (Biologic) Drugs



Plenary Discussion: Drug Product

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Key Messages

- Use a systematic approach where every component of the quality information contributes to the overall assessment.
- Compare all drug substance and drug product batch results and look for variability, inconsistencies.
- Ensure stability testing is adequate for the type of product and intended use.
- Use a benefit / risk approach where other factors such as the phase of development, subject population, and manufacturer's experience contribute to the assessment.
- Available Quality (CMC) data is expected to progress through product development phases.
- Often involves a case-by-case judgement call on extent of quality data requirements at time of application or as a post-approval commitment



Thank You!

Questions?



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References: Pharmaceuticals

ICH Quality Guidance for Pharmaceuticals:	
Q1A Stability New Drugs/Substances	http://www.ich.org/LOB/media/MEDIA419.pdf
Q1B Photostability	http://www.ich.org/LOB/media/MEDIA412.pdf
Q1C Stability New Dosage Forms	http://www.ich.org/LOB/media/MEDIA413.pdf
Q1D Stability Bracketing & Matrixing	http://www.ich.org/LOB/media/MEDIA414.pdf
Q1E Evaluation of Stability Data	http://www.ich.org/LOB/media/MEDIA415.pdf
Q3A Impurities Drug Substance	http://www.ich.org/LOB/media/MEDIA422.pdf
Q3B Impurities Drug Product	http://www.ich.org/LOB/media/MEDIA421.pdf
Q3C Residual Solvents	http://www.ich.org/LOB/media/MEDIA423.pdf
Q6A Specifications: New Drugs	http://www.ich.org/LOB/media/MEDIA430.pdf
Health Canada Quality Guidance	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qual_cta_dec_e.pdf
GMP: Manufacture of Drugs Used in Clinical Trials	www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compl-conform/clin_trials-essais_cln_e.pdf



References: Biologics

ICH Quality Guidance for Biologics:	
Q5A Viral Safety Cell Lines	http://www.ich.org/LOB/media/MEDIA425.pdf
Q5B Analysis of Expression Construct (rDNA)	http://www.ich.org/LOB/media/MEDIA426.pdf
Q5C Stability Testing: Biotech/Biological	http://www.ich.org/LOB/media/MEDIA427.pdf
Q5D Characterization of Cell Substrates	http://www.ich.org/LOB/media/MEDIA429.pdf
Q5E: Comparability	http://www.ich.org/LOB/media/MEDIA1196.pdf
Q6B Test Procedures and Acceptance Criteria	http://www.ich.org/LOB/media/MEDIA432.pdf
EMA Note for Guidance Minimizing TSE Risk	http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf
GMP Annex for Schedule D (Biologic) Drugs	http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compl-conform/sched_d_part1-annexe_d_part1-eng.pdf



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Expectations for Updating Quality Data for Clinical Trial Drugs

Presentation to:
APEC Advanced Workshop on Review of Drug Development in Clinical Trials
Bangkok Thailand Feb 2-6 2009

Willem Stevens Ph.D., Chief
Plasma Derivatives Division
Centre for Biologics Evaluation
Biologics & Genetic Therapies Directorate



Rationale

- Within the framework of evaluation for Clinical Trial drugs, decisions are made appropriate to the developmental stage of the investigational drug based on the available information and the intended use in Clinical Trials.
- When these parameters change, it is appropriate to re-visit the ongoing applicability of the decisions made.
- Based on the extent of the changes made filing of amendments or new applications may be warranted.



Context for Review

- What is the intended use, patient population, size of trial?
- What is the phase of trial and stage of development of the drug?
- What is already known about the product?
 - Previous trials
 - Drug development
- Is product type/class known to have specific quality concerns (e.g. problematic impurities, previous safety issues)
- What is the level of experience of the manufacturer and the degree of their involvement in drug development?
- Is there enough data present to assess the safety of the drug from a Quality (CMC) standpoint and is the data supportive?



Amendments (Pharmaceutical DS)

- Introduction of new ingredients (including those removed in the manufacturing process).
- Identification of a new impurity or degradation product.
- Removal or relaxation of a Drug Substance specification.



Amendments (Pharmaceutical DP)

- Introduction of new ingredients (including those removed in the manufacturing process).
- Changes to the manufacturing process for sterile products where the sterilization process has changed.
- Removal or relaxation of a Drug Substance specification, or replacement of a test method with a less sensitive one.
- Where Clinical trials change Phase, updated Quality (CMC) information should be filed to conform to expectations for increased understanding and control through development. Where templates are different, this could trigger filing of a new application.



Amendments (Biologics 1)

- In addition to those described for Pharmaceutical drugs, amendments are expected for extension to shelf life where the original expiry dating was < 18 mo. and where modifications to existing facilities are proposed.
- For more significant changes, a new Clinical Trial Application may be required



Amendments (Biologics 2)

- A new Clinical Trial Application may be required when:
 - A new facility is used for fabrication
 - Changes are made to biological starting materials
 - Changes are made to expression systems
 - Changes are made to the purification process
 - Changes are made to the dosage form (e.g. lyo to liquid formulation), or to final product strength)
 - Significant changes to DS or DP specifications



Plenary Discussion: Amendments

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Thank You!



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Selected Quality Issues for Clinical Trial Drugs

Presentation to:
**APEC Advanced Workshop on Review of Drug Development in Clinical Trials
Bangkok Thailand Feb 2-6 2009**

**Willem Stevens Ph.D., Chief
Plasma Derivatives Division
Centre for Biologics Evaluation
Biologics & Genetic Therapies Directorate**



Context for Review

- What is the intended use, patient population, size of trial?
- What is the phase of trial and stage of development of the drug?
- What is already known about the product?
 - Previous trials
 - Drug development
- Is product type/class known to have specific quality concerns (e.g. problematic impurities, previous safety issues)
- What is the level of experience of the manufacturer and the degree of their involvement in drug development?
- Is there enough data present to assess the safety of the drug from a Quality (CMC) standpoint and is the data supportive?



Issue: Indirect Access to data

- In some cases the Clinical Trial Sponsor has limited access to detailed manufacturing information. Approaches include:
 - Parallel data filing by fabricator and sponsor
 - Reference to an existing approved submission
 - Reference to a Drug Master file
- Necessary to treat proprietary data appropriately



Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Issue: Limited Stability Data

- Is there data in place to support the continued acceptability of the product for the duration of the trial
- If full data isn't available is there a commitment to monitor actual clinical batches (or representative batches) throughout the duration of the trial and a summary of the testing to be performed and the test stations?
- Is accelerated stability data provided?
- For drug products that are reconstituted or diluted, is there data to support the proposed in-use period?
- Should be using principles in ICH Q1A-E (Pharmaceuticals) and Q5C (Biologics)



Issue: Limited Stability Data

Expectation: Data to support that product will remain in specification for the duration of the trial.

- Data often limited in terms of # of lots and real-time data
- From data available is there evidence for changes to key parameters on storage?
 - Do these changes have implications for Safety? Efficacy?
- Is there a commitment to conducting ongoing real-time stability studies and lots enrolled? For Biologics: may need an amendment to extend expiry dating



Case Study # 1



Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Issue: Pharmaceutical Development

- As development of formulation and manufacturing process proceeds expect some changes in formulation and process optimization. Is there a comparison of the current formulation (or process) with earlier iterations? Do these changes impact the relevance of earlier studies (e.g. stability)?
- Is there an assessment of the potential impact of changes on extrapolation of results from pre-clinical earlier clinical trials to the proposed trial?
- The scientific rationale for the approach taken should be provided



Issue: Pharmaceutical Development

- Whenever the manufacturing or purification process is adjusted (e.g. to address an undesirable impurity) the potential exists for introduction of new impurities or product variants.
- If the product attributes have changed, is the necessary data in place to link current and previous materials? Is it still possible to use results from pre-clinical or earlier clinical trials to support the proposed trial?
- There should be a continuous “storyline” leading from early studies to the product intended for market.



Case Study # 2



Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Issues: Analytical Methods/Specifications

- It is fairly common for analytical method development and validation to proceed along with the development of the product and manufacturing process.
- The amount of data in place required to support the suitability of analytical methods is dependant on several factors:
 - Stage of clinical development
 - Criticality of parameter measured
 - Specification limits for parameter measured
 - Type of measurement being made



Case Study # 3



Plenary Discussion

- Concerns?
- Unresolved issues?
- Additional Clarification?
- Experiences to Share



Thank You!

Questions?



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Review principles of dose selection

Junko Sato

Review Director, Office of New Drug I
Pharmaceuticals and Medical Devices Agency
(PMDA)

Current guideline

Dose-Response information to support Drug Registration http://www.ich.org/LOB/media/MEDIA480.pdf	ICH-E4, 1994
Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications http://www.fda.gov/cder/guidance/5341fn1.pdf	FDA, 2003
Point to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antimicrobial Medicinal Products http://www.emea.europa.eu/pdfs/human/ewp/265599en.pdf	EMA, 2000

How to choose dosage ? -at beginning of Ph2-

- ◆ Non-clinical data
 - ❖ Pharmacology
 - ❖ Toxicology
 - ❖ PK/PD in animal models
- ◆ PK in healthy volunteers (PhI)

➔ 2 or more dosages
will be chosen for
Ph3 studies



How much ? How often ?

How to choose dosage ? -at beginning of Ph3-

- ◆ Result of Ph2
 - ❖ Which dosage is more effective than other dosage?
 - ❖ Which dosage is safer than other dosage?

↓

Benefit/Risk balance is important !



How to judge benefit/risk balance ?

- ◆ Benefit > Risks
- ◆ All drugs have some side effects.
 - ❖ Can the risk be managed?
 - ❖ How to manage the risks?
- ◆ Does the benefit exceed the risk?
- ◆ Benefit/Risk balance is not judged by absolute value of ADRs. It is judged relatively.

	AC*
	N=1492
Treatment administration	
Mean number of cycles	3.8
Total cycles	5676
Adverse events, % of patients	
Leukopenia	
Grade 3 (1,000-1,999 /mm ³)	3.4
Grade 4 (<1000 /mm ³)	0.3
Thrombocytopenia	
Grade 3 (25,000-49,999 /mm ³)	0
Grade 4 (<25,000 /mm ³)	0.1
Shock, sepsis	1.5
Systemic infection	2.4
Nausea and vomiting	
Nausea only	15.5
Vomiting ≤12 hours	34.4
Vomiting >12 hours	36.8
Intractable	4.7
Alopecia	
Partial	92.4
Complete	22.9
Weight loss	
5-10%	6.2
>10%	2.4
Weight gain	
5-10%	10.6
>10%	3.8
Cardiac function	
Asymptomatic	0.2
Transient	0.1
Symptomatic	0.1
Treatment-related death	0

Example:

These ADRs are reported in the clinical trial of oral antimicrobial agents.

Can you approve it ?

Pharyngitis ?



Is benefits larger than risks ?

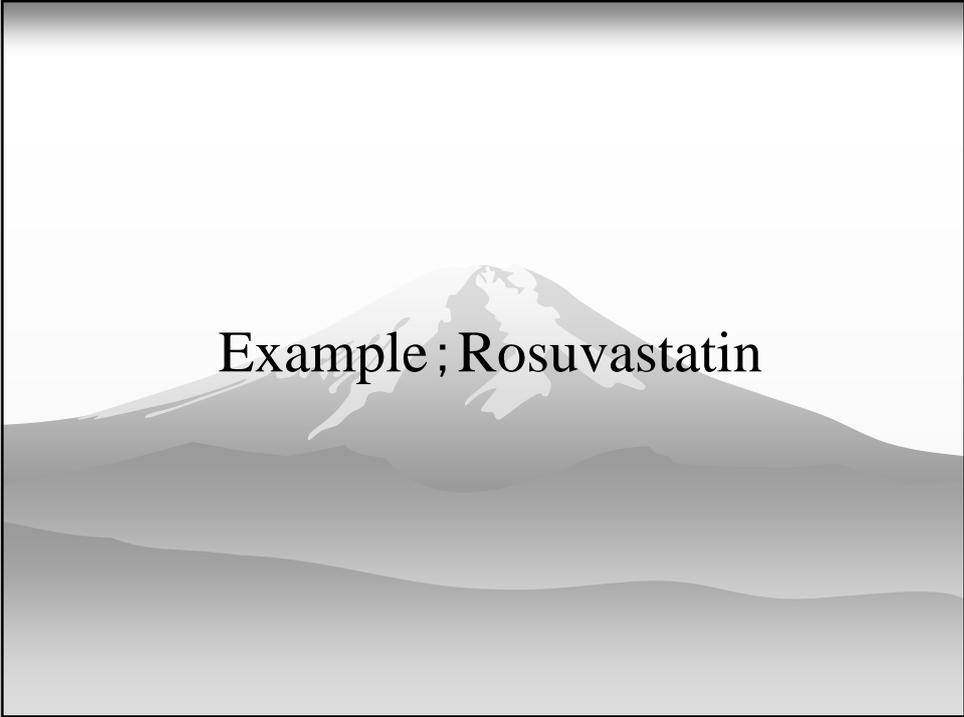
Tonsillitis ?

Table 6: Common (≥1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN®

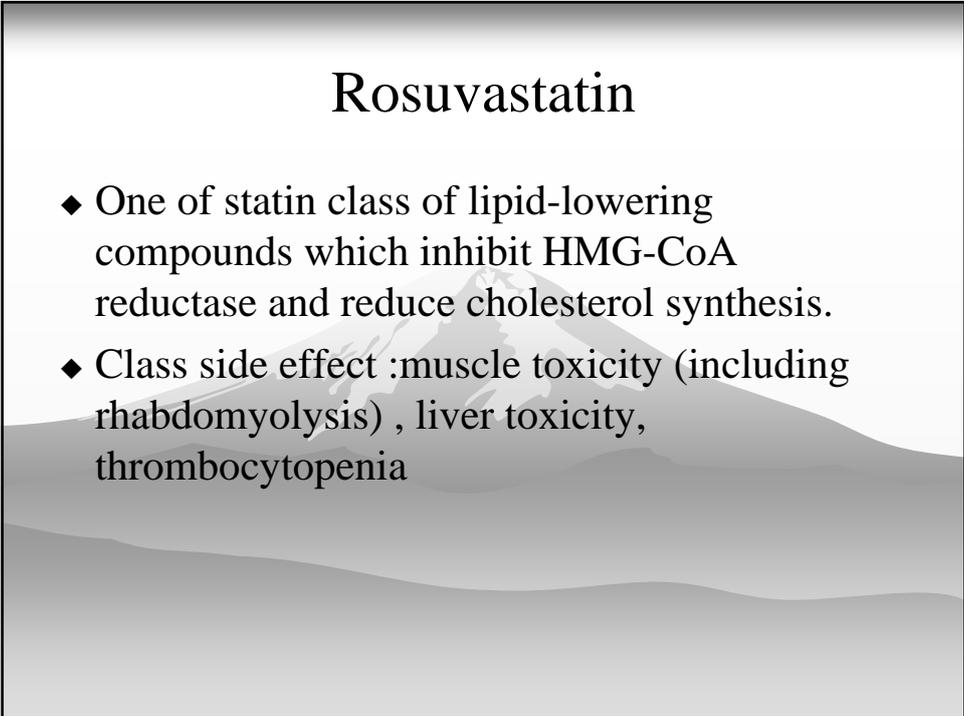
System/Organ Class	Adverse Reaction	% (N=7537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia ^a [see Warnings and Precautions (5.5)]	4
Nervous System Disorders	headache	6
	dizziness [see Warnings and Precautions (5.5)]	3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea [see Warnings and Precautions (5.2)]	1
Gastrointestinal Disorders	nausea	7
	diarrhea	5
	constipation	3
	abdominal pain	2
	vomiting	2
	dyspepsia	2
Skin and Subcutaneous Tissue Disorders	rash [see Warnings and Precautions (5.2)]	2
	pruritus	1
Reproductive System and Breast Disorders	vaginitis	1 ^b
General Disorders and Administration Site Conditions	edema	1
	injection site reaction	1
	chest pain	1

Acceptable risks

- ◆ Magnitude of acceptable risks depend on magnitude of benefit
- ◆ If available benefit are large, magnitude of acceptable risk will be large.
- ◆ Manageable ?
 - ❖ Measure to avoid risks
 - ❖ Early detection



Example ; Rosuvastatin



Rosuvastatin

- ◆ One of statin class of lipid-lowering compounds which inhibit HMG-CoA reductase and reduce cholesterol synthesis.
- ◆ Class side effect : muscle toxicity (including rhabdomyolysis) , liver toxicity, thrombocytopenia

Efficacy

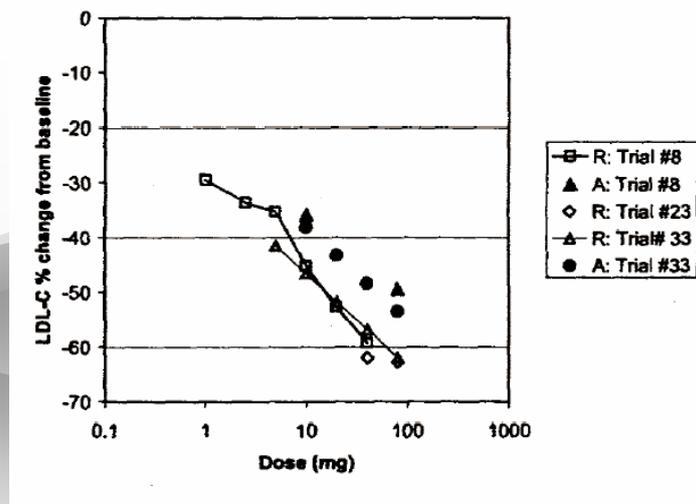
Table 1
Rosuvastatin Dose Response vs. Placebo
Mean % Change from Baseline to Week 6
Type IIA/IIIB Dyslipidemia: Trials 8 and 23 Pooled*

Efficacy Endpoint	Placebo	Rosuvastatin Dose						
	(N=31)	1.0 mg (N=14)	2.5 mg (N=15)	5 mg (N=18)	10 mg (N=17)	20 mg (N=17)	40 mg (N=34)	80 mg (N=31)
LDL-C								
BL, mg/dL	194	191	190	191	190	191	185	188
LS mean %	-3.8	-33.2***	-39.6***	-42.6***	-49.8***	-53.1***	-62.2***	-64.9***
change (SE)	(1.7)	(2.8)	(2.7)	(2.6)	(2.6)	(2.6)	(1.6)	(2.1)
TC								
BL, mg/dL	271	267	265	268	267	268	261	263
LS mean %	-2.5	-22.5***	-28.1***	-31.1***	-34.4***	-38.4***	-45.1***	-46.8***
change (SE)	(1.4)	(2.3)	(2.2)	(2.1)	(2.1)	(2.1)	(1.4)	(1.7)
HDL-C								
BL, mg/dL	53	55	49	53	50	51	52	51
LS mean %	3.2	9.4	8.8	13.7*	14.6*	8.2	10.1	14.1**
change (SE)	(2.1)	(3.5)	(3.3)	(3.2)	(3.2)	(3.2)	(2.0)	(2.6)
TG								
BL, mg/dL	122	116	133	121	135	134	117	119
LS mean %	-1.9	-17.0	-11.6	-34.2**	-8.9	-21.9	-27.4**	-24.6**
change (SE)	(4.8)	(7.8)	(7.6)	(7.2)	(7.2)	(7.2)	(4.5)	(5.8)

Table 5 LSE Data derived from tables on pages A63, A66, A69, A72, A84, A87, A101, A597 to A604 in Appendix A.
 * Main analysis of LOCF data from the ITT population. BL = baseline; N = All subjects in ITT population; SE = standard error.
 p<0.05 versus placebo; ** p<0.01 versus placebo; *** p<0.001 versus placebo.

Rosuvastatin : D/R relationship

D/R : Dose/Response



Compare efficacy with other statins

Percent Change in LDL-C From Baseline to Week 6 (LS Mean*)

Treatment	10 mg	20 mg	40 mg	80 mg
CRESTOR	-46 [†]	-52 [‡]	-55 [§]	---
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	---

(sample sizes ranging from 156–167 patients per group)

Safety

- ADRs in each dosage -

Adverse Reactions	CRESTOR 5 mg N=291	CRESTOR 10 mg N=283	CRESTOR 20 mg N=64	CRESTOR 40 mg N=106	Total CRESTOR 5 mg – 40 mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

* Adverse reactions by COSTART preferred term.

(% of Patients)

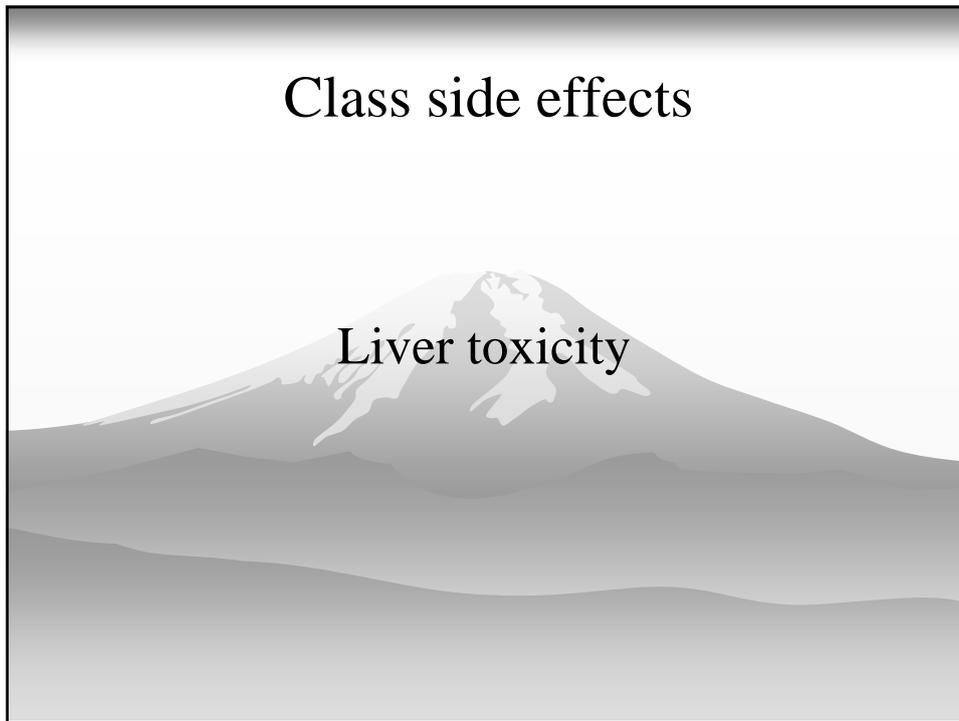


Table 6
ALT Elevations in the Rosuvastatin All Controlled/Uncontrolled and RTLD Pool

	5mg		10mg		20mg		40mg		80mg	
	N	%	N	%	N	%	N	%	N	%
Single elevations	(1317)		(7726)		(3882)		(3957)		(1574)	
>3xULN	14 ^a	1.1	61 ^a	0.8	26	0.7	44 ^a	1.1	62 ^a	3.9
>6xULN	0	0	9	0.1	2	0.05	4	0.1	15 ^b	1.0
>9xULN	0	0	3	0.04	1	0.03	1	0.03	8 ^b	0.5
Multiple elevations										
>3xULN	5	0.4	9	0.1	4	0.1	15	0.4	22	1.4
>6xULN	0	0	3	0.04	0	0	1	0.03	6	0.4
>9xULN	0	0	0	0	0	0	1	0.03	4	0.3

^aWhile rhabdomyolysis can also be associated with elevations in transaminases most of the mild elevations in ALT > 3xULN reported here were not associated with CK elevations > 10xULN. Only 19/207 pts with ALT > 3xULN also had CK elevations >10xULN. One on 5 mg, two on 10 mg, four on 40 mg and 12 on 80mg.

^bAt the higher transaminase elevations 6/30 patients with ALT>6xULN and 2/13 with ALT >9xULN also had CK > 10xULN but all were at the 80 mg dose of rosuvastatin

Data were derived from AV_LUBR.xpt data file submitted 5/20/03. Where the lab ULN was not known from data in the Lab.xpt dataset submitted 6/26/01, it was assumed that 3xULN=75 which was true for most values in the dataset.

Table 7
Dose Related Incidence of Persistent Transaminase Elevations in Statins in Clinical Trials

Statin	Placebo	10 mg	20 mg	40 mg	80 mg
Pravachol	0.3%			0.3%	
Mevacor	0.1%		0.1%	0.9%	1.5%
Lipitor		0.2%	0.2%	0.6%	2.3%
Zocor				0.9%	2.1%
Lescol			0.2%	1.5%	2.7%

Data taken from currently approved labels or NDA19898/Se8-042.

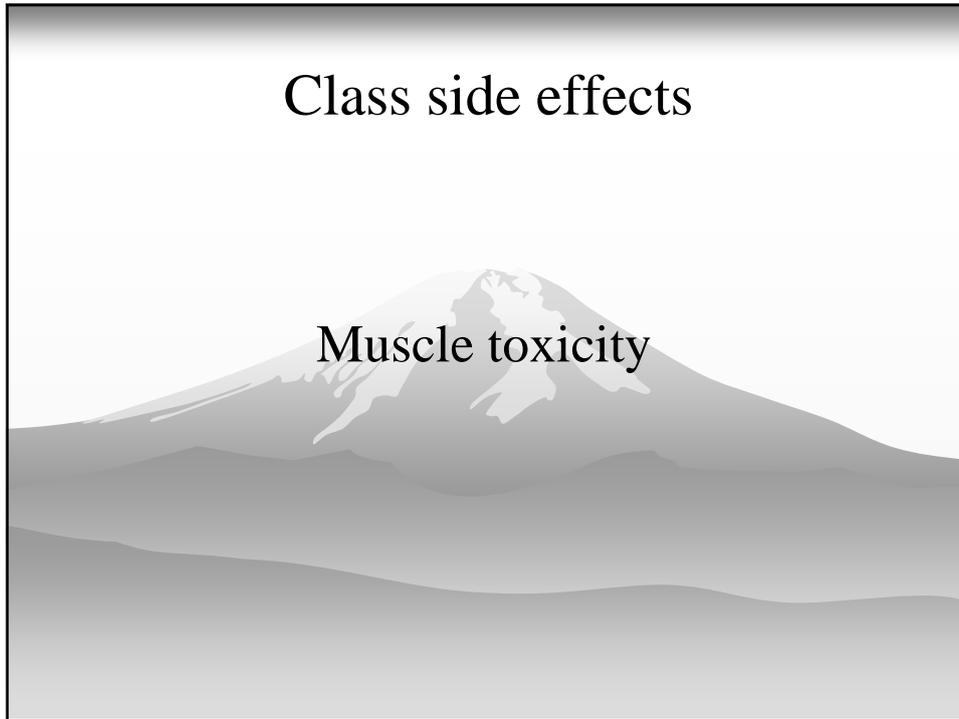


Table 8
CK ELEVATIONS IN THE ALL CONTROLLED POOL*

	5mg		10mg		20mg		40mg		80mg	
Rosuvastatin	N=833	%	N=3193	%	N=2113	%	N=2804	%	N=988	%
CK >5xULN	7	0.8	8	0.3	7	0.3	28	1.0	11	1.1
CK >10xULN	3	0.4	4	0.1	3	0.1	11	0.4	9	0.9
	Placebo		10mg		20mg		40mg		80mg	
Atorvastatin	N=381	%	N=1573	%	N=1772	%	N=522	%	N=555	%
CK >5xULN	0	0	8	0.5	7	0.4	3	0.6	2	0.4
CK >10xULN	0	0	1	0.1	2	0.1	0	0	0	0
			10mg		20mg		40mg		80mg	
Simvastatin			N=163	%	N=127	%	N=532	%	N=501	%
CK >5xULN			2	1.2	2	0.2	0	0	3	0.6
CK >10xULN			2	1.2	1	0.1	0	0	2	0.4
			10mg		20mg		40mg			
Pravastatin			N=161	%	N=416	%	N=751	%		
CK >5xULN			2	1.2	2	0.5	0	0		
CK >10xULN			0	0	0	0	0	0		
					0.3mg		0.4mg		0.8mg	
Cerivastatin					N=64	%	N=54	%	N=45	%
CK >5xULN					0	0	0	0	1	2.2
CK >10xULN					0	0	0	0	0	0

*Data were derived from AV_LBUR.xpt submitted 5/20/03 to the EDR. Data includes only patients on monotherapy lipid lowering drugs and excludes patients in OLE (open label extension), i.e. ISS-ALL CONTROLLED STUDIES= Yes.

Table 9
CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN IN THE ALL CONTROLLED/UNCONTROLLED and RTLD POOLS*

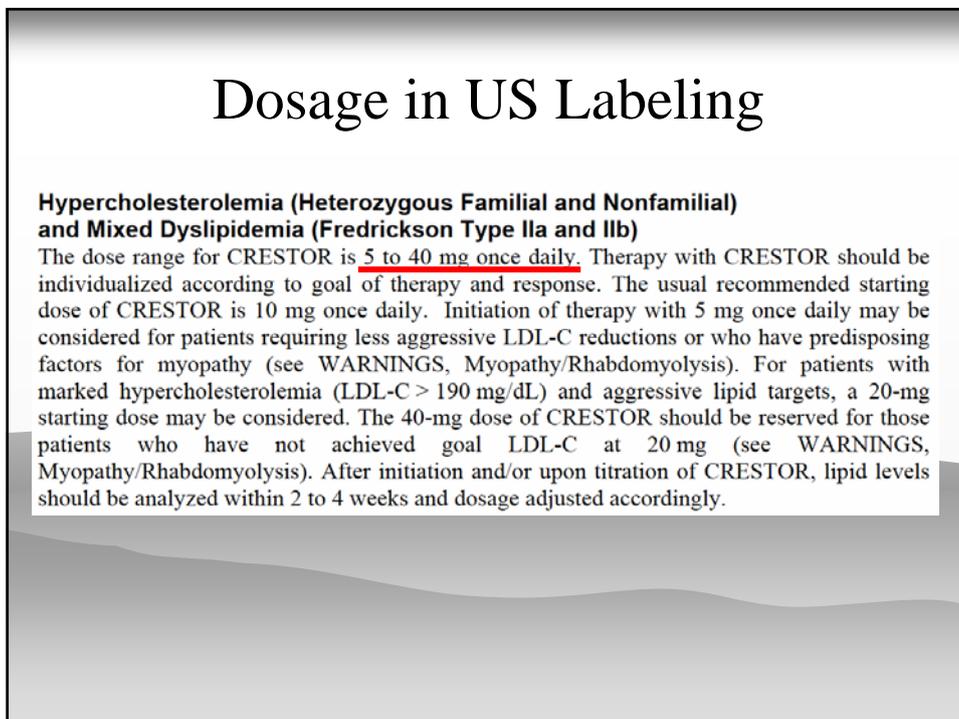
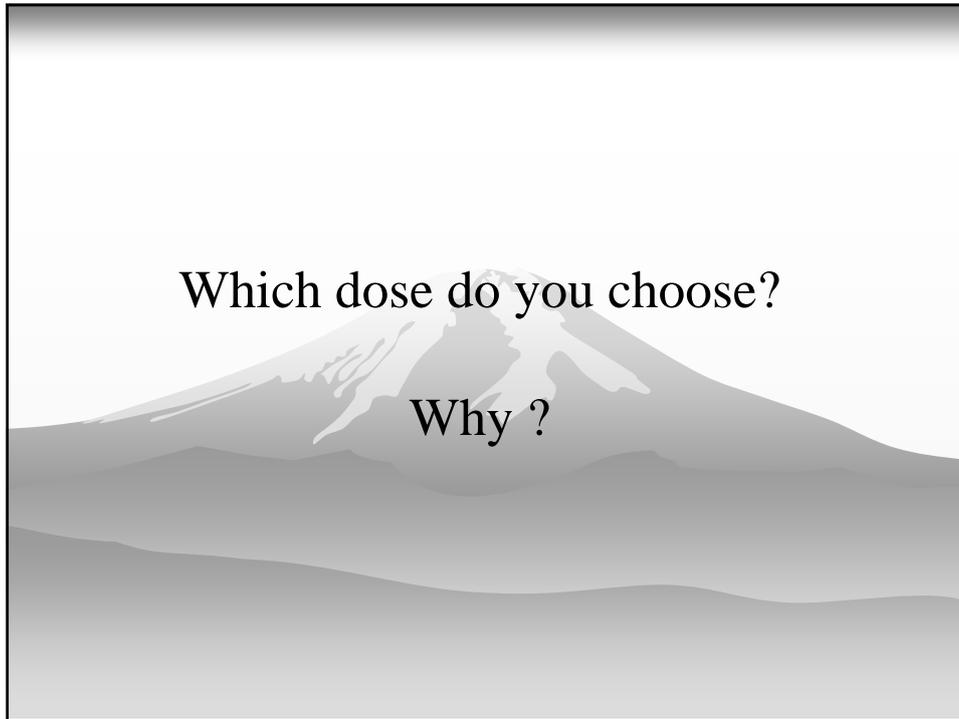
	5mg		10mg ^b		20mg		40mg		80mg	
	N (1317)	%	N (7727)	%	N (3883)	%	N (3700)	%	N (1574)	%
Single CK elevations										
CK >5xULN	14	1.1	69	0.9	19	0.5	39	1.1	55	3.5
CK >10xULN	5	0.4	17	0.2	7	0.2	15	0.4	30	1.9
Multiple CK elevations										
CK >5xULN	3	0.2	11	0.1	3	0.08	7	0.2	21	1.3
CK >10xULN	3	0.2	1	0.01	1	0.03	5	0.1	12	0.8
Single CK elevations associated with Alt >3xULN^c										
CK >5xULN	1	0.08	2	0.03	0	0	4	0.1	16	1.0
CK >10xULN	1	0.08	2	0.03	0	0	4	0.1	12	0.8
Single CK Elevations associated with clinical symptoms										
Myopathy (All)	3	0.2	9	0.1	4	0.1	6	0.2	16	1.0
Myopathy (Not related to exercise or injury)	0	0	1	0.01	1	0.03	1	0.03	11	0.7
Rhabdo or IV hydration ^d	0	0	1	0.01	0	0	0	0	7	0.4

*Data were derived from AV_1BUR.rpt submitted 5/20/2003 to the EDR. Data includes only patients on monotherapy with rosuvastatin and includes patients in double-blind controlled and open-label extension phases. Data includes RTLD pool and data from local labs. Data on 40mg patients does not include patients down titrated from 80mg. Patients with CK elevations in both controlled pool and open label extension were counted only once.
^bIncludes data from a initial Med Watch report on a 75 y/o female in the GISSI-HF study diagnosed with rhabdomyolysis on 4/20/03 see appendix for full case report
^cALT: 75UL. ^dAll patients diagnosed with rhabdomyolysis received IV hydration, two other patients who had peak CK's of 34,548 and 16,280 U/L with increased plasma myoglobin were also hospitalized for IV hydration but did not get a formal diagnosis of rhabdomyolysis.

Table 10
CK Elevations, Myopathy and Rhabdomyolysis in Pre-Approval Clinical Trials

Statin	Approval	NDA Dose	Pts N	CK>10xULN % (N)	Myopathy % (N)	Drug Stopped % (N)	Hospitalized IV Hydration % (N)
Pravastatin 19-898	Oct. 1991	5-40	1,925	0.1% (2)	0.1% (2) (1 clofibrate)	0.2% (3)	0
S-046 Se-000 4F	Dec. 2001 (Phase IV)	80	581	0.9% (5)	0.4% (2)	0.3% (2)	0
Unapproved (Phase IV)		160	604	0.3% (2)	0	0.2% (1)	0
Simvastatin 19-766	Dec. 1991	5-40	2,423	0.6% (13)	0.04% (1)	0.1% (2)	0
S-026	July 1998 IIs, III	80	669	0.7% (5)	0.5% (5) (1 nefazodone + clarithromycin, 1 verapamil)	0.7% (5)	0
Merck press release 5/19/97	GEM extended release form	160	-400	-0.8% (3)	-0.8% (3)		-0.8% (3)
Fluvastatin 20-261	Dec. 93	20-40	2,342	0.1% (3)		0.1% (2)	0
21-192	Nov. 1999	40	543	0.4% (2)			0
21-192	Nov. 1999	80 XL	912	0%			0
Atorvastatin 20-702	Dec. 1996	10-40	1,965	0.4% (8)			0
	April 2000	80	346	0.9% (3)			0
Protocol A2581042	Phase IV	10-40	688	0.3% (2)	0%	0.1% (1) (20mg)	0
	"	80	231	0%			0
Lovastatin 19-643	Aug. 1997	5-80	873	N/A	N/A	0	0
Cerivastatin	June 1997	0.05-0.3	2,815	0%			0
S-002	May 1999	0.4	448	0.2% (1)		0.7% (3)	0
S-008	July 2000	0.4	193	1.55% (3)	1.55% (3) (1 gemfibrozil)		0*
S-008	July 2000	0.8	770	2.1% (16)	1.0% (8)		0*
Rosuvastatin		5	1,317	0.4% (5)	0.2% (3)	0.2% (2)	0
		10	7,728	0.2% (17)	0.1% (9)	0.04% (3)	0.01% (1)
		20	3,883	0.2% (7)	0.1% (4)	0.08% (3)	0
		40	3,700	0.4% (15)	0.2% (6)	0.1% (4)	0
		80	1,574	1.9% (30)	1.0% (16)	0.8% (13)	0.4% (7)

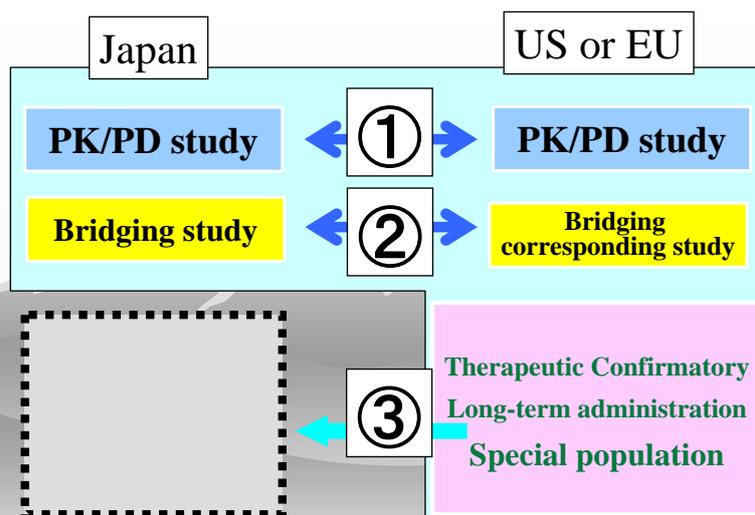
*Possible cases of rhabdomyolysis may have been labeled as myopathy only.



Review of rosuvastatin in Japan

- ◆ Rosuvastatin was approved in US with 5-40mg in US before approval in Japan.
- ◆ ‘Bridging’ strategy was used for development in Japan.

Clinical Data Package in Bridging Strategy



Ethnic difference in LDL Level

- ◆ Serum cholesterol level in US subjects is higher than Japanese subjects.



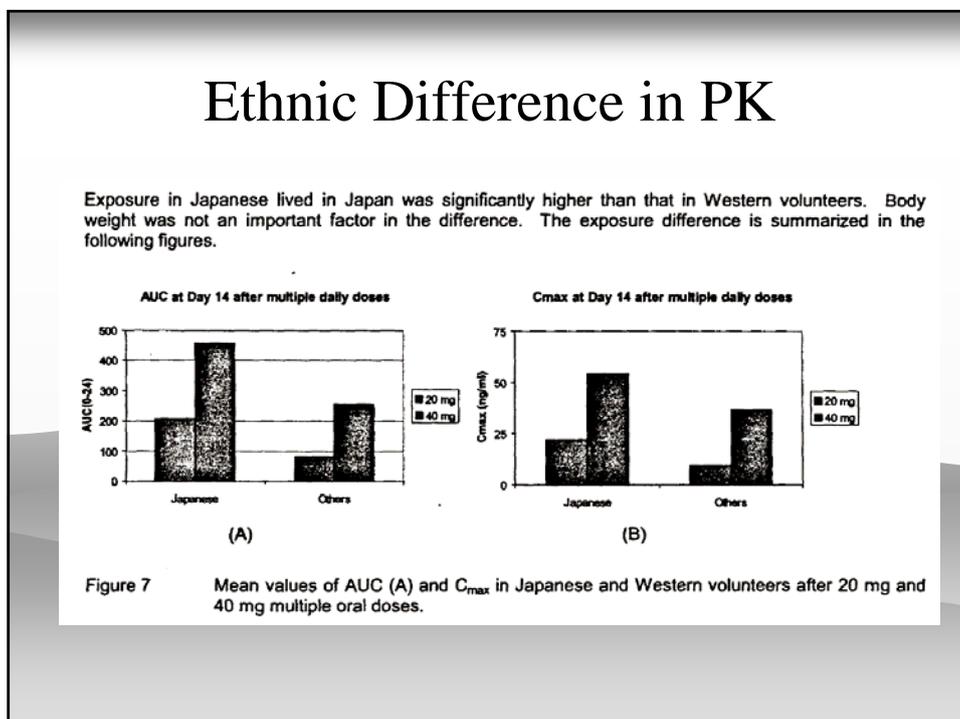
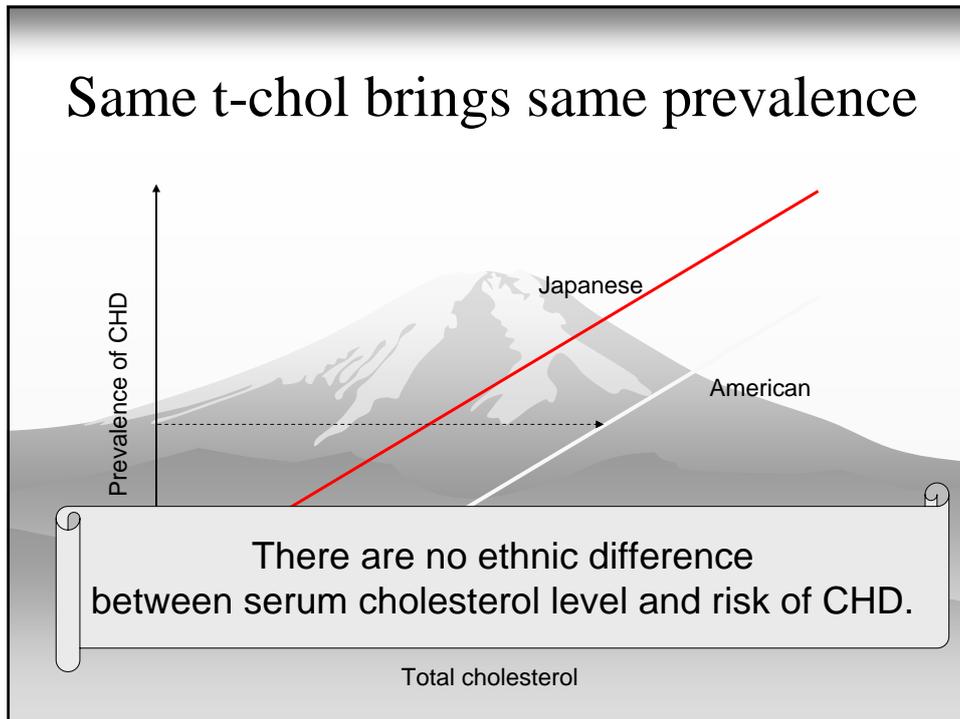
Dose the difference influence efficacy ?

- ◆ Prevalence of coronary heart disease in the Japanese is 1/4 of foreigners.

How to consider these differences ?

From Review report in Japan

- ◆ Serum cholesterol level & prevalence of coronary heart disease are different between Japanese and foreigners.
- ◆ There are no difference below;
 - ❖ Relationship between total cholesterol & prevalence of CHD
 - ❖ Relationship between total cholesterol & mortality



How about E/R ?

LDL-C(F式)		プラセボ 11例	本薬群					
			1 mg 15例	2.5 mg 17例	5 mg 12例	10 mg 14例	20 mg 18例	40 mg 13例
前値 ^a (mg/dL)	平均 ±SD	190.04 ±13.79 (15例)	184.04 ±14.96 (16例)	184.93 ±11.89 (18例)	181.27 ±12.06 (15例)	182.19 ±15.93 (15例)	185.84 ±15.93 (19例)	181.00 ±10.40 (14例)
6週時値 (mg/dL)	平均 ±SD	182.00 ±16.03	117.40 ±20.45	101.29 ±13.38	86.58 ±11.13	92.50 ±39.48	76.22 ±14.32	62.08 ±8.39
変化率 (%)	平均 ±SD p値 ^b	-3.88 ±7.74 —	-35.63 ±10.29 <0.0001	-44.99 ±6.35 <0.0001	-52.49 ±5.83 <0.0001	-49.60 ±20.94 <0.0001	-58.32 ±9.22 <0.0001	-65.77 ±5.04 <0.0001

a: -2, -1, 0週時の平均値、b: Williams検定 (対プラセボ)

LDL-C(F式)		プラセボ 12例	ロススタチン群					
			1 mg 13例	2.5 mg 13例	5 mg 17例	10 mg 16例	20 mg 13例	40 mg 18例
前値 ^a (mg/dL)	平均 ±SD	196.8 ±15.0	188.7 ±17.0	188.6 ±14.8	192.8 ±15.8	190.0 ±16.2	183.8 ±16.9	184.2 ±19.3
6週時値 (mg/dL)	平均 ±SD	182.0 ±23.3	119.9 ±15.0	108.8 ±14.5	106.7 ±16.6	90.7 ±20.4	75.2 ±19.8	67.8 ±16.4
変化率 (%)	LS mean ±SE	-7.3 ±2.5	-36.2 ±2.4	-42.7 ±2.4	-44.5 ±2.1	-52.4 ±2.2	-58.9 ±2.4	-63.4 ±2.1
プラセボ群との比較	差 (%)	—	-28.9	-35.4	-37.1	-45.1	-51.6	-56.1
	差の95%CI	—	-35.7	-42.2	-43.5	-51.6	-58.5	-62.5
	p値 ^c	—	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

N No. of ADR(Pts.) % No. of ADR(events)	プラセボ 15例	ロススタチン群						合計 97例
		1 mg 18例	2.5 mg 15例	5 mg 15例	10 mg 19例	20 mg 14例	40 mg 14例	
3	0	7	3	2	9	6	27	
20.0	0.0	38.9	20.0	13.3	47.4	42.9	27.8	
4	0	17	4	3	11	30	65	
General disorder	腹痛腫脹	0	0	1(5.6)	0	0	1(5.3)	0
	腹痛	1(6.7)	0	2(11.1)	0	0	1(5.3)	1(7.1)
	顔面浮腫	0	0	1(5.6)	0	0	0	0
	頭痛	0	0	0	0	0	0	1(7.1)
Cardio	心電図異常	0	0	0	0	0	1(5.3)	0
	便秘	1(6.7)	0	0	0	0	0	1(7.1)
GI	下痢	0	0	1(5.6)	0	0	1(5.3)	1(7.1)
	消化不良	0	0	0	0	0	0	1(7.1)
	胃腸出血	0	0	0	0	0	1(5.3)	0
	歯肉炎	0	0	0	0	0	0	1(7.1)
	口過	0	0	0	0	0	1(5.3)	0
Hepato-biliary	肝臓毒	0	0	0	0	1(6.7)	0	1(1.0)
	γ-GTP上昇	0	0	1(5.6)	1(6.7)	1(6.7)	0	3(3.1)
	LDH上昇	0	0	0	1(6.7)	0	0	1(1.0)
	血清 GOT (AST)上昇	0	0	0	0	0	0	2(2.1)
	血清 GPT (ALT)上昇	0	0	0	0	0	1(5.3)	2(2.1)
blood	貧血	0	0	1(5.6)	0	0	0	1(1.0)
	白血球減少症	0	0	0	0	0	0	1(7.1)
metabo	CK上昇	0	0	0	2(13.3)	0	1(5.3)	1(7.1)
	体重増加	0	0	1(5.6)	0	0	0	1(1.0)
muscle	筋痛	0	0	0	0	0	1(5.3)	0
	浮腫性めまい	0	0	1(5.6)	0	0	1(5.3)	1(7.1)
neuro	高血圧	0	0	1(5.6)	0	0	0	1(1.0)
	筋緊張亢進	0	0	1(5.6)	0	0	0	1(7.1)
	視覚	0	0	1(5.6)	0	0	0	2(2.1)
speci-sence	血糖例糖	0	0	0	0	1(6.7)	0	1(1.0)
	アルブミン尿	0	0	0	0	0	0	3(21.4)
Urinary disorder	膀胱炎	0	0	0	0	0	0	1(7.1)
	血尿	0	0	0	0	0	0	1(7.1)
	尿門柱	0	0	0	0	0	0	1(7.1)
	尿異常	0	0	0	0	0	0	2(14.3)

How to choose the dosage?

- ◆ 5-10mg of the drug is superior to 10mg of atorvastatin, 20mg of pravastatin and simvastatin.
- ◆ 80mg wasn't approved in US by occasion for safety, cf. myopathy.
- ◆ The range of efficacy overlapped for 20 mg and 40mg in Japanese, as well as 40mg and 80mg in American.
- ◆ 10mg and 20mg in Japanese weren't overlapped, but risk is a little higher than lower dosage.

Approved dosage in Japan

- ◆ Starting dose : 2.5mg QD
- ◆ If sufficient efficacy is not available after 4 weeks from starting or increasing dose, dose can be increased by 10mg, eventually.
- ◆ If reduction of LDL is insufficient by 10mg administration, dose can be increased by 20mg. 20mg is restricted to use for severe subjects.

Benefit/Risk Balance is Key !

- ◆ If the effect rises along with increasing the dosage, we would like to select higher dosage.
- ◆ But, if risk also increase with dose up, we cannot select higher dosage.
- ◆ On risk evaluation,
 - ❖ Frequency of ADRs
 - ❖ Severity of ADRs
 - ❖ Tolerability in physically and philosophically
 - ❖ Manageable or not
 - ◆ To avoid
 - ◆ For early detection

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Approach to the Critique of High Risk Clinical Trials



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

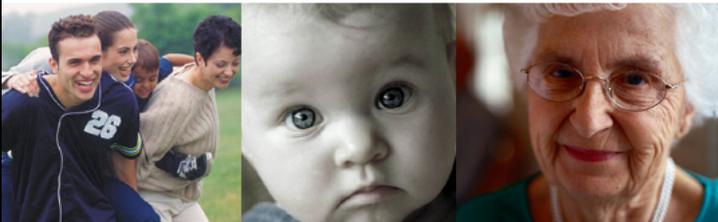
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Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

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If passion drives you, let
reason hold the reins

~ Benjamin Franklin ~



La Raison avant la passion or
Reason over passion

~ Pierre Trudeau

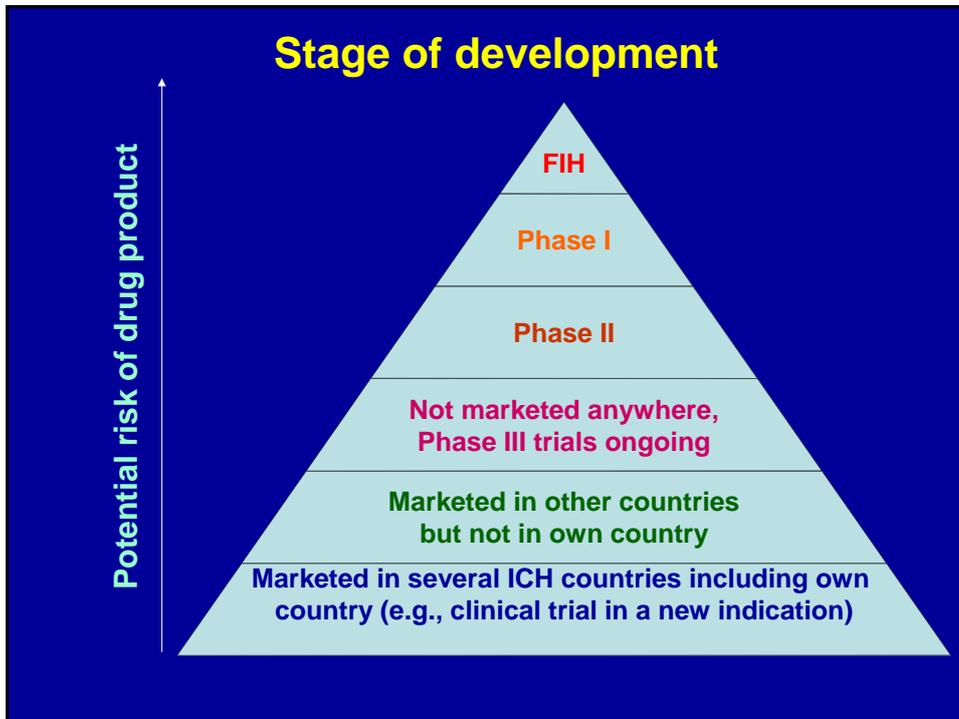
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Fundamental Element

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.



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THE PRINCIPLES OF ICH GCP

E6: 13 elements

1. Clinical trials should be conducted in accordance with the **ethical principles that have their origin in the Declaration of Helsinki**, and that are consistent with GCP and the applicable regulatory requirements.
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. **A trial should be initiated and continued only if the anticipated benefits justify the risks.**
3. The **rights, safety, and well-being of the trial subjects are the most important considerations** and should prevail over interests of science and society.
4. The **available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.**

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ICH GCP: E6: 13 elements

5. Clinical trials should be scientifically sound, and described in **a clear, detailed protocol**.
6. A trial should be conducted in compliance with the protocol that has received **prior** institutional review board (IRB)/independent **ethics committee** (IEC) **approval**/favourable opinion.
7. The **medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician** or, when appropriate, of a qualified dentist.
8. **Each individual involved in conducting a trial should be qualified** by education, training, and experience to perform his or her respective task(s).
9. **Freely given informed consent should be obtained from every subject prior** to clinical trial participation.



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ICH GCP: E6: 13 Elements

10. All **clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification**.
11. The **confidentiality of records** that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable **good manufacturing practice** (GMP). They should be used in accordance with the approved protocol.
13. Systems with **procedures that assure the quality of every aspect** of the trial should be implemented.



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EMA guidance: FIH CTs with IMPs Strategies to identify and mitigate risks

Considers

- *Quality*
- *Non-clinical*
- *Clinical testing strategies and designs*



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FIH guidance (like most) is not stand alone

Should be considered with:

- Non clinical guidance on
 - Quality of pharmaceuticals - M3
 - Preclinical safety of biotechnology derived products - S6
 - QT interval prolongation - S7B
 - Safety pharmacology – S7A
 - Toxicokinetics – S3A
- Clinical aspects
 - GCP – E6
 - general considerations – E8
 - Monitoring and Pharmacovigilance

Does not apply to Gene and Cell therapies



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FIH CTs as in all CTs Safety is Paramount

- Experimental approaches should be science based
- Justified on a CASE-BY-CASE basis
- Ability of non-clinical testing may be limited
- Dose determination is key both, initial and subsequent escalations and intervals between doses
- defining a development program is an iterative process integrating safety needs from many sources - includes the regulator



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Quality

- Attributes should not be a source of risk!
- Should be considered in a risk assessment preceding FIH trials
- Non-clinical studies should be representative of the material for FIH



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Non-clinical Aspects

- Demonstration of relevance of animal model
- Pharmacodynamics
- Pharmacokinetics
- Safety pharmacology
- Toxicology
- Estimation of first dose
 - NOAEL - No Observed Adverse Effect Level
 - MABEL - Minimum Anticipated Biological Effect Level



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Identifying Factors of Risk

- Mode of Action
- Nature of the target
- Relevance of the animal models
- All case-by case



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Mode of Action

- Novelty / extent of knowledge of supposed mode of action
- Nature and intensity; extent, amplification, duration, reversibility
- Dose response linear or non-linear?
- Connected to multiple signally pathways?
- Biological Cascade or cytokine release
 - eg. immune system, blood coagulation system
- Related to compound with similar modes of action
- Are there animal models?
 - Transgenic, knock-in or knock-out animals
 - Enhanced receptor interaction



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Nature of Target

- Structure
- Tissue distribution (including expression in/on human immune cells)
- Cell and disease specificity, regulation
- Polymorphisms of target in relevant animal species
- Does the relevant animal model take into account the following comparisons to humans;
 - Target
 - Structural homology
 - Distribution
 - Signal transduction pathway
 - If model is questionable should be considered by the sponsor!



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Drug Product, Type or Class

- Route of administration: oral, intravenous, intramuscular, subcutaneous, inhalation, intranasal, topical (local or systemic)
- Pharmaceutical, biologic, radiopharmaceutical: is it a novel class of drug substance/product? (e.g., nanosuspension, oligonucleotide, gene therapy)
- Potential risks with drug product or class, such as:
 - immunogenicity (e.g., PRCA)
 - hypersensitivity
 - human-sourced excipients (e.g., risk of BSE, viruses, etc.)
 - immunosuppression
 - birth defects
 - QT-prolongation
 - drug-dependence
 - liver toxicity
 - other...



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Disease Target

- Morbidity and mortality of the disease
- Prevalence of the disease
- Availability of current therapies
- Current clinical practice guidelines
- Potential for exaggerated pharmacodynamic effects



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Subject Population

- Healthy adults
- Adult patients
- Elderly patients
- Pregnant women
- Paediatric
- Vulnerable patients
- *Pharmacogenomic considerations*



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Clinical Aspects

- General
 - Design to mitigate risk; study population, trial sites, route and rate of administration, # per dose (cohort size), sequence and interval between dosing within a cohort, dose escalation increments and transition, stopping rules,
 - Rapid access to treatment allocation of codes (for placebo if applicable)
- Choice of subjects
 - Should be fully justified on case-by-case
 - Is risk quantified and justified and include short and long term toxicity?
 - Is the lack of relevant animal model addressed?
 - Have the potential pharmacogenomics differences between a targeted patient group and health volunteers been considered?
 - Could the trial interfere with the patients potential ability to benefit from other products, interventions or trials?
 - Are the subjects involved or recently involved in another CT?



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Protocol Design

- Route and rate of IV infusion
- Precautions between doses in the same cohort
- Precautions to apply between cohorts
- Dose escalations scheme
- Stopping rules
- Monitoring and communication of ADRs
 - expedited reporting of SUSARS to National Competent Authority (regulator) , REB and Investigators
- Facilities and personnel
 - Adequate and appropriately trained
 - Immediate access to resuscitation and stabilizing equipment for;
 - Cardiac emergencies
 - Anaphylaxis
 - Convulsions
 - Hypotension
 - Cytokine release syndrome
- Ready availability to an ICU
- Adequate rationale for more than a single site



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Strategies for mitigating risk

- Calculation of initial dose
- Subsequent dose escalations
- Conduct of the CT



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Scanning the Application

- *To determine the amount of risk and if there could be major gaps – As a manager or Chief – who do you assign this review to???*
- This helps in prioritization, obtaining information and mobilizing expertise for decision-making:
 - Stage of development / phase of trial?
 - Disease target?
 - Subject population?
 - Potential safety concern(s) in drug class?
 - Sponsor?



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Who is the Sponsor ?

- Large pharmaceutical company
- Small pharmaceutical or biotech
- Domestic or foreign
- Academic
- Disease cooperative or group

Protection of clinical trial participants always prevails



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Informed Consent

Section 4.8 of ICH E6

The ICH definition:

Process by which a subject voluntarily confirms their willingness to participate in a particular trial after having been informed of all aspects of the trial that are relevant to a subject's decision to participate. It is documented by means of a written signed and dated ICF.



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20 Elements (a) – (t) of the ICF according to GCP

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- (a) That the trial **involves research**.
- (b) The **purpose** of the trial.
- (c) The **trial treatment(s) and the probability for random assignment** to each treatment.
- (d) The **trial procedures** to be followed, including all invasive procedures.
- (e) The **subject's responsibilities**.



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20 Elements (a) – (t) of the ICF according to GCP

- (f) Those aspects of the trial that are **experimental**.
- (g) The reasonably **foreseeable risks or inconveniences** to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- (h) The **reasonably expected benefits**. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- (i) The **alternative procedure(s) or course(s) of treatment** that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated prorated payment, if any, to the subject for participating in the trial.
- (l) The anticipated expenses, if any, to the subject for participating in the trial.



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20 Elements (a) – (t) of the ICF according to GCP

- (m) That the subject's **participation in the trial is voluntary and that the subject may refuse to participate or withdraw** from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory **authority(ies) will be granted direct access to the subject's original medical records for verification** of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- (o) That **records identifying the subject will be kept confidential** and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- (p) That the subject or the subject's legally acceptable representative will **be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial**.



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20 Elements (a) – (t) of the ICF according to GCP

- (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- (r) The **foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.**
- (s) The **expected duration** of the subject's participation in the trial.
- (t) The **approximate number of subjects** involved in the trial.



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Can Risk Benefit Concerns be Mitigated Through the ICD?

- More clearly state availability of alternative treatment
- More clearly identify risks, including all procedures
- Clearly identify voluntary aspect of both enrolment and continuation
- Ensure benefits are not overstated
- Language is appropriate
 - easily understood by subjects



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FIH Overview

TeGenero Exercise



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

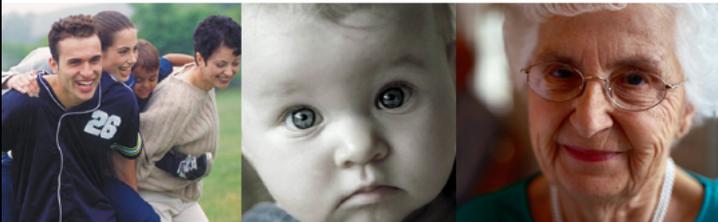
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February 02, 2009

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FIH Overview

- Phase 0
- Phase 1
- Core Toxicology
- Considerations for Biologics
- Preclinical testing for Cytotoxic / Cytostatic Drug
- Dosing in Oncology

TeGenero Exercise



3

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Common Deficiencies of Phase I Proposals

- Insufficient pre-clinical data
- No animal model or data in animals is unreliable
- Healthy volunteers vs. patients
- Early human data driven by lack of resources
 - “to get some human data”
- Limited human data is from a patient population that is irrelevant to CT proposal



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Phase 0 Trials

- Oncologic drug discovery
- Increased insights into basic tumour cell biology
- Only 5-10 % progress beyond early phase
 - Leading cause of attrition now lack of clinical activity versus toxicity
- Lack of predictability of toxicity and effect using traditional animal models
- Attempt to shorten cancer drug development timelines
- “Exploratory IND” FDA guidance pages 13-17
- Proof of principle, pharmacodynamically driven, phase 0 trials



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Phase 0 - Patient perspective

- Potential
 - Harm (including biopsies)
 - Delay in participation in CTs with possible therapeutic benefit
 - Balanced by lower dose and limited exposure - thus reduced toxicity
- Ethical responsibility to obtain useful results
 - Testing of each biopsy specimen
 - Rigorous attention to assay development
 - Potential for validated assays becoming surrogate markers
- Most likely to provide important information for Investigational Agents that fail to modify intended targets



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Characteristics of Phase I Trials

- Subject population:
 - for lower risk products: **healthy volunteers**
 - for higher risk, potentially toxic (eg. Oncology) or most biologics, **patients are recruited**
- Sample size typically around 20
- Single-dose escalation or repeat-dose range or escalation
- Randomized double-blind parallel group or cross-over
- Single arm, proof-of-concept
- Thorough QT/QTc studies



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Characteristics of Phase I Trials

Endpoints:

- Safety, including effects on QT/QTc interval
- MTD, Recommended Phase 2 Dose (RP2D)
- PK/PD (AUC_t , C_{max} , T_{max} , vs PD markers)
- Bioavailability
- Metabolism and elimination (elimination half-life)
- Drug and food interactions
- Formulation testing / bioequivalence



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Goals of Preclinical Safety Evaluation

The primary goals of preclinical safety evaluation are (ICH S6):

- 1) To identify an initial safe dose and subsequent dose escalation schemes in humans
- 2) To identify potential target organs for toxicity and for the study of whether such toxicity is reversible
- 3) To identify safety parameters for clinical monitoring



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Core Toxicity Evaluation

For single-dose phase I and repeat-dose phase I studies of up to 14 days duration:

- ADME/toxicokinetics in rodent and non-rodent animal species
- Safety pharmacology (cardiovascular, CNS, respiratory – ICH S7A)
- Non-clinical evaluation of the potential for QT-prolongation (ICH S7B)
- Single-dose in 2 mammalian species (ICH M3)
- 14-day repeat-dose in rodent and non-rodent animal species (ICH M3)



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Core Toxicity Evaluation

Genotoxicity studies (ICH S2B):

- A test for gene mutation in bacteria
- An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells **or** an *in vitro* mouse lymphoma tk assay
- An *in vivo* test for chromosomal damage using rodent hematopoietic cells



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Core Toxicity Evaluation

Reproductive toxicity studies (ICH M3):

- Male and female reproductive organs should always be evaluated in the repeated-dose toxicity studies
- Japan - assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial
- EU - assessment of embryo-fetal development should be completed prior to Phase I trials in women of childbearing potential and female fertility studies prior to Phase III trials



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Core Toxicity Evaluation

Reproductive toxicity studies (ICH M3, continued):

- US & Canada - women of childbearing potential may be included in early, carefully monitored studies without reproduction toxicity studies provided appropriate precautions are taken to minimise risk (male and female reproductive organs are evaluated in repeated-dose toxicity studies)
- Pregnant women - Prior to the inclusion of pregnant women in clinical trials, all the reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted, and safety data from previous human exposure are generally needed



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Core Toxicity Evaluation

Local tolerance

- assessment of local tolerance may be part of other toxicity studies



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Considerations for Biologics

ICH S6:
Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- Specifications of test material:
 - It is preferable to rely on purification processes to remove impurities and contaminants rather than to establish a preclinical testing program for their qualification
 - The product should be sufficiently characterised to allow an appropriate design of preclinical safety studies
 - In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies



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Considerations for Biologics

Preclinical safety testing should consider:

- selection of the relevant animal species
- age
- physiological state
- the manner of delivery, including dose, route of administration, and treatment regimen
- stability of the test material under the conditions of use



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Considerations for Biologics

- Safety evaluation programs should normally include two relevant species
- A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)
 - **Comparative affinity Binding data for dose considerations**
- Sample size adequate to assess potential toxicity; frequent and prolonged monitoring (e.g., when using non-human primates)



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Considerations for Biologics

- Measurement of antibodies should be performed when conducting repeated dose toxicity studies
- The effects of antibody formation on PK/PD parameters (**neutralizing effect**), incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered
- Attention should also be paid to the evaluation of possible pathological changes related to immune complex formation and deposition



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Considerations for Biologics

- Standard battery of genotoxicity studies generally not applicable
- Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals
 - To explore carcinogenic potential, may use malignant and normal cell lines
 - When *in vitro* data give cause for concern about carcinogenic potential, further studies in relevant animal models may be needed



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Preclinical Testing for Cytotoxic/Cytostatic Drugs

EMA: Note for guidance on the pre-clinical evaluation of anticancer medicinal products

Drug Activity:

- In vitro activity profile on panel of cell lines
- In vivo animal tumour model

Evaluate Toxicity:

- To establish the MTD to be used to define the starting dose in Phase I
- To identify effects on vital functions and target organ toxicity in relation to drug exposure and “treatment cycles” to support dose escalation in Phase I studies and duration of therapy



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Preclinical Testing for Cytotoxic/Cytostatic Drugs

- Safety pharmacology for compounds with a novel mechanism of action
- Single-dose studies in mice and rats to determine MTD
- Repeated-dose toxicity study of limited duration (2 to 4 weeks or 1 to 2 cycles) in two rodent species to assess target organ toxicity and reversibility of effects
- Rodent and non-rodent for drugs with novel mechanism of action
- Genotoxicity/carcinogenicity not required prior to Phase I and II
- Reproduction toxicity studies not required
- Local tolerance



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Phase I in Oncology

Objectives of Phase 1 oncology trials

- Evaluate safety and tolerance
- Determine dose-limiting toxicity
- Define maximum tolerated dose
- Define optimal biologically active dose
- Determine dose and schedule for initial Phase II efficacy trials
- Evaluate pharmacokinetics (ADME)
- Evaluate effects on molecular target or pathway
- Observe for preliminary evidence of antitumour activity

(Br J Clin Pharmacol. 2006 July; 62(1): 15–26)



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Phase I in Oncology

Goal is to escalate to the MTD rapidly, but safely, to minimize the likelihood of treating patients at doses that are too low to yield benefit or too high that they do harm



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Phase I in Oncology

Approaches to determine starting dose:

- 1/3 of the toxic dose low (TDL) in a large animal species (TDL = the lowest dose that produces drug-induced pathological alterations in hematological, chemical, clinical, or morphological parameters and which, when doubled, produces no lethality)
- 1/10 of lethal dose in mice (expressed in mg/m^2) if nontoxic in large species



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Dose-Escalation Methods

- Modified Fibonacci sequence (100%, 67%, 50%, 40%, and 33%), with 3 patients treated per cohort
 - for sake of clarity, better to label decreasing increment schemes as such, specifying the increments, without invoking Fibonacci.
- Target dose-limiting toxicity rate (e.g., 33%, 50%) chosen based on whether or not the drug has potential for unpredictable, irreversible, or life-threatening toxicity
- DLT = consists of serious or life-threatening side effects, but reversible
- Escalation methods are “adaptive”



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Leonardo of Pisa (Fibonacci)



Posed, and solved, a problem involving the growth of a hypothetical population of rabbits.

The number sequence was known to Indian mathematicians as early as the 6th century, but it was Fibonacci's *Liber Abaci* that introduced it to the West.

Sequence of numbers, each number is the sum of the previous two numbers. Thus the sequence begins 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, 233, 377, 610, 987, etc.

The number sequence, wherein the next number equals the sum of the two previous numbers (1, 1, 2, 3, 5, 8, 13, 21, . . .) is familiar to many people, but the modification used in phase I trials to give progressively smaller increases (2n, 3.3n, 5n, 7n, 9n, 12n, 16n as multiples of the initial dose, or 100%, 65%, 52%, 40%, 29%, 33%, 33% increase over the previous dose) is not so straightforward.

For the sake of clarity, perhaps better to label decreasing increment schemes as such, specifying the increments, without invoking Fibonacci

*Letter to Editor: Modified Fibonacci Search by George A. Omura University of Alabama at Birmingham, Birmingham, AL

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Dose-Escalation Methods

- **For toxicity rate of 33%:**
 - If 0/3 patients has DLT, then escalate
 - If 2/3 or 3/3 patients have DLT, then escalation stops and the current dose is the MTD
 - If 1/3 patients has DLT, then 3 additional patients are treated; the dose is escalated only if none of the 3 additional patients has DLT

MTD = dose at which ≥ 2 patients experience DLT

RP2D = next lower dose at which no more than 1/6 patients has DLT



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Dose-Escalation Methods

- **For toxicity rate of 50%:**
 - If 0/3 patients has DLT, then escalate
 - If 3/3 patients have DLT, then escalation stops, and the current dose is the MTD
 - If 1/3 or 2/3 patients has DLT, then 3 additional patients are treated. The dose is escalated only if $\leq 2/6$ patients have dose-limiting toxicity

MTD= dose at which ≥ 3 patients experience DLT

RP2D= next lower dose at which $\leq 2/6$ patients have DLT



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Dose-Escalation Methods

- Bayesian methods where set of prior information and data on each subject is taken into consideration in deciding the dose for the subject
- For newer targeted therapies, goal may be to determine the biological effect level rather than the MTD



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Dose-Escalation Methods

Dose-limiting toxicities should be defined:

- Specific toxicities may be defined based on the known toxic effects of the drug (e.g., haematological toxicity) and/or
- Defined as any toxicity of a pre-defined threshold grade
- Grading of toxicities must be based on an established toxicity scale such as the NCI CTCAE v.3



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Approach in Review

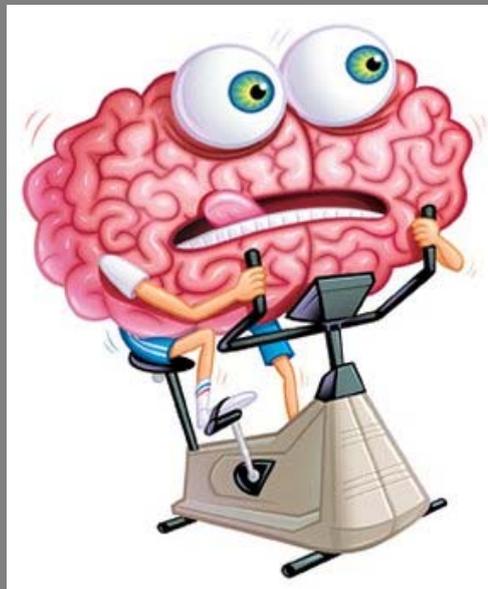
Benefit / risk judgement call:

- Lower risk products → healthy volunteers
- Higher risk products → patients
- Potential toxicity with drug target (e.g., immune system, coagulation pathway)
- Route of administration
- Adequacy of pre-clinical program
- Extent of toxicological findings

Regardless of study population, always link the nonclinical toxicological findings to the clinical safety assessments



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Exercise

Health Products and Food Branch

Background regarding TeGenero

- FIM, first in class superagonist monoclonal Antibody “specific” to CD28 Antigen of T Lymphocytes
- 8 NHRV – 2 of them placebo (first of 4 cohorts to be administered escalating doses of IV infusions of TGN1412)
- To assess safety, PK and immunogenicity
- 10 minute infusions – whole cohort dosed in ONE hour



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Exercise Using Two TeGenero Literature Articles

American Journal of Therapeutics

“First-in-Man (FIM) Clinical Trials Post-TeGenero: A Review of the Impact of the TeGenero Trial on the Design, Conduct, and Ethics of FIM Trials.”

Therapeutic Commentary

American Journal of Therapeutics (AJT), 14(6):594-604, Nov/Dec 2007
Nada, Adel MD, MS, CPI 1*; Somberg, John MD 2

Lancet

“Establishing Risk of human experimentation with drugs: lessons from TGN1412”

Viewpoint

Lancet 2006; 368:1387-91, Oct 14, 2006
Kenter, MJH, Cohen, AF



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TeGenero Questions Lancet

1. What are the key factors that should have been considered in assessing the trial?
2. How was the review done by the MHRA – UK regulator?
3. What key test(s) should have been done?



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TeGenero Questions AJT – A review of the Impact

More Emphasis on Controversy, reaction, general approach to FIH trials, ethics

1. What were the issues identified with the determination of the starting dose?
2. What ethical issues were raised that are not generally in the Regulators domain?
3. Any other comments on analysis? (critical thinking exercise)



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TeGenero Questions
Lancet

Health Products and Food Branch

1. What are the key factors that should have been considered in assessing the trial?

Answers should include:

- *Preclinical data incomplete*
- *Related CTs of similar Antibodies not included in the package*
- *Specificity of action overestimated*
- *Accuracy of “100% homology”*
 - *restricted to one area*
 - *NO sequence comparison provided*
- *Fraction of NOAEL dose used but ignored some data*



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TeGenero Questions
Lancet

Health Products and Food Branch

2. How was the review done by the MHRA – UK regulator?

Answers should include:

- *3 distinct sub-reports (without interdisciplinary communication)*
 - *Medical*
 - *Pharmaceutical*
 - *pharmaco-tox – safety*

3. What key test(s) should have been done?

Answers should include:

- *Affinity binding (in-vitro testing)*
- *Sequence comparison of human, rhesus and cynomolgus monkey should have been provided*



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TeGenero Questions
AJT Health Products and Food Branch

1. What were the issues identified with the determination of the starting dose?

Answers should include:

- *NOAEL, MSD, HED - factor of 10, versus alternate approaches to determining dose*
 - *MABEL,*
 - *Micro dosing*
 - *NOEL*
- *ICH S6 warns tox studies in non-relevant species may be misleading – Species specificity especially with biotechnology derived products*
- *On and off target (exaggerated pharmacologic action and idiosyncratic) related side effects or adverse events should have been discussed*



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TeGenero Questions
AJT Health Products and Food Branch

2. What ethical issues were raised that are not generally in the Regulators domain?

Answers should include:

- *Participant compensation for risk assumption*
- *Participant compensation for research related injury*
- *Not part of Risk Benefit analysis – important to understand the limits of review*

3. Any other comments on analysis? (critical thinking exercise)

Answers should include:

- *overanalyzed wrt statistical evaluation, cohort size, PIs*

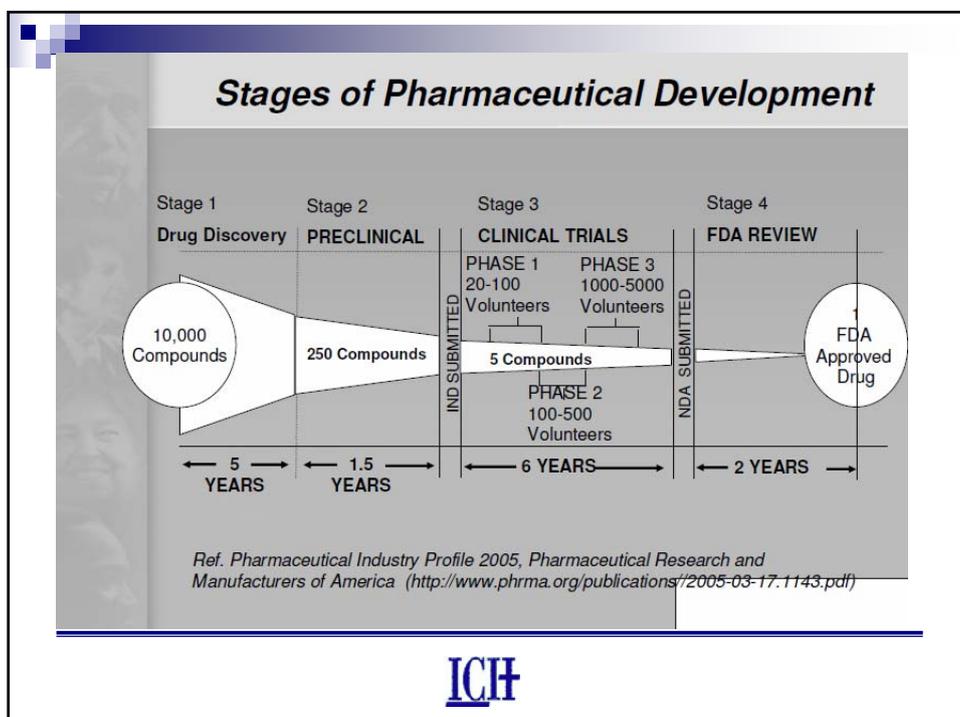


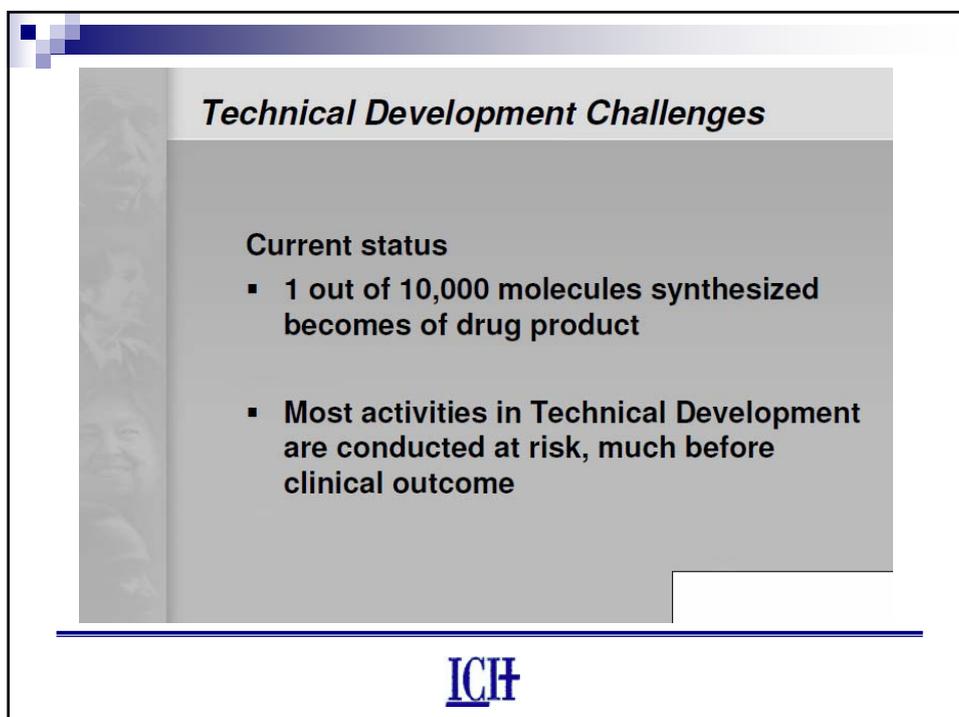
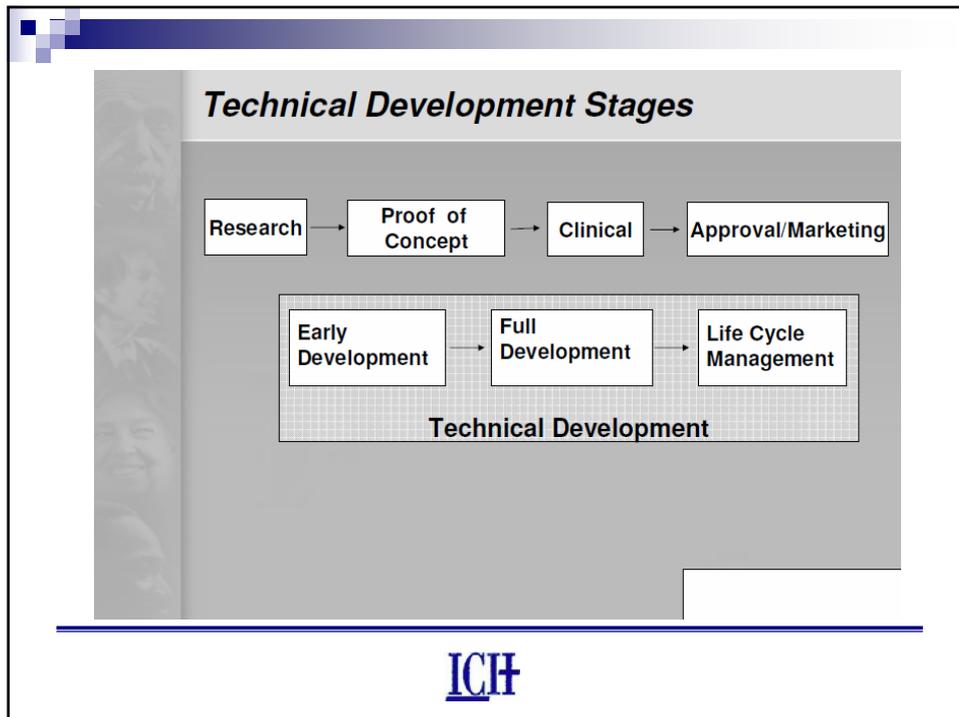
40

Development to 1st in Man

Sudhichai Chokekijchai M.D.
Chief Scientific Officer
Novartis (Thailand)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use **ICH**





How Does Technical Development Manage Risks?

- Minimize attrition: Select 'right' molecules through development-discovery interaction ('developability assessment')
- Identify optimal drug substance forms early (salts, polymorphic forms)
- Identify formulation principles and development hurdles early
- Assess potency with respect to drug product development
- Keep early clinical trial materials and formulations simple (caveat: bioequivalence)
- Keep processes simple

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Selecting Right Molecule for Development

Technical Development conducts Developability Assessment

Target & hit identification, hit validation, lead selection

Lead optimization

Candidate selection process

Early clinical development

... through strong collaboration with Discovery

<ul style="list-style-type: none"> ▪ Synthesis considerations ▪ Solubility considerations 	<ul style="list-style-type: none"> ▪ Assess physicochemical & biopharmaceutical properties of drug substance ▪ Assess synthesis hurdles ▪ Dosing vehicles selection ▪ Assess formulation feasibility ▪ Assess impact of dose on potential dosage forms 	<ul style="list-style-type: none"> ▪ Get a complete picture of bioavailability issues ▪ Assess impacts of drug substance properties and formulation on bioavailability
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10

ICH

Drug Product Design

Selection criteria for dosage forms

- Clinical needs
- Dose/Onset/Duration of action
- Product performance
- Patient acceptance
- Marketing considerations

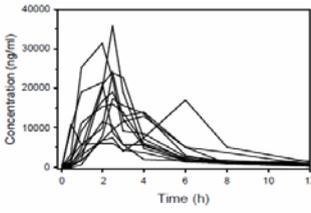


PK in Drug Development

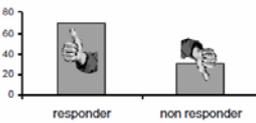
different patients



different exposure



different response

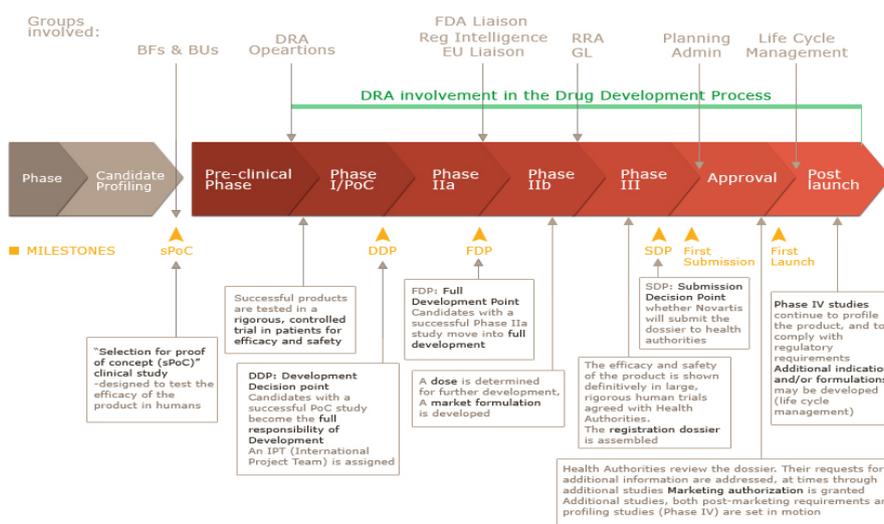


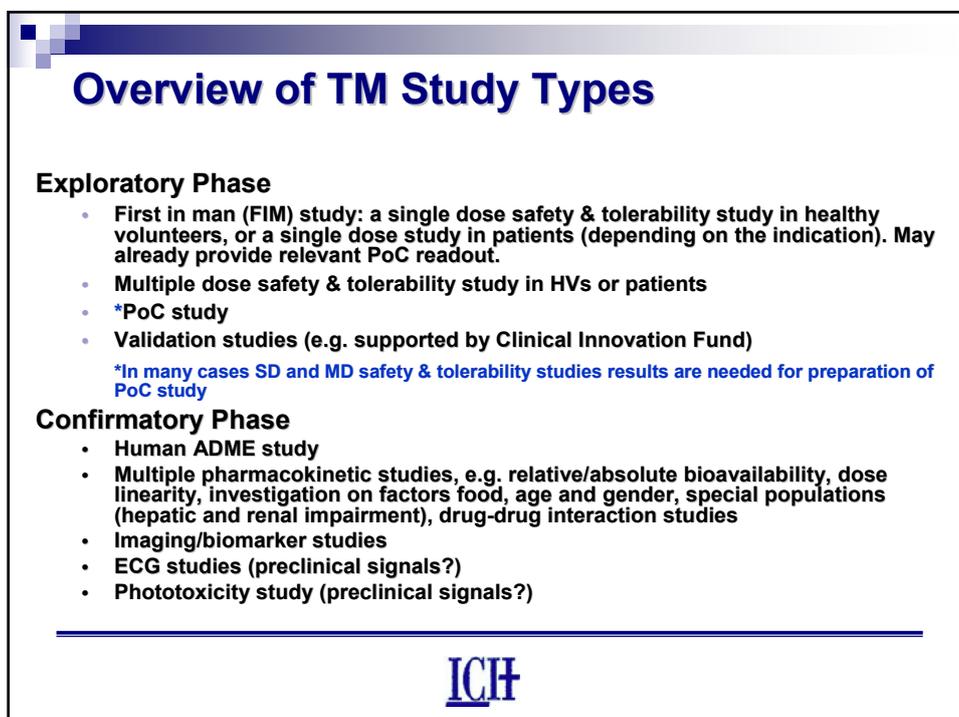
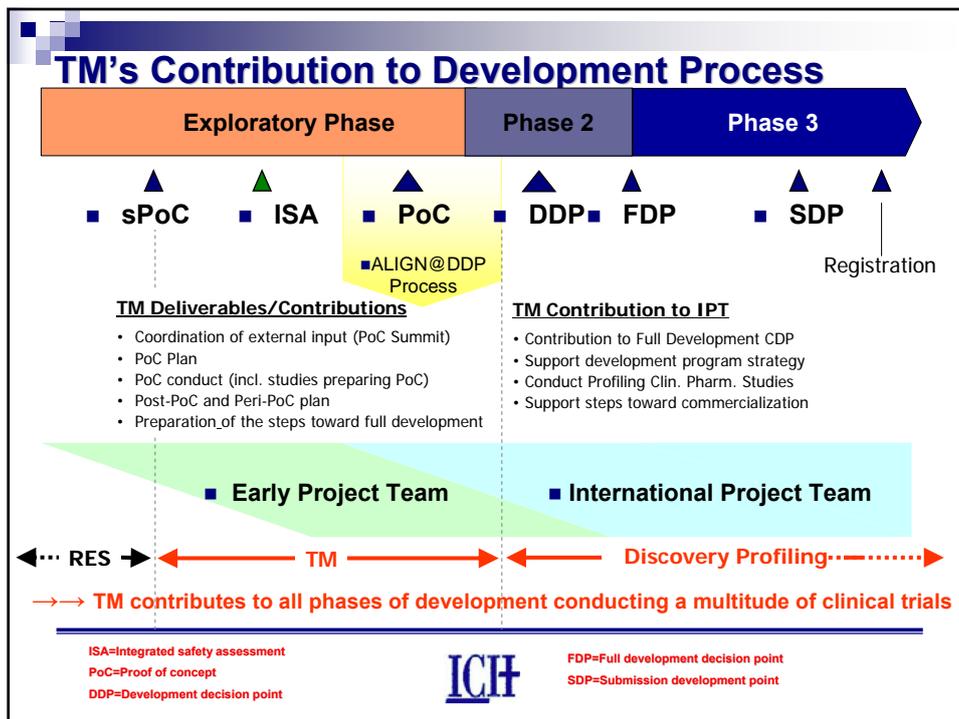
Mission Statement – Translational Medicine

..... drives Innovative and Cutting Edge Science from
Discovery to the Market through the selection, profiling
and effective global development of successful
Novartis medicines to enhance the quality of people's
lives



Clinical development milestone





The Package Insert

ADME

PK

MoA

Special Popn

Renal

Hepatic

Gender

DDI

Pediatric

Geriatric

Dosing

QTc

INDICATIONS

CONTRAINDICATIONS

WARNINGS

PRECAUTIONS

ADVERSE REACTIONS

PHARMACOLOGY

ADME

PK

MoA

Special Popn

Renal

Hepatic

Gender

DDI

Pediatric

Geriatric

Dosing

QTc

Types of studies – Classic Clinical Pharmacology

■ About 60% of the studies run by TM are simple studies with either a PK or safety focus

- FIM
- QTc
- Drug/drug interaction
- Bio-equivalent
- Bio-availability (absolute or comparative)
- Food effect
- ADME
- Special populations
 - Renal/ Hepatic/ Japanese

ICH

Types of studies (2) – Complex scientific studies

■ About 40% of the studies run by TM are complex studies with a Pharmacodynamic or safety focus

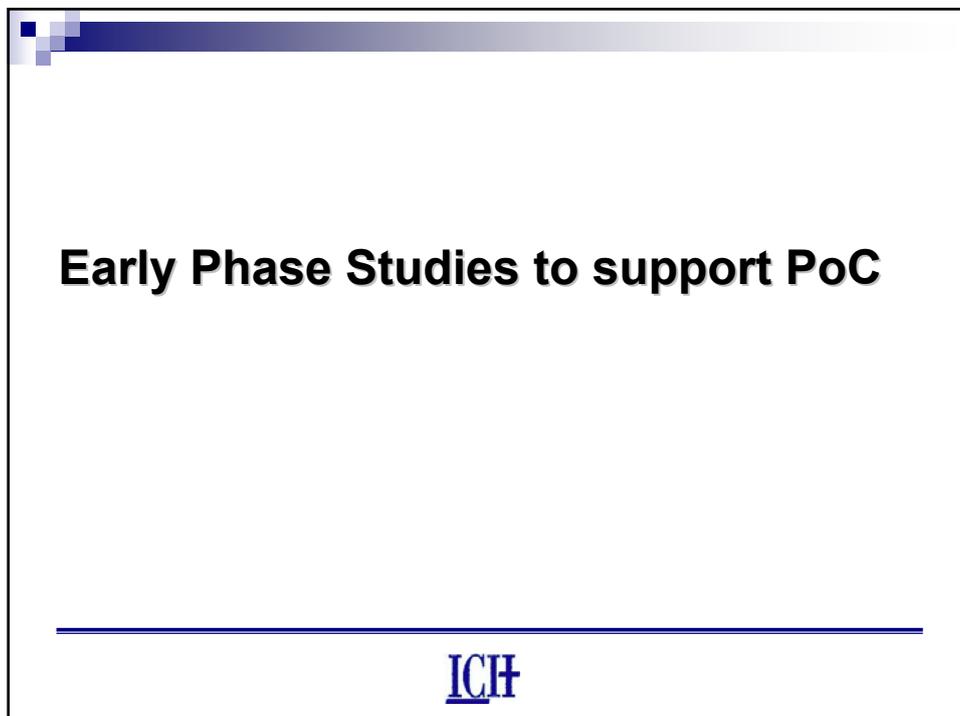
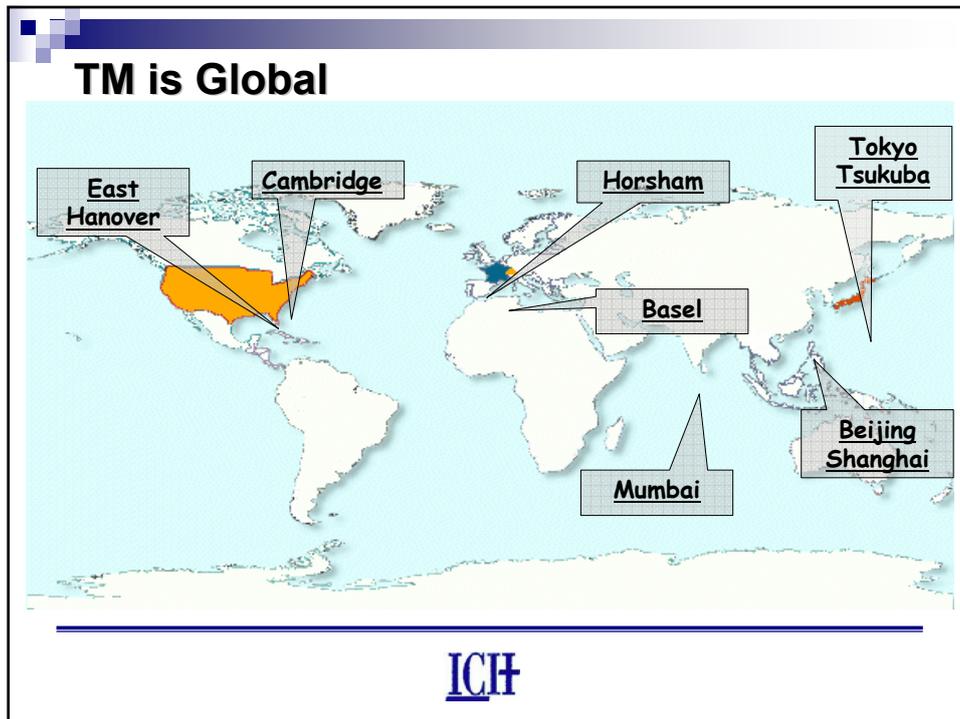
- FIM (Multiple dose)
- POM
- POC
- Methodology
- PK/PD
- Adaptive

ICH

Phase I (Healthy Volunteers) CROs Specialized Hospital Clinics (Patients)



ICH



Single Ascending Dose Study: Interleaved Design

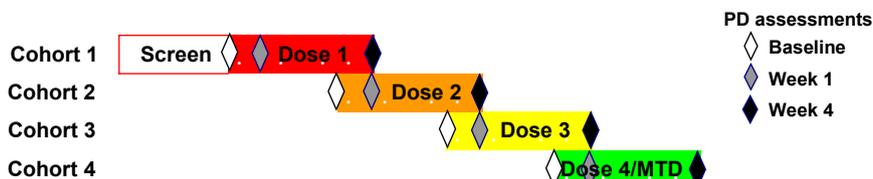
Weeks		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Cohort 1	A	5 mg			50 mg			Plac		
	B	5 mg			Plac			400 mg		
	C	Plac			50 mg			400 mg		
Cohort 2	A		10 mg			100 mg			Plac	
	B		10 mg			Plac			800 mg	
	C		Plac			100 mg			800 mg	
Cohort 3	A			20 mg			200 mg			Plac
	B			20 mg			Plac			1600 mg
	C			Plac			200mg			1600 mg

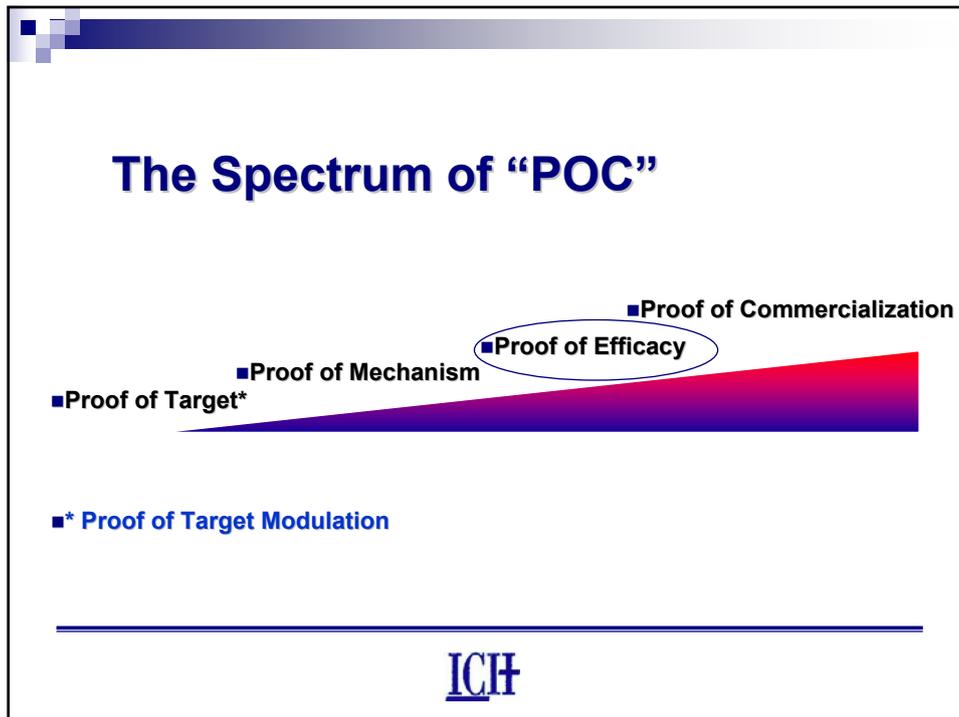
Randomized, double blind, interleaved, ascending dose study with placebo substitution in 36 healthy volunteers (12 per cohort)



Multiple Ascending Dose Study: Classical Design

- Design: **Randomized, double-blind, placebo-controlled, parallel group, time-lagged, ascending multiple oral dose study**
- Objectives: **Safety, tolerability, PK and/or PD of ascending multiple oral doses in healthy volunteers**
- Sample size: **24 – 36 subjects (depending on number of doses)**





- ## Characteristics of PoC Trials
- PoC trials typically are short and involve relatively few patients/healthy subjects
 - Studies should enable intelligent Go/No-Go decisions
 - Studies often lack power for statistical significance
 - This places an emphasis on the quality of the read-outs (e.g. pharmacodynamic parameters, biomarkers) to yield insights into the relevant human physiology
 - To ensure high-quality read-outs investigators have to be adequately trained and relevant procedures closely monitored.
-
- ICH

Concluding Remarks

- The journey of a new molecular entity (NME) from a chemist's/biologist's bench to a drug product in a patient's bedside is a difficult, costly and high risk process.
- There is a continued pressure to shorten the journey (reduce development time) and save costs.
- Most pharmaceutical companies are developing innovative technologies and processes.
- For example, Novartis developed Gleevec® from Phase I clinical to regulatory submission in just 2.7 years, all at risk; the industry standard is 5.9 years!

ICH

 Health Canada Santé Canada

Your health and safety...our priority Votre santé et votre sécurité... notre priorité

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Science Based Approach Review of Drug Development Article and Recent Example



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009


 Health Canada Santé Canada

Your health and safety...our priority Votre santé et votre sécurité... notre priorité

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009


Health Products and Food Branch

An integrated science-based approach to drug development

Editorial overview
Current Opinion in Immunology 2008, 20:426-430
Paul WHI Parren and Jan GJ van de Winkel



3

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Monoclonal Antibodies and related molecules

- Antibody fragments
- Fusion proteins
- Conjugates
- Approximately 2 dozen approved to date
- CTs of this class of therapeutic proteins is accelerating
- Technological advances from fully mouse to fully human has reduced immunogenicity



4

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Concept centers around 3 main aspects

- Target
- Antibody
- Patient



5

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Target – 1st Step

- ‘Exquisite’ target specificity
- Requires extensive knowledge of the target
 - Ability to modulate disease outcome
 - ‘Drugability’
 - Overexpressed in pathogenesis, low or absent in other tissue/organs
 - Often cell surface receptors or their ligands
 - EGF receptors, TNF alpha



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Antibody Design – 2nd step

- Must bind with high affinity and specificity
- High throughput screening can do both in parallel
- Now improved understanding / manipulation of Fc portion
 - Protein engineering
 - Glyco-engineering
- IgG1 versus IgG2 and IgG4 (cancer versus immune function)
 - Can In vivo stability issues be overcome with novel approaches
- Combining therapeutic antibodies with drugs/toxins



7

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The Patient – where it really counts

- Addressing safety
 - Proof of concept
 - Efficacy
- Inter-individual genetic heterogeneity or polymorphisms**
- Herceptin is only effective against breast Ca that over-expresses the ErbB2
 - (or Her-2) target
- Disease associated mutations**
- Erbitux or Vectibix (anti-ErbB1 or EGF receptors) not effective in patients containing tumours with a mutated K-ras



8

Trends in therapeutic antibody development

- Now 'centre stage'
 - Overtaking more traditional (small molecules)
- Demonstrating efficacy in 1st line and long term treatments
- Being used as cocktails but with some increased risk
 - Natalizumab associated with JC virus activation causing Progressive Multifocal Leukoencephalopathy (PML) *with other immune modulators*



9

From the Breastcancer.org site

There are three tests for HER2-positive cancer:

- **IHC test** (*IHC stands for ImmunoHistoChemistry*)
 - The IHC test shows if there is too much HER2 receptor protein in the cancer cells.
 - The results of the IHC test can be 0 (negative), 1+ (negative), 2+ (borderline), or 3+ (positive).
- **FISH test** (*FISH stands for Fluorescence In Situ Hybridization*)
 - The FISH test shows if there are too many copies of the HER2 gene in the cancer cells.
 - The results of the FISH test can be "positive" (extra copies) or "negative" (normal number of copies).
- **SPoT-Light HER2 CISH test** (SPoT stands for Subtraction Probe Technology and CISH stands for Chromogenic In Situ Hybridization)
 - The SPoT-Light test shows if there are too many copies of the HER2 gene in the cancer cells.
 - The results of the SPoT-Light test can be "positive" (extra copies) or "negative" (normal number of copies).

"Find out which HER2 test you had. This is important. Only cancers that test IHC "3+" or FISH or SPoT-Light "positive" will respond well to therapy that works against HER2. An IHC 2+ test result is called borderline. If you have a 2+ result, you can and should ask to have the tissue tested with the FISH or SPoT-Light test."



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Health Products and Food Branch

Posted January 15th, 2009

- The American Society of Clinical Oncology (ASCO) today released its first "Provisional Clinical Opinion" on the use of KRAS gene mutation testing in patients with metastatic colorectal cancer to guide use of the epidermal growth factor receptor (EGFR) inhibitors cetuximab (Erbix) and panitumumab (Vectibix).
- ASCO's Provisional Clinical Opinion recommends that all patients with metastatic colorectal cancer who are candidates for anti-EGFR therapy have their tumors tested for KRAS gene mutations before receiving these agents.

"Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumour tested for *KRAS* mutations in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment."



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Recent Example

- Large Sponsor with new 'Antibody Fusion Protein'
- Aggressive development program (5 trials at once)
- Trouble with 'scale up'
- BGTE worked together as a team



12

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Synopsis of the response to C&M IR

- All clinical trials to date have been conducted with the Early Process Material EPM (Phase 1 and 2)
- Current Process Material CPM has a significantly higher impurity (5-9% of 6AA + AB fusion protein)
- The variant is not biologically active
- No bioequivalence studies were carried out.
- CPM shows a similar profile to the EPM in terms effect
- In addition mean plasma concentration over time is similar between the two materials - mouse study
- No specific in vitro studies were conducted to evaluate tissue cross reactivity or secondary pharmacodynamics. These studies were performed with EPM



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Clinical IR

- Upon review of the impurity profiles for the 'Antibody Fusion Protein' produced by the EPM compared with the CPM - BGTD has determined that the products do not appear to be comparable.

The majority of the submitted supporting data from non-clinical and clinical studies has utilized the EPM.

- Therefore to support the proposed later stage clinical development program, further non-clinical and possible clinical data should be provided utilizing the CPM.



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Clinical IR cont'd

According to our review it appears that CPM has been utilized in the following non-clinical studies:

1. In vitro testing
2. Single dose subcutaneous acute 'disease specific' mouse model to determine pharmacodynamic activity
3. Single dose subcutaneous acute 'ordinary' mouse model to determine pharmacokinetic activity
4. In-silico assessment for immunogenicity
5. An ongoing 52-week primate study for chronic toxicity



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Clinical IR cont'd

BGTD believes that the final data from the 52-week primate toxicity study is required to support the proposed later stage clinical development program.

This data should include full toxicity safety data, local tolerance data and immunogenicity data relative to EPM.

As such, it is recommended that you withdraw the current proposed clinical trials until the final data from the 52-week monkey study is available for review.

It is also possible that following review of the chronic toxicity data there may be further recommendations such as to perform a formal bridging clinical trial

We urge you to consider requesting a pre-CTA meeting prior to re-submitting

If there is no further data to support these submissions and you choose not to withdraw BGTD will issue Non Satisfactory Notices before the default dates

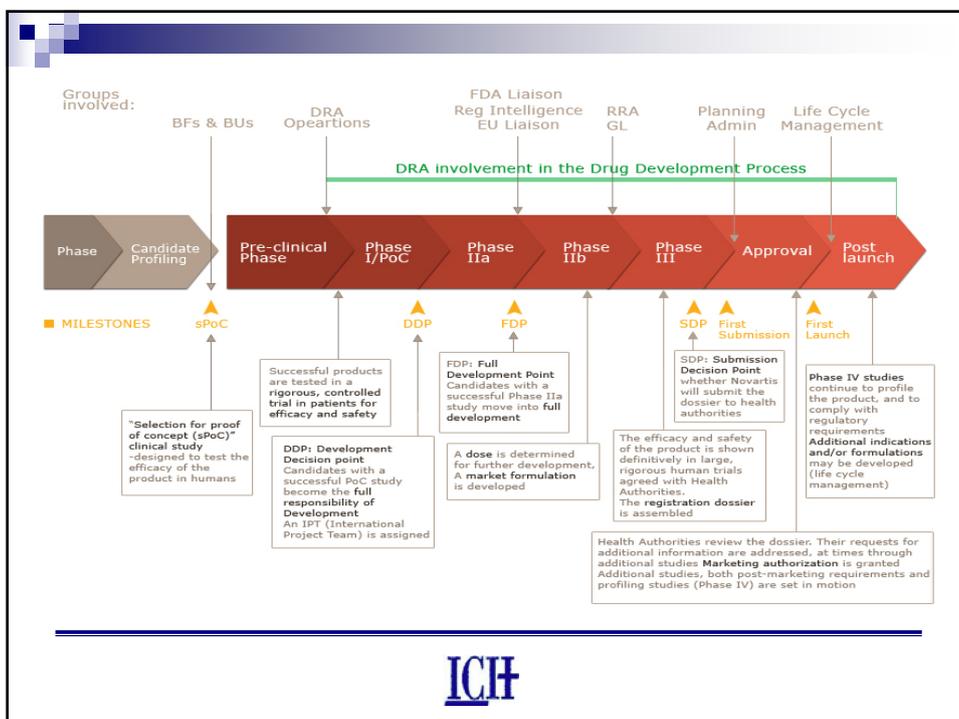


16

Overview of Drug Development: Adaptive Seamless Design

Sudhichai Chokekijchai M.D.
Chief Scientific Officer
Novartis(Thailand)

International Conference on Harmonisation of Technical
Requirements for Registration of Pharmaceuticals for Human Use 



<h2>Clinical Trials</h2>	
Definition	Study types included
<p>Phase I A study that has Tolerability or PK as primary endpoint in the protocol, independently of the study population and of secondary parameters</p>	<ul style="list-style-type: none"> ■ Safety & Tolerability studies (SD or MD in patient or HV) ■ Oncological studies in patients with tolerability / MTD as primary endpoint (efficacy might be a secondary endpoint) ■ Drug-Drug interaction & Food Effect ■ PK in renal or hepatic impaired patients
<p>Phase IIA An exploratory (non-pivotal) study that has as a primary endpoint either clinical efficacy, PD, or biological activity, irrespective of whether conducted in patients or healthy volunteers.</p>	<ul style="list-style-type: none"> ■ Proof of concept, efficacy, or mechanism ■ Mechanistic studies ■ Dose range exploration ■ Pilot studies
<p>Phase IIB A definite dose range finding study in patients with efficacy as primary endpoint. Exceptionally, Phase II studies can be used as pivotal trials (see below), if the drug is intended to treat life-threatening or severely-debilitating illnesses (e.g., in oncological indications)</p>	<ul style="list-style-type: none"> ■ Definite dose finding studies ■ Extension studies of Phase IIB studies



<h2>Clinical Trials</h2>	
Definition	Study types included
<p>Phase IIIA A study that is a pivotal* trial, e.g., a trial designed and executed to get the statistically significant evidence of efficacy and safety as required by HAs for approval of a NDA or sNDA. This also includes studies with the aim to include claims into the label as well as postmarketing commitments.</p>	<ul style="list-style-type: none"> ■ Pivotal studies (vs placebo or comparator) ■ Long term safety studies required for registration ■ Local registration studies ■ Post marketing study commitments ■ Phase III A extension studies
<p>Phase IIIB A study that is started prior to approval and whose primary intention is the support of publications rather than registration or label changes, e.g. results are not intended to be included in the submission dossier.</p>	<p>All studies intended to support publication claims or to prepare launch, which start before approval but are not intended for regulatory submissions</p>
<p>Phase IV A study that is started after approval and whose primary intention is the support of publications rather than registration or label changes, e.g. results are not intended to be included in a submission dossier.</p>	<p>Post marketing surveillance studies Studies intended to support publication claims</p>



Pivotal Trial

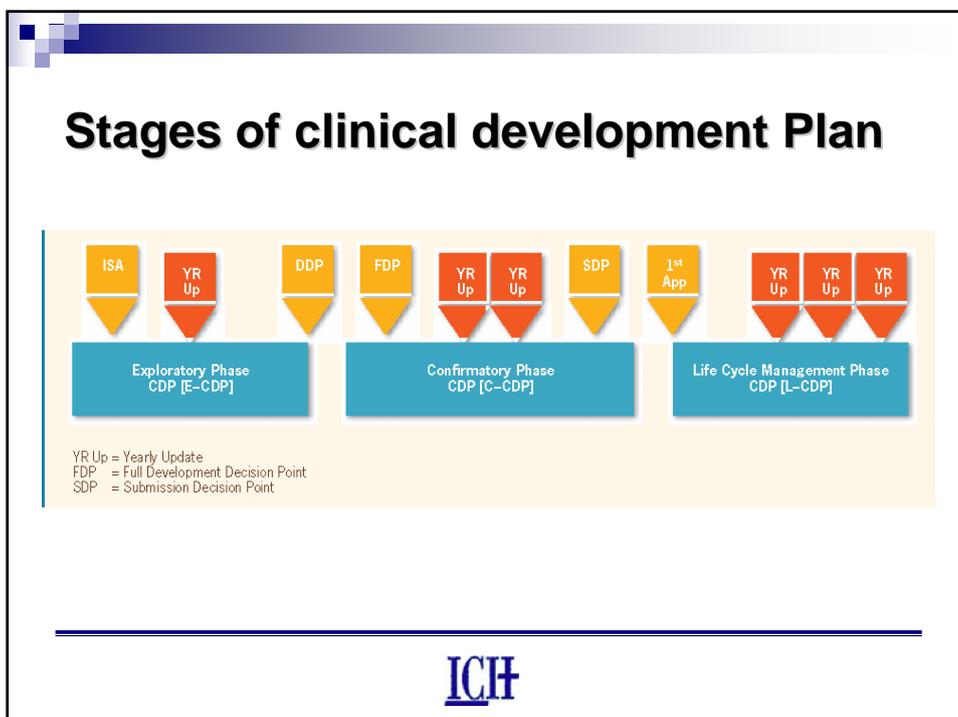
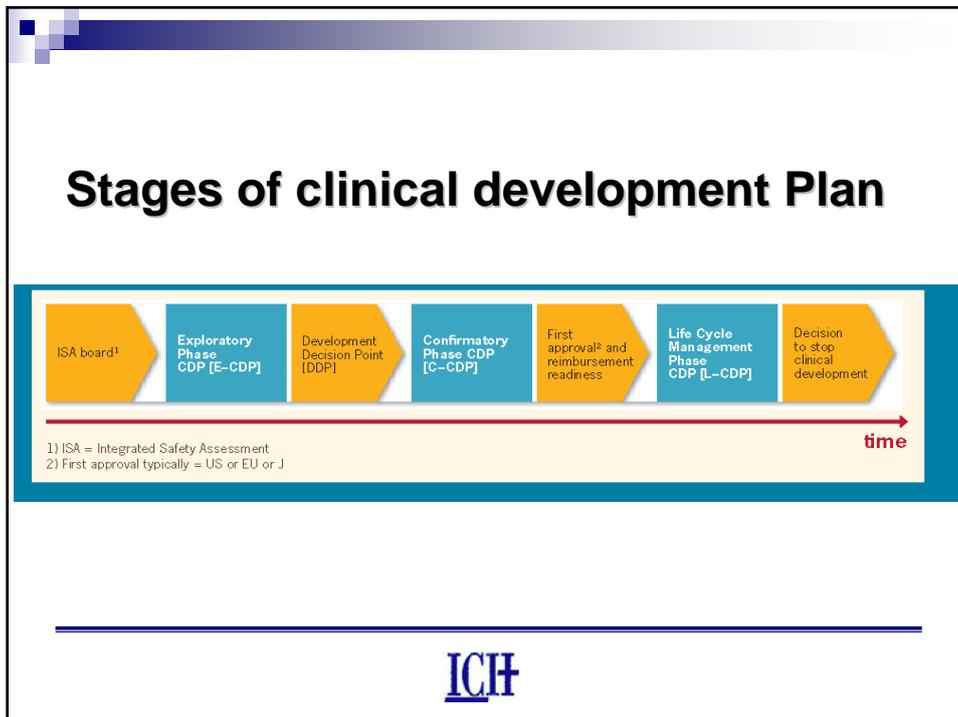
- **A pivotal trial is a trial designed and executed to get the statistically significant evidence on efficacy and long term safety as required by HAs for approval of an NDA or sNDA.**
- **This also includes studies with the aim to include claims into the label.**

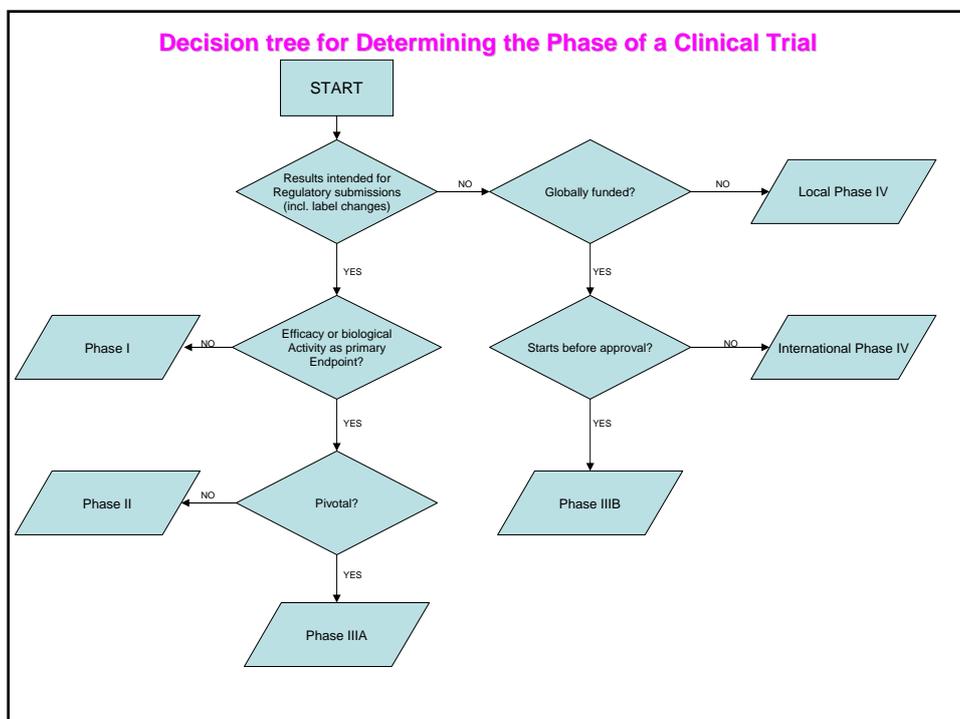
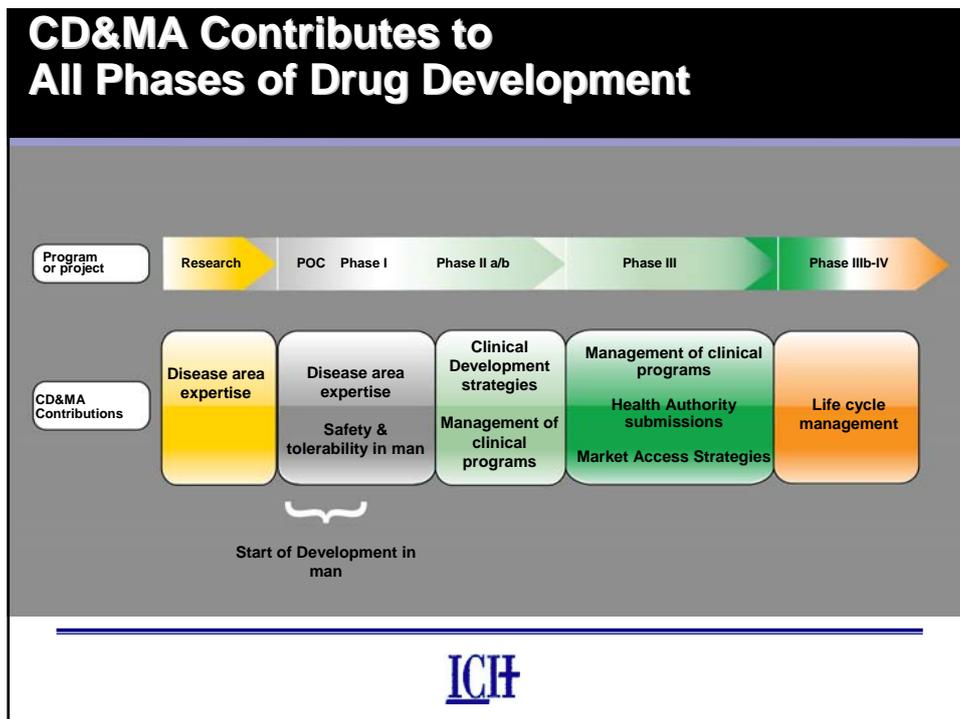
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Clinical Development Plan

- **The Clinical Development Plan (CDP) is the tool that “bridges the gap between vision and the day-to-day activities of large multidisciplinary organizations. The vision is transformed into distinct implementation phases and discrete steps, called clinical studies, each with well-defined milestones and deliverables.”**

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Adaptive Designs in Clinical Development

- Introduction and motivation for Adaptive Designs
 - Adaptive and Seamless designs
- Classical vs. Seamless development
- Example of Adaptive Seamless Design
- Final Remarks

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Possible Adaptations

- **Adaptive designs:** using accumulating data to decide on how to modify aspects of the trial without undermining the validity and integrity of the trial
- **Adaptations can include**
 - Early stopping (futility, early rejection)
 - Sample size re-assessment
 - Treatment allocation ratios
 - Treatment arms (dropping, adding arms)
 - Hypotheses (Non-inferiority vs. superiority)
 - Population (inclusion/exclusion criteria; subgroups)
 - Test statistics
 - **Combine trials / treatment phases (Adaptive Seamless Designs)**

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Classical Full Development

- **Fixed Trial Designs Paradigm**, in particular for Phase III
 - Standard trial designs allow **little learning** during the conduct of the trial
 - “Established” adaptations are used in **group-sequential trials** where stopping for superiority or futility can be done according to pre-defined rules at interim analyses
 - Clearly **separated development phases** (II and III)
 - If applied to all clinical projects one **misses opportunities** for better use of information and more ethical drug development

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Classical Phase III: Confirmation, Hypothesis Testing and Error Control

- **Proof of efficacy in phase III trials:**
 - Show that observed treatment effect is ‘real’ and not just random via testing of statistical hypotheses
 - **Regulatory practice and guidelines (e.g. ICH E9) ask that the false positive error rate is controlled for pivotal trials (usually 2.5%)**
 - Trial designs, analysis and decisions rules at interim analysis **are pre-defined**
 - Emphasis on trial ‘**integrity**’ (e.g., regarding confidentiality of interim results)
- **Error control:**
 - Multiple hypothesis testing or changes of design characteristics at interim **alters the false positive error rate** of a standard statistical test

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Adaptive /seamless phase II/Phase III trial

Primary objective - to combine “treatment selection” and “confirmation” in one trial

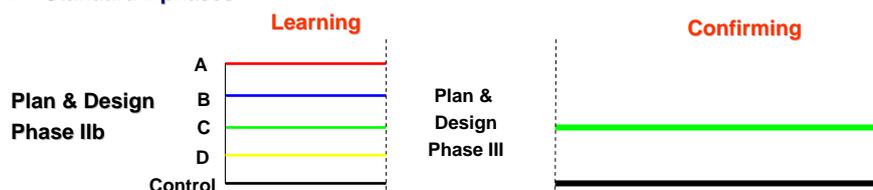
- Enroll patients into the trial
- During the trial, select the optimal dose (or population) based on interim data based on surrogate marker, early read-out of endpoint, or primary endpoint
- Enrollment continues only on the selected dose and the comparator arm

All data from chosen arm and comparator is used in final analysis, using novel statistical methods for combining evidence from first **and** second stage to control of false positive error rate and maintaining trial integrity



Comparison of ASD for treatment selection with separate phase II and III trials (1)

Standard 2 phases



Adaptive Seamless Design



■ Dose Selection



Comparison of ASD for treatment selection with separate phase II and III trials (2)

■ Advantages of adaptive seamless designs

- Shorter overall development time → effective drugs are made available earlier for the patients
- Increase of information value given the same number of patients
- Long term safety available earlier (extension of Stage I patients)

■ Logistical differences

- Number of treatment groups can change during trial → resulting implications in drug supply
- Centers would have to be made aware of flexible sample sizes
- Informed consent may need to be modified at interim
- Sufficient time for Health Authority interaction
- Careful consideration of trial integrity issues, including the interim analysis decision process and personnel



RAD001+Femara, advanced breast cancer

■ Motivation for adaptation

Selection of appropriate **patient sub-group** and confirmation of benefit in one seamless **phase II/III** trial

■ Design specifications: 2-stage seamless adaptive design

Stage 1

- sub-group selection (options: sub-group or all-patients)
- futility decision at two time points
- sub-group considered is defined upfront, based on evidence external to the trial
- Sample size could be adjusted at interim points

Stage 2

- achieve confirmation of treatment benefit while maintaining integrity of trial (false positive rate and bias are controlled)



RAD001+Femara, advanced breast cancer

- **Adaptive trial design was reviewed by FDA and EMEA, and considered acceptable for the trial**
- **Careful consideration and detail was required for the interim analysis and decision process**
 - What data will be needed to decide to adapt?
 - Who will see this data, and make this decision?
 - Will the results of this decision bias the trial?
- **Overall, a positive response**

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Final Remarks

- **Need for making drug development process more efficient is recognized by all parties**
- **Key value of adapting is not in reducing sample size, but given a constant sample size, increase the information value, thus making adaptive designs more ethical/efficient**
- **Ethical reasons justify novel adaptive designs, which combine learning and confirmation in one single trial while controlling the overall type I error rate**
- **Novartis is committed and dedicated to invest in Research & Development of ASD on a global level while being in continuous discussions with Health Authorities**

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 Health Canada Santé Canada

Your health and safety...our priority Votre santé et votre sécurité... notre priorité

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Ethics in CTs

The Role of the Regulator

versus

The Role of the REB



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

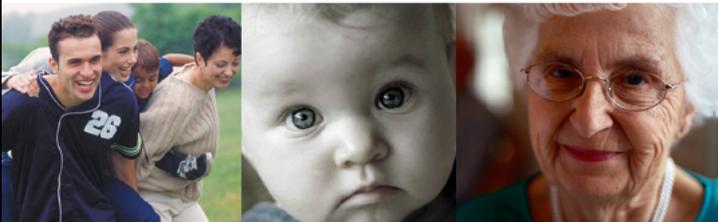
Canada

 Health Canada Santé Canada

Your health and safety...our priority Votre santé et votre sécurité... notre priorité

Helping the people of Canada maintain and improve their health Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



Norman Viner, MD
Biologics and Genetic Therapies Directorate
February 02, 2009

Canada

Health Products and Food Branch

Review Ethic Article

Ethics in clinical Trials and Drug Development
Pharma Focus Asia
Clinical Trials
Issue 4 / 2007
Klein, Agnes

<http://www.pharmafocusasia.com/magazine/archives/issue4.htm>



3

Health Products and Food Branch

Introduction

- Ethical elements relative to cultural realities of different jurisdictions
- Within the context of ICH GCP
- Never a single answer
- Series of dilemmas which can lead to consensus building following debate of widely divergent opinions



4

Health Products and Food Branch

Role of Ethics in CTs

- Most aspects of a trial can involve ethical decisions including; design, conduct, reporting
- In the context of National and International principles, guidelines and where applicable prescribed governance

Study Design and Conduct is critical

- Little or no probability of success to demonstrate the hypothesis it is generally unethical



5

Health Products and Food Branch

Role of Ethics in CTs

Inclusion Criteria and subject selection

- Important to consider if all those to be treated will derive potential benefit from the proposed therapy.
- Also important to consider if the proposed population will be exposed to undue risks
- Generally exclusion criteria are used to increase the focus and safety of CTs

Patient Follow up

- Clear delineation between the Investigator and other treating health professionals
- Ensure data integrity



6

Health Products and Food Branch

Role of Ethics in CTs

Informed Consent

- Adequate information should be imparted to subjects
- Should be fair and balanced
- Full disclosure of risk
- If there is not full disclosure the data integrity is not considered to be assured



7

Health Products and Food Branch

How is it ensured that CTs are conducted in an ethical manner?

Different levels of ethical review

- Ranging from a single layer under national authority
- To decentralized multilayer review



8

Health Products and Food Branch

Why do we need ethical review?

- To deal with potential conflicts of interest
- Assist with openness and full disclosure of results
- Consider the use of placebos from an ethical perspective



9

Health Products and Food Branch

Issues of Governance

- In many jurisdictions Ethic review is required (mandated by regulations)
- Ethics Committees are largely self-governing
- Mostly subject to ethical guidelines without regulatory oversight
- Indirect regulation does occur via ICH GCP as a high standard to help guide many aspects of CTs
- CT inspections (including REBs) provide assurance that all provisions (including ethical ones) have been respected



10

Health Products and Food Branch

**Are subjects in a position to judge whether
The information provided in an ICF is
complete?**



11

Health Products and Food Branch

**Health Canada - Division 5
Drugs For Clinical Trials Involving Human Subjects**

Application for Authorization

C.05.005. An application by a sponsor for authorization to sell or import a drug for the purposes of a clinical trial under this Division shall be submitted to the Minister, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer and **shall contain the following information and documents:**

- (a) a copy of the **protocol for the clinical trial;**
- (b) a copy of the statement, as it will be set out in each informed consent form, that **states the risks and anticipated benefits** arising to the health of clinical trial subjects as a result of their participation in the clinical trial;



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Health Products and Food Branch

Example 1 of Ethics Review Issues

- A Reviewer requested that the wording of an ICF:
 - Declaration by the subject that: "This Study has been fully explained to me"
 - This is equal to "I certify the completeness of disclosure"
 - The REB in question uses "I think I understand..."
 - FDA information sheet suggests that although not prohibited, statements like this may be inappropriate

<http://www.fda.gov/oc/ohrt/IRBs/informedconsent.html>
- It was pointed out to Health Canada that the ICF review should be limited to Risk Benefit
- Agreed by senior management to leave "Ethics Review to the REBs"



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Health Products and Food Branch

Can the Informed Consent Document or Informed Consent Form (ICD/ICF) be considered as part of the Protocol?



14

Health Products and Food Branch

Health Canada - Division 5 Drugs For Clinical Trials Involving Human Subjects

Notification

C.05.007. If the sale or importation of a drug is authorized under this Division, the sponsor may make one or more of the following changes if the sponsor notifies the Minister in writing within 15 days after the date of the change:

- (a) a change to the chemistry and manufacturing information that does not affect the quality or safety of the drug, other than a change for which an amendment is required by section C.05.008; and
- (b) a change to the protocol that **does not alter the risk to the health of a clinical trial subject, other than a change for which an amendment is required by section C.05.008.**

Amendment

C.05.008.....

2) For the purposes of subsection (1), amendments are

- (a) amendments to the protocol that affect the selection, monitoring or dismissal of a clinical trial subject;
- (b) amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;
- (c) **amendments to the protocol that alter the risk to the health of a clinical trial subject;**
- (d) amendments to the protocol that affect the safety evaluation of the drug;
- (e) amendments to the protocol that extend the duration of the clinical trial; and amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.



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Health Products and Food Branch

Example 2 of Ethics Review Issues

- An CT Notification was reviewed
 - It was noted that the sponsor had deleted important safety information from the ICF.
 - It was decided after a brief review and discussion with the Sponsor to correct the deficiency and resubmit the information as an amendment.
- As a result an acting manager received 14 amendments
 - Turned out the error affected 14 trials!
- Confusion ensued
 - The acting manager believed that the ICF was separate from the protocol
 - Changes to the ICF did not qualify as an amendment



16

Pharmacovigilance

- Regulatory perspective -

Junko Sato

Director for Risk Management, Office of Safety
Pharmaceuticals and Medical Devices Agency
(PMDA)



Agenda

- Concept of Pharmacovigilance
- Current Regulation & Challenge in Japan
- Summary
 - What should we do ?



Concept of Pharmacovigilance



Pharmacovigilance

- Not only post-approval ...
 - Traditionally it focused on detection and evaluation of signals in post-approval
 - But now, it is defined to cover from pre-approval to post- approval by CIOMS VI
- Necessity from first in human until withdrawal through the lifecycle of drugs
 - Seamless transition from development stage to the post-approval period



Purpose of PhV

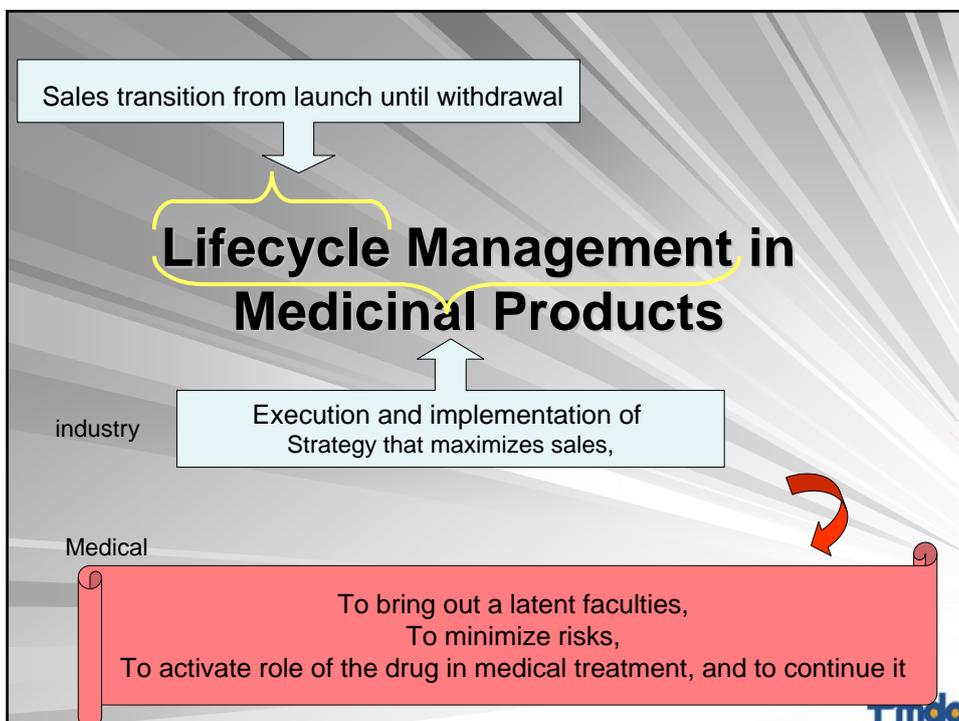
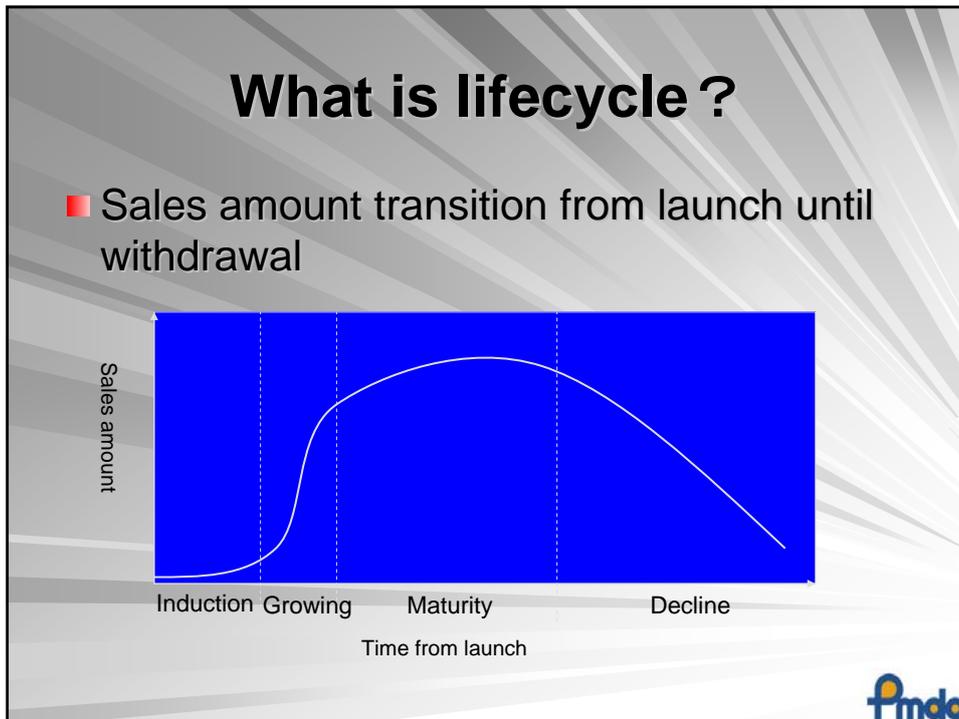
- To secure early detection of new adverse reactions or patients subgroups of exceptional sensitivity
- To introduce measures to manage those risks



Pharmacovigilance and Risk Management

- Post-approval phase is inseparable from development
 - Necessity of cooperation between development Div. and Pharmacovigilance Div.
- Approval is just 'passing point' of drug lifecycle
- Continuous Safety Specification from early development phase to post-approval is important.
- To consider how to manage the risks if they are identified.
- Don't forget the possibility that more effective dosage might exist.
- The concept of CIOMSVI and DSUR must be useful tools on pharmacovigilance and risk management





Lifecycle Management

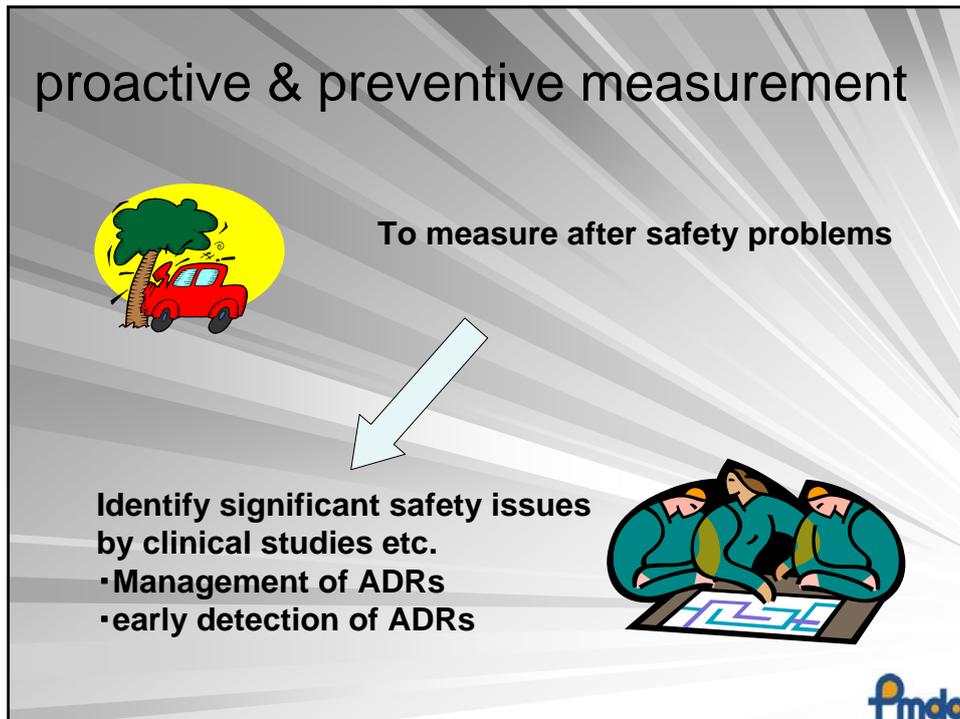
- Concept of LM was occurred in marketing area
- To prolong lifecycle, it is important to keep share and to boost sales
- For the purpose, industry have to make efforts continuously



For well control of Lifecycle

- More effective
- Safer
- More convenient style to use
- To avoid misuse





Current Regulation
&
Challenge in Japan



Re-examination

- The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval.
- The surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP (GPSP), GCP or GLP depending on their objective.
- The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs.
 - Reexamination period of drugs containing new active ingredients: 8 years (maximum 10 years)

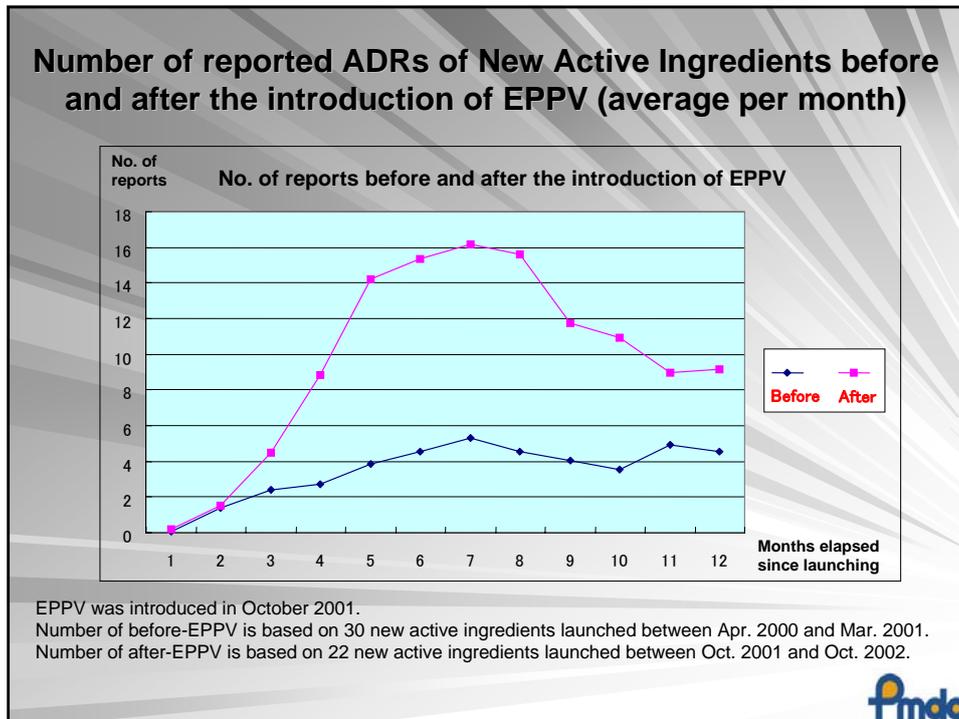


Early Post-Marketing Phase Vigilance : EPPV

Enforced on Oct 1, 2001

- 1. To ensure necessary information for appropriate use (contraindication, careful administration etc) is explained to the medical institutions 2 weeks before delivery.**
- 2. To request medical institutions to use the drugs carefully and report serious ADRs, if occurred, immediately to pharmaceutical companies**
- 3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.**





- ## PhV Plan and J-NDA
- Pharmacovigilance plan is a component of CTD (if the plan has been prepared)
 - PMDA recommend to prepare PhV plan until NDA submission through consultation
 - PhV is an important discussion point under review
 - Description on review report
 - Monitor and review the data
 - Submission of a local periodic report with PSUR
-

Risk management on review

- Brand name
 - To avoid misuse
- Package
 - To avoid misuse
- Risk communication tool
 - For healthcare professionals & patients
 - Package insert, leaflet, website ...etc.



What do we consider in review ?

- We hope for drugs which don't have any ADRs, but all drugs have ADRs.
- We do not review the drug is dangerous or not.
- It is important that all stakeholders comprehend the character of the drug, including ADRs

Benefit / risk balance is key in review !



Appropriate measures in Japan

- Some situations are different between Japan and other regions
 - Medical practice
 - Medical Representatives (MR, sales and information distributor)
- What is appropriate measure for the drug in Japan ?



What do we expect PMS ?

- The concept is described in ICH-E2E
 - What is potential risk ?
 - What is missing data ? etc.
- We recommend the MAH to conduct meaningful PMS, but ...



Zenrei-chosa

- Observational study of all cases
- A kind of Drug Use Investigation
- All cases of use over some period of time
- Number of cases and time period designed at the discussion with PMDA



New Initiative on the RMP in PMDA

- PMDA's Office of Safety has launched a pilot program to establish a new drug safety measures
 - To monitor safety issues throughout the life-cycle of a drug
 - To accelerate PhV
 - To detect safety signal earlier
 - Prospect & Pre-avoid measurement



Expectations for new initiative

- Assessment of safety profile of drugs at development stage
 - Safety for subjects/patients
 - Preparation of post-marketing studies
- Assessment of safety profile of drugs NDA review stage
 - agreement between PMDA and industry on details of post-approval surveys and clinical studies prior to the approval



Introduction of Risk Management System - Product Management -

- Purpose of RM System
 - PMDA will collect, compile, evaluate and manage all the safety information on new drugs from development to post approval stages to give guidance and advice to companies on PMS at early stage and in a timely manner.
- PMDA RM System will help the life cycle management of drugs in safety aspect
 - Identification safety specification from development stage
 - Guidance and advice on designing post-approval surveys, studies and other activities at review stage
 - Evaluation and advice on outcome and problems of post-approval surveys, studies and other activities etc

Tentatively called 'Product Management'



Possible benefits of new risk management system

- *Efficient preparation of effective PMS plan*
- *Consistent safety management throughout lifecycle both in PMDA and companies*
- *Preventing withdrawal of new drugs (at early stage)*
- *Completion of lifecycle of a drug*
- *Protection of patients especially at early stage of marketing*



What should we do ?



We should consider...

- What data are needed for more effective, safer and optimal use of the drug?
 - At each milestone of the development
 - Revised at that time, if necessary

- Which data should be collected early post-approval stage?



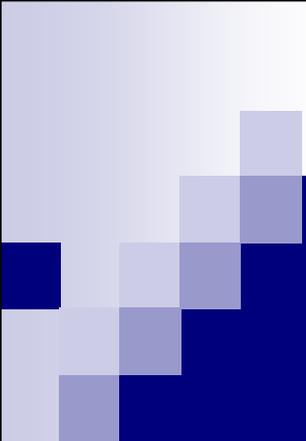
**Minimize risk
Maximize benefit
to patients**

**What should we do ?
What can we do ?**



Integration • share • continuation !





Overview of Risk Management

Risk Management Plans- An Industry Perspective
Dr. Sudhichai Chokekijchai ,
CSO Novartis (Thailand) Limited

(adapted from an RMP training by Dr Judith Sills, Global Head, Medical Safety Operations, DS&E, Novartis)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 

New Paradigm for Pharmacovigilance: The Emergence of Risk Management

A few years ago

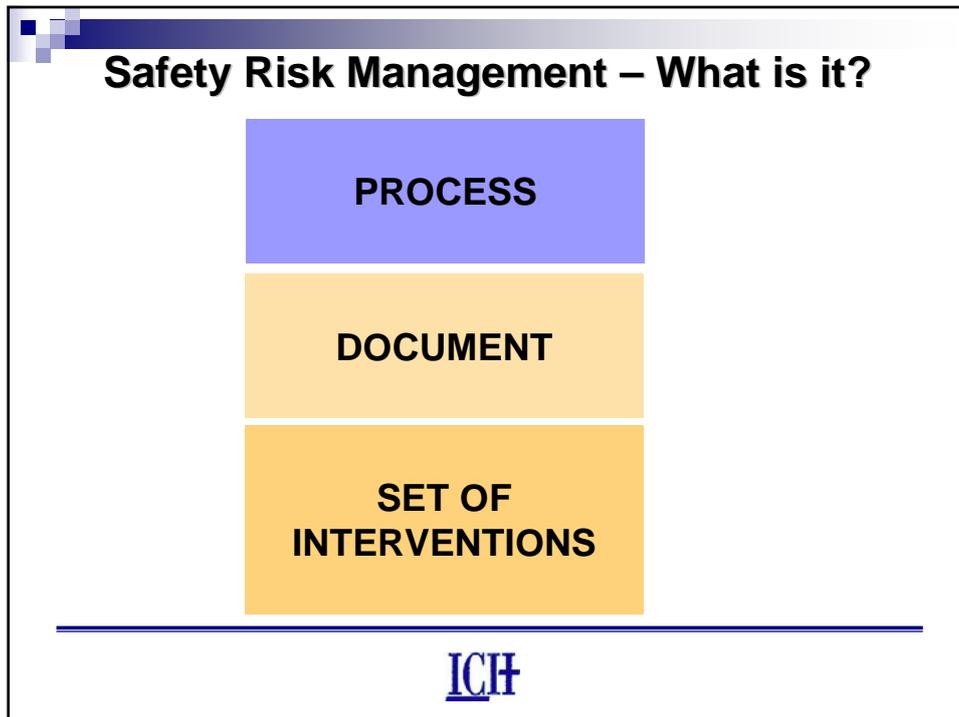
1. Safety divided into pre- and post-marketing
2. Reactive management through passive observation
3. Reliance on SR databases
4. Burden on HAs to detect risks
5. Risk management plans rare, drug specific
6. Routine pharmacovigilance is the standard
7. Risk activities generally not disclosed to public

➔

Today

1. HAs view safety as a life-cycle discipline
2. Prevention is focus of earlier and better risk management
3. New databases and technologies emerging
4. HA and sponsor share risk detection responsibilities
5. Risk management plans with most new dossiers
6. Drug-specific PV often requested
7. Risk activities made public by HA

Adapted from ICH training by Dr. Judith Sills, Global Head, Medical Safety Operations, Novartis



The Safety Risk Management Plan (RMP)

- Is a **regulatory document** submitted to Health Authorities
 - With an application for a new marketing authorization, with Periodic Safety Update Reports (PSUR), as a stand alone document
- Document which is **legally binding**
 - Once the RMP is accepted by the Health Authorities, the Market Authorization Holder (MAH) has a **legal** obligation to perform the activities described in the RMP

The icon shows a scale of justice on the left and a gavel on the right, both rendered in a simple, stylized manner. The scale has two pans, and the gavel is positioned horizontally.

Below the icon is a horizontal line, and underneath the line is the ICH logo.

What are the objectives of a Safety RMP?

The specific objectives of RMPs are three-fold:

- To specify what is and is not known about safety of a drug at the time of submission ([Safety Specification](#))
- To further characterize the safety risks post authorization ([Pharmacovigilance Plan](#))
- Where necessary, to define appropriate measures to minimize known risks to patients and to monitor the success of those measures ([Risk Minimization Plan and Evaluation of Effectiveness](#))

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RMP allows pro-active handling of safety issues

- **Business gains for proactive handling of safety issues**
 - **No/fewer delays of approval** due to safety issues (fewer safety questions by Health Authorities during approval review and shorter time required to answer those questions)
 - **Better control** of which safety risk management activities are required if risk identified internally and risk management activities proposed by MAH rather than mandated by Health Authorities
 - **Decreased risk of marketing restrictions**, unfavorable label changes and product withdrawals from market
 - **Improved reputation and trust** with Health Authorities and public resulting from proactive, responsible, and transparent handling of safety issues
 - **Internal consistency around communication** and knowledge of safety information of projects/products

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Regulatory Requirements for Safety RMPs

- **Required for all EU Submissions**
- **Australia adopted the EU Guidelines on Risk Management Systems, as described in Volume 9A, on 13 Nov 2008**
- **FDA Risk Evaluation and Mitigation Strategies (REMS) effective March 2008**
 - **REMS provided to FDA in addition to Global RMP**

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Regulatory Basis for Safety Risk Management

European Union

- **Volume 9A serves as legal basis**
- **Detailed EMEA Guideline for mandatory RMPs issued late 2005**
- **Detailed template released in 2006**
 - **Safety Specification summarizing risks**
 - **Pharmacovigilance plan**
 - **Evaluation of need for risk minimization activities**
 - **Risk minimization plan (if appropriate)**
- **Revised template based on 2-year experience expected in 2008**
- **EMEA approach focuses more on process - FDA approach focuses more on assessments**

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Regulatory Basis for Safety Risk Management

United States

- FDA Risk Management Guidances issued Mar 2005
 - Pre-marketing risk assessment
 - Good pharmacovigilance practices and assessment (case series, safety signals, pharmacovigilance plans)
 - Risk minimisation action plan (RiskMAP)
- Safety risk management plans requested by FDA for most NDAs
- Risk Evaluation and Mitigation Strategies (REMS) effective Mar 2008
 - To gradually replace RiskMAPs
 - "Evaluation of need for REMS" and/or actual REMS plan mandatory for all new NDAs
 - Significant focus on risk minimization metrics

Canada and Australia

- Draft legal requirements similar to EU recently proposed

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When do we prepare a safety RMP?

- At the time of a request for approval of a new drug, new indication, new patient population, etc.
 - RMP to be submitted with submission dossier
- Upon identifying a significant new safety concern
- At the request of health authorities



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When do we **update** an existing safety RMP

According to Volume 9A of the Rules Governing Medicinal Products in the European Union (version dated March 2007), Risk Management Plans should be updated:

- When **new information is available** that may impact the current Safety Specification, Pharmacovigilance Plan or Risk Minimization activities
- Within **60 days of an important milestone** (pharmacovigilance or risk minimization activity) being reached or the results of a study becoming available
- At the **request of a Health Authority**

Consider whether new risk minimisation activities are needed:

- New safety concern
- Existing safety concern but data suggests that current strategy not effective

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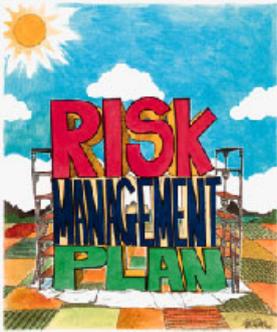
Risk management continuum



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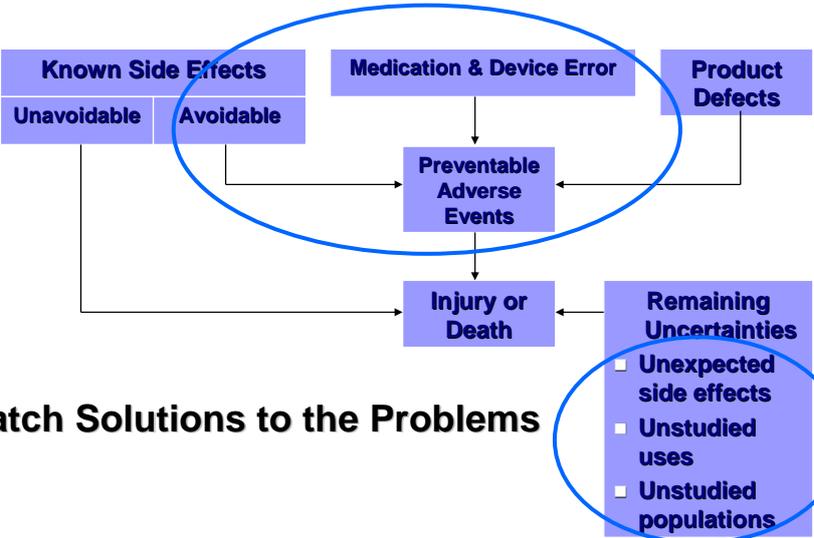
Different parties involved in risk management

- **Patients:**
 - effectiveness at no risk
 - freedom to choose
- **Health care professionals:**
 - good effectiveness at low risk
 - litigation fear
- **Regulators, payers, politicians:**
 - good effectiveness, acceptable risk
 - fear of litigation and fear of the media
 - resource constraints
- **Pharmaceutical companies:**
 - enough effectiveness, acceptable risk
 - fear of litigation and fear of the media
 - resource constraints
 - return maximization: shareholders



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Sources of Risk from Medical Products



```

graph TD
    subgraph KnownSideEffects [Known Side Effects]
        direction LR
        Unavoidable[Unavoidable]
        Avoidable[Avoidable]
    end
    Medication[Medication & Device Error]
    Product[Product Defects]
    
    Unavoidable --> Preventable[Preventable Adverse Events]
    Avoidable --> Preventable
    Medication --> Preventable
    Product --> Preventable
    
    Preventable --> Injury[Injury or Death]
    
    subgraph RemainingUncertainties [Remaining Uncertainties]
        direction TB
        Unexpected[Unexpected side effects]
        UnstudiedUses[Unstudied uses]
        UnstudiedPopulations[Unstudied populations]
    end
    RemainingUncertainties --> Injury
    
```

Match Solutions to the Problems

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Examples of RMP Goals and Objectives

Drug	Goal	Objective
Clozapine	No agranulocytosis	WBC monitoring
Thalidomide	No fetal exposure	Pregnancy prevention and monitoring for pregnancy
Lindane	Minimize CNS toxicity and death	No misuse (overdose or extended use)
Dofetilide	Minimize arrhythmia (torsade de pointes)	Dose adjustment in renal impaired, hospitalize pts while initiating therapy

■ Adapted from C.Karwoski, FDA – presentation at DIA Annual Mtg, June 2006



■ Thank you for your attention !

■ Questions ????



 Health Canada Santé Canada
Your health and safety...our priority. Votre santé et votre sécurité...notre priorité.

Pharmacovigilance *Challenges*



MedEffect Canada
Together we can improve health product safety

MedEffet Canada
Ensemble nous pouvons améliorer l'innocuité des produits de santé

Norman Viner MD
Chief, Clinical Trial Division
Health Canada
February 05, 2009



 Health Canada Santé Canada
Your health and safety...our priority. Votre santé et votre sécurité...notre priorité.

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop



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Provide Overview of some of the Challenges of Pharmacovigilance *Canadian Perspective*

- History
- Global Perspective
- Canadian Approach
- Challenges



3

History and Evolution

Definition

- From the Greek word 'Pharmacon': *DRUG*
- Latin 'Viigilare': *TO KEEP WATCH, AWAKE OR ALERT*
- **SYSTEM** for tracking the safety of products
- Consists of:
 - Regular and timely review,
 - Appraisal and
 - Communication of safety information critical to risk management of products



4

Key historical events that stimulated regulations

- First UK law to seek to regulate drugs was the 1868 Pharmacy Act
- USA: 1902 Biologics Control Act
- USA: the 1938 Federal Food, Drug and Cosmetic Act was passed, which required proof of safety before the release of a new drug. The category of 'Prescription-Only' drugs was codified into law by 1951.
- The thalidomide tragedy in the early 1960 heralded the modern regulatory system in most western countries.



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Safety Elements

- Increasing importance globally
- Safety related activities
 - Regulatory authority has been more limited and indirect
- Moving toward more active Pharmacovigilance
 - PSURS
 - Post marketing studies
 - Registries
 - Risk Management plans (periodicity driven by risk)
 - Improved communication



6

Periodic Safety Update Reports - PSURs

- Present worldwide safety experience of a medicinal product at defined times post-authorization:
 - Report all relevant new safety information;
 - Relate to patient exposure;
 - Summarize market authorization status in different countries
 - Any significant variations related to safety;
 - Create periodically the opportunity for an overall safety re-evaluation;
 - Indicate whether changes should be made to product information in order to optimize the use of the product.



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Two Phases of Safety Reporting

1. Development / Premarket

- ADR reports
- Special reports of unexpected clusters
 - DSMBs, Clinical Trial Steering committees, REBs;
- DSURs
 - Periodic safety reporting during clinical trials (modeled after the PSUR for marketed products).

2. Premarket / Marketed

- PSUR
 - Periodic Safety Update Reports
- Pharmacovigilance Planning



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Global Perspective

Pharmacovigilance just as drug development, is an Iterative process → Life Cycle

- Starts with discovery/identification of a molecule
- Screening in animals
 - PD, PK, Toxicology
- Is it safe for humans?
- Phases (1,2,3) of testing start
- Submission for marketing in a 'given indication'
- Other Indications, Conditions of Use – under development
- Benefit Risk assessment depend on data and indication
- Safety information builds with time
- Principles of Pharmacovigilance Plans
 - Life-cycle and Science-based approach to risk documentation, effective, harmonized, collaboration between regulators and industry



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Global Perspective

MedDRA

Medical Dictionary for Regulatory Activities

- Standardized terminology for classification, retrieval, presentation and communication of medical information
- Scope: symptoms, signs, diseases and diagnoses, investigations and tests, therapeutic indications, surgical and medical procedures, & medical, social and family history
- Includes medication error related terms
- Sharing of data requires consistency of data coding and assessment
- Facilitates standardized electronic transmission of medical information



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ICH

Harmonisation of regulatory requirements pioneered by the EU
Formed at a meeting in April 1990 comprised of :

- **Six Parties** that are directly involved, EU, EFPIA, MHLW, JPMA FDA and PhRMA
- **Three Observers**
WHO, CANADA and the EFTA, (represented by Swissmedic, Switzerland)
- **IFPMA**



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Global Perspective

ICH - Efficacy Guidelines (Clinical Safety)

E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E2E	Pharmacovigilance Planning
E2F	Development Safety Update Report



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Regional Pharmacovigilance programs

- MedWatch – FDA
- EudraVigilance – EMEA
- CanadaVigilance
- Early-Phase Post Marketing Vigilance (EPPV) Japan



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US FDA Model

- US FDA does not require RMPs with drug submissions for all products.
- FDA provides guidance documents to industry that focus on risk assessment and minimization during different stages of a drug's life cycle and gives direction regarding the development, implementation and evaluation of risk management activities.
- The US FDA will focus on products that pose an unusual type or level of risk. The proposed legislation is to use REMS (Risk Evaluation and Mitigation Strategies) that would require manufacturers to submit RMPs.



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European Medicines Agency Model

- The legislation requires that an RMP (Risk Management Plan) be submitted to regulators for (almost) all new products from MAHs.
- The EMEA states:
 - RMP submitted with applications for new medicines and generic products
 - When there is a significant change in conditions of use for an authorized product
 - When a safety concern is identified
 - When requested by a national regulator
 - The EMEA focus is on an RMP on activities that take place after a drug is marketed.



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Scope

The Canada Vigilance Program collects adverse reaction reports for the following marketed health products approved for use in humans:

- Pharmaceutical drugs (prescription and non-prescription)
- Biologics (Schedule D, biotechnology products, therapeutic and diagnostic vaccines and fractionated blood products)
- Radiopharmaceutical drugs
- Natural health products



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Adverse Reaction Reports

- Domestic Adverse Reaction Reports
 - Serious Adverse Reactions
 - Reports concerning reactions occurring in Canada to a product that is marketed in Canada
 - Market Authorization Holder report within 15 calendar days of receiving the information (expedited reporting)
 - Unusual failure in efficacy reports for new drugs
- Foreign Adverse Reaction Reports
 - Serious Unexpected Adverse Reactions
 - Reports concerning reactions occurring outside Canada to a product with the same combination of active ingredients that is marketed in Canada
 - Market Authorization Holder reporting within 15 calendar days of receiving the information (expedited reporting)



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Reporting to Canada Vigilance

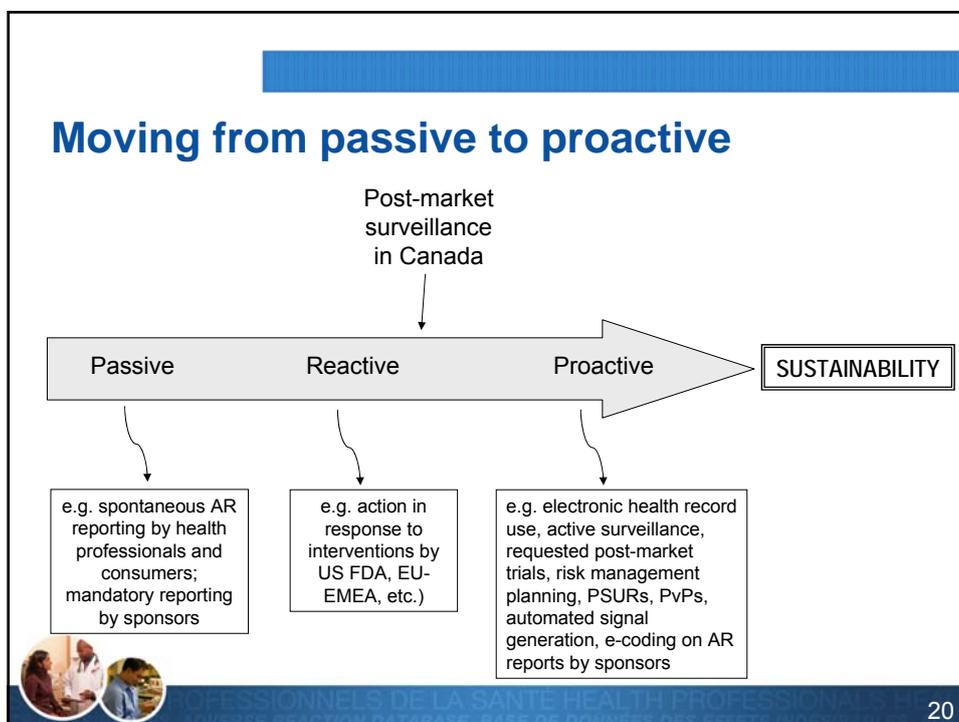
- Adverse reaction reporting form
 - Available Regional/National Offices, MedEffect website, Compendium of Pharmaceuticals and Specialties (CPS)
- Submit by fax or mail
- On-Line www.healthcanada.gc.ca/medeffect
www.santecanada.gc.ca/medeffet
- Toll Free Telephone and Fax
- Verbal reports accepted
- Postage paid mail



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Risk Communication Documents

		Target Audience	
		Public	Health Prof. / Hospitals
Responsibility for Issuance	HC	<ul style="list-style-type: none"> • Public Warning • Public Advisory (PA) • Health Product Recall Notice • Foreign Product Alert (FPA) • Information Update • It's Your Health (IYH) • Fact Sheets and Backgrounders 	<ul style="list-style-type: none"> • Health Canada Issued Health Professional Communication – Dear Health Care Professional Letter (HPC_DHCPL) • Health Canada Issued Health Professional Communication – Notice to Hospitals (HPC-NtoH) • Canadian Adverse Reaction Newsletter (CARN)
	MAH with HC	<ul style="list-style-type: none"> • Industry Issued Public Communication (MAH-PC) 	<ul style="list-style-type: none"> • Industry Issued Health Professional Communication – Dear Health Care Professional Letter (HPC-DHCPL) • Industry Issued Health Professional Communication – Notice to Hospitals (HPC-NtoH)



Canada Vigilance Database

Business Requirements:

- Clinical trial AR requirements
- Post market AR requirements
- Signal Detection & powerful query tools
- ICH compliant (E2B, MedDRA, ESTRI-Gateway)
- Management & ICSR reporting
- Scanning and Imaging
- Capability for future integration

Oct 2006 – Contract signed with ArisGlobal

- Products/services are used by industry including 9 pharmaceutical companies
- Participation in regulatory activities such as FDA's e-Prompt group, EMEA's joint working groups, MHLW's E2B Pilot
- Currently working on the implementation of a French language version of their software at the French Regulatory Agency (l'Agence française de sécurité sanitaire des produits de santé (AFSSAPS))
- Currently in Implementation Mode

Integrated and complementary suite of 3 applications which include:

- Core application
- Signal detection tool
- ESTRI gateway module



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Implementation of Canada Vigilance Database is a 2 phased approach:

- **Phase 1:**
 - Implementation of core product – March 2008
 - Data Migration
 - Testing, Validations etc. of product & data
- **Phase 2:**
 - Electronic Reporting by Market Authorization Holders – 2009
 - Communication with stakeholders
 - Establish technical interface protocols
 - Establish small manufacturer reporting interface
 - Reporting requirements
 - Pilots to validate



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Consumer Reporting Form

- Project to develop form is underway and usability testing of form to take place February/ March 2008
- Guideline document to be developed



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Signal Detection: Adverse Reaction Data

- Reports vary widely in quality, accuracy, and completeness
- Each report represents the suspicion, opinion or observation of the individual reporter i.e. rarely proven associations
- Significant under-reporting domestically and internationally
- Cause and effect relationships have not been established in the vast majority of reports submitted
- Population exposure data often unavailable
- AR may be result of non-compliance of patient, medication error, or other system factors
- May resemble progression of disease



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Challenges

Surveillance Programs for Health Products

Health Canada

- Medical device adverse incident reporting
- Acute transfusion reaction monitoring, blood and blood components
- Cells, Tissues and Organs reporting system
- Canada Vigilance: Monitoring system for spontaneous adverse reaction and medication incident reporting for pharmaceuticals, biologic and biotechnology products, natural health products (dietary supplements)
- Monitoring for veterinary drugs

Public Health Agency of Canada

- Preventive vaccines surveillance (scheduled immunization, travel, flu)
- Transfusion Transmitted Injuries Surveillance System
- CJD surveillance program



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Challenges

Increased expectations

- **Pharmacovigilance (PV) depends heavily on collaboration**
 - Reach to health care professionals through risk communications has limitations (passive)
- **Operations in need of better integration**
 - Currently Pre and Post Market regulatory structure is in separate organizations - not conducive to life-cycle management
 - Roles & responsibilities need updating.
- **Public scrutiny of PV is higher than ever**
 - Surveys indicate increased need for transparency and openness
 - Expectations for public input and participation in defining major orientations
- **Adverse Reaction monitoring, detection, assessment and risk mitigation more comprehensive due to the sophisticated capabilities offered by modern technology**
 - Our IM/IT needs better integration



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Challenges

Health Canada is developing a RMP Model

- The proposed RMP Approach would involve a regulatory standardized and systematic review of Pharmacovigilance Plans, a document outlining the product safety specifications and proposed pharmacovigilance activities and resulting data/information.
- Proposed RMP Program would be a hybrid of the current Canadian Status Quo and a Canadianized version of the EMEA Model.



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Challenges

Pharmacovigilance Regulatory Authority Issues

- HC dependent on the voluntary submission of adverse reactions (ARs) by health professionals, manufacturers and the public.
- Manufacturers (Market Authorization Holders-MAHs) must report ARs if they have serious or serious unanticipated impact on health.
 - they are not obliged to report on evolving global knowledge and experience with marketed health products
- Canada is working towards the use of complementary information sources (eg. PSURs, PVP) and not yet harmonized with international best practices.
- No authority to compel additional post-market studies/data, labelling changes or risk communication issuance



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Challenges

Broader Regulatory Issues

- While Canada's health and safety regime has served Canadians well, it requires modernization:
 - More complex products, more rapid innovation to market, new source countries
 - Consumers want more choice and involvement
- Canada's health protection system was developed in an earlier era
 - Food and Drugs Act, 1953
 - International counterparts (US, European Union, Australia) have moved to update their health and safety regimes
- Modern legislation is required to successfully implement Canada's Food and Consumer Safety Action Plan



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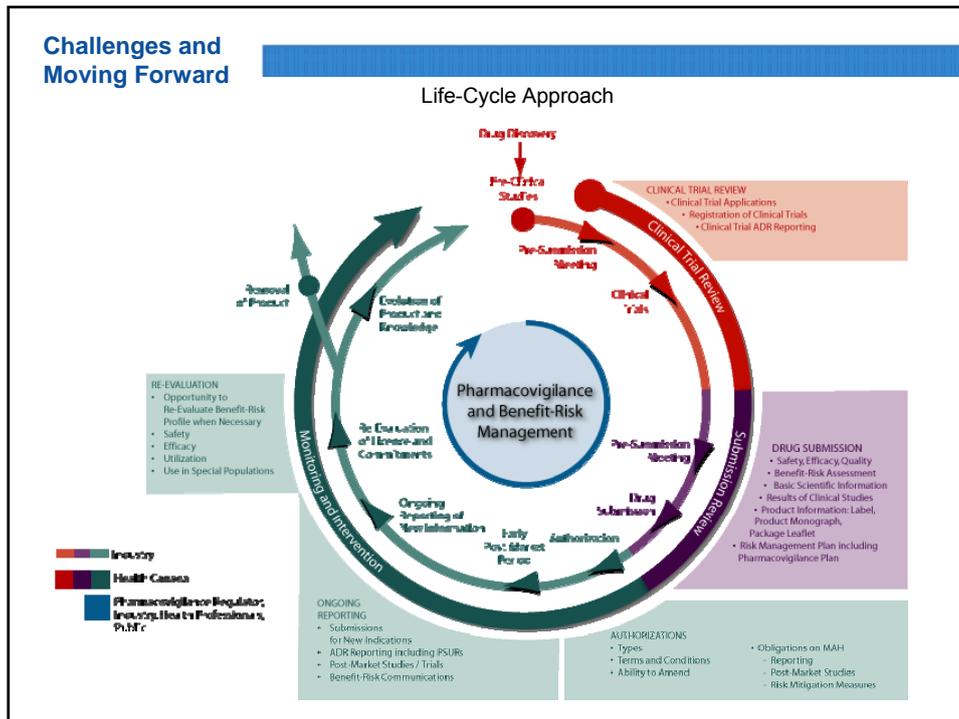
Challenges

Modernizing the Food and Drugs Act (Bill C51)

- Health Canada proposes a comprehensive modernization of the *Food and Drugs Act* that anticipates the present and future needs of Canadians
- Amendment updates will consist of
 - Life-cycle approach to regulating drugs
 - Mandatory reporting
 - Compliance and enforcement
 - Openness and transparency
 - Food safety



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Challenges

Defining Confidential Business Information (CBI)

- **Issue:** The lack of a definition and framework to define CBI has led to inconsistent disclosure practices and has hampered Health Canada's efforts to be open and transparent.
- **Proposal:** To define a framework for how to assess CBI in legislation.
- **Safeguards:** The framework would be consistent with the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement and would respect Canada's obligations under the North American Free Trade Agreement (NAFTA); other federal statutes; and regulatory frameworks of other jurisdictions.
- **Regulatory Amendments:** For greater certainty, regulations will be used to define: the types of information that are not considered to be CBI; when information ceases to be CBI; and, the timing and conditions under which such information might be disclosed.



Challenges

Sharing information with other governments and organizations

- **Issue:** Health Canada has actively pursued strong partnerships with key regulatory counterparts to facilitate information sharing on the safety and/or efficacy of health products, food and consumer products. Some countries are reluctant to exchange information with HC, including CBI, without specific legislative authorities and corresponding safeguards.
- **Proposal:** The Department is seeking an authority to enable the exchange of information with its regulatory counterparts in other jurisdictions.
- **Safeguards:** Information disclosure could be done through signed confidentiality agreements.
- **Regulatory Amendments:** The Department does not foresee the need for regulations with this proposal.
- **Policy Instruments:** Memorandum of Understanding



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Conclusions

- The shift from pre-market review to assessing and managing the risks and benefits of products throughout their entire life-cycle is good for all stakeholders (MAH, Regulators and the consumer).
- Canada is moving forward to modernize and harmonize their Regulations to enable effective Drug Regulation and Pharmacovigilance in line with the best practices globally.



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Thank You

- Thailand, APEC, ICH, Novartis
- Health Canada
 - Dr Agnes Klein
 - Heather Sutcliffe
 - Mike Ward



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 close of the "Advanced Workshop : Review of Drug Development in Clinical Trials" provided an opportunity for open comments or suggestions from all facilitators and participants to identify gaps and challenges for implementation, and suggestion for future cooperation.

The comments from facilitators and participants are listed below

Gaps and Challenges for Implementation

- Lacks of human resources
- 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.
- The regulatory scientific review/evaluation of investigational drugs and their clinical trials are not yet existed in a few economies and not fully functioned in some economies
- In the world of global drug development, many therapeutic innovative medicines are coming out and ready to be tested in clinical trials. Drug Regulatory Agencies need to perform scientific evaluation in both quality and safety aspects.
- Pharmaceutical Industries become more interested to conduct higher risk trials, e.g. First in Human trial, Adaptive Design, etc, in developing economies.

Suggestion for Future Cooperation

- Basically, do the best with the tools you have
- If the trial has too much risk particularly the higher risk trials, you should seek for help e.g. collaboration, consultation.
- Pharmaceutical and Medical Devices Agency offers support interested participants with practice guidelines, which could be translated from Japanese to English by request
- The training course should continue every year or every other year to update and sustain knowledge, experience sharing, and networking opportunities.

- The training could be a back to back meeting at APEC Life Sciences Innovation Forum. APEC should provide supports, e.g. technical support, experts from competent drug regulatory agencies, and some financial support.
- The keys to reduce the gap are to establish collaboration and information sharing to improve the system
- Suggested future topics of interests are
 - o Review process for design of clinical trials
 - o Pharmacovigilance plan
 - o Review of new study design

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 : Review of Drug Development in Clinical Trials

Bangkok, Thailand, 2-6 February 2009

Part A for Participants

Number of respondents was 22 among 26 participants.

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

- We had learnt the principle and essential issues in developing the review mechanism and gained how to conduct the review of clinical drug development in aspects of quality and safety of both investigational pharmaceutical and biological products
- The workshop give all information regarding review of drug development in clinical trial, the strategies how to handle new therapeutic life sciences innovations through the best practice of clinical trial by evaluation of clinical drug development in order to strengthen our drug regulatory authority in clinical trial aspect according to GCP guideline
- The workshop will be of help for the regulatory authority to prepare or develop more effective process to evaluate the clinical research protocol especially for new emerging products and technology to be innovative and substantially safeguard the public health
- Will establish clinical trial review system in our economy
- Will be beneficial for international cooperation and regulatory network in APEC region
- The knowledge gained would help us to refine existing system in clinical trial review
- This course has imported useful and significant knowledge and experience through the various discussions had amongst the different regulatory agencies with participation from industry, which could be applied in the setting up of a clinical trial review system in our economy

- Will improve the organization and procedure to review clinical trials, and Pharmacovigilance for both pre and post marketing
- The techniques and knowledge sharing from the course had benefited me to improve how the clinical trial application review and how to approach problems on possible risks that subjects may undergo should be done
- The knowledge from this workshop would be very beneficial to improve our guidelines for clinical trial review
- Knowledge of how developed economies (e.g. Japan, Canada) are doing clinical trials would prepare developing economies to some of the challenges ahead
- From the sharing of participants from each member economy represented, we were able to compare and learn the best practice in evaluation of clinical trial submission
- Will lead to better standards hence attracting foreign investors to invest in our economy in clinical research

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

- Gained skill on how to establish Clinical trial review system
- Gained skill on how to evaluate clinical trial protocol
- Gained still on pharmacovigilance in clinical trials
- Gained a lot of knowledge including Global Factors on R&D, Quality (CMC) Review of Clinical Trials, Review of early phases of clinical trial,e.g. first in man, Review of non clinical data, Review Principles of Dose Selection, Novel Designs in Clinical Trials, Ethics in Clinical Trials and Pharmacovigilance issue, etc
- The new knowledge of CMC review will help us develop the CMC review system
- It is important to share experience from different economies to strengthen the regulation of clinical trials
- The difference of each economy present in region does not mean there is a difference in their aim
- Having a more critical outlook in evaluation of clinical trials
- Learned to be more critical of specific items in clinical trials, e.g. informed consent document, protocol, reporting of adverse events, impact management, were also introduced.
- Risk management is also an important aspect that must be regimed to protect the rights of the subjects
- Understand in-depth of new innovative approach to design the clinical trials e.g. adaptive design

- Ethical consideration of clinical trials
- All speakers taught us to be more considerate about something that often lacks in protocol and how to reveal it.
- Development of Review Mechanism (Tools and approaches)
- How to conduct the consultation with applicant

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

- Update guideline for review of clinical trial
- Update guideline on pharmacovigilance plan
- Update the existing clinical trial framework and regulations
- Establish/Improve the CMC review for biologics
- Improve Clinical Trial Application Review and share the knowledge to other reviewers
- Improve the requirements for Biological Products
- Improve internal process to accelerate the review and availability
- It is important to have clinical trial team work within the office of new drug, pre and post marketing Pharmacovigilance work with more coordination.
- Discuss with the higher management knowledge gained from this workshop and try to formulate action plans that would enable the DRA's to safeguard our economy against studies that were banned in developed economies to be done in our economy to protect the public
- Propose to our management the establishment of mechanism and regulation for a closer oversight of clinical trials in our economy, which may be done through a more thorough selecting of the protocol as well as adherence to GLP, GMP and GCP
- Improve the strategies for review of clinical trial application in quality and safety aspect to ensure that the human subject's right, safety, and the clinical trial's data are credible
- We should be able to do better in choosing the best drugs in affordable price
- Need more practice on review of documents
- Need to strengthen our internal expert
- Implement the scientific review on clinical drug development

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

- Next steps
 - o Train our staff on review of clinical trial
 - o Cooperation among APEC economies to build/strengthen of clinical trial research aspect
 - o Preparation of human resources, regulation, etc, to take care of clinical trial in the economy
- The next project should provide
 - o Expand pharmacovigilance plan
 - o Short course training to discuss specialized topics e.g. adaptive design
 - o The project may be built by forming regional workshop on a special project, e.g. co-evaluation of the clinical study and inspection
 - o Pre clinical research evaluation of clinical trial submission
 - o Need the same project to strengthen our staff
 - o It should be a continual project in order to provide the more confident in reviewing the clinical trial
 - o The continuation of the project to make the loop of trainees and trainers further
 - o Make it the annual meeting, back to back with APEC LSIF (at the beginning) and stand alone meeting/seminar, if possible
 - o On site inspection practice
 - o It may also be beneficial to have speakers from US FDA or MHRA to share their experience and other matters that have not been covered in this course
 - o Review for Marketing authorization
 - o Each economy should organize similar training activities

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

- To enhance review of clinical trial, pharmacovigilance plan, and challenges facing regulatory
- A Clinical Trial forum could be started as part of APEC LSIF meeting so that regulators have a platform to share information pertaining to clinical trial development in their economies
- Peru would probably have an agreement with other economies, e.g. Chile.

- May be APEC LSIF or ASEAN PPWG should have a committee to discuss issues regarding clinical trial especially concerning its regulations
- To create projects for my economy on CMC review especially for biologic products and safety management for clinical trials
- Integration in terms of evaluating clinical research between APEC economies need to be established
- Our organization must prepare for evaluation and monitoring of clinical trial especially for the early phase trials
- To strengthen and create internal review teams to fulfill in term of clinical drug development and scientific review as WHO prequalification programme

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

- [5] (good) : 19 (86%)
- [4] : 3 (14%)
- [3] : 0
- [2] : 0
- [1] (poor) : 0

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

- Great project, it helps in understanding of clinical trial regulation
- The project met our expectations and learning objectives
- The speakers were excellent as they shared experiences and approached discussions/topics in a very realistic way
- The project is very effective with qualified speakers, discussion, case studies, Q&A session and good training programme
- The overall of the project was carried out is good and interactive. Participants could learn from each other experiences and opinions
- The information presented are very informative and would provide a useful source as future reference and knowledge
- It gave us an insight to the practices in clinical trial evaluation around the world as well as some insights into how some companies are doing clinical trials which is an effective way to help strengthen the capability of the DRA's in this field
- The project is effective and helpful to build regional cooperation in regulation of clinical trial

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

- Just Right (20) 91%
- Too Detailed (0)
- Not Detailed Enough (2) 10% need more time for discussions
- N/A(0)

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

- Need more exercises or case studies detailing to focus for each exercise in providing understanding
- More focus on Pharmacovigilance plan
- Similar workshops should be organized for other economies in order to benefit more professional of each authority
- New topics should be how to assess clinical trial report and points to consider, pre-clinical study evaluation, and bioequivalence study evaluation
- Sometimes language barrier hinders easier and in depth understanding of the topics
- Should have more speakers from developed economies and countries, e.g. US FDA, EMEA, Australia, New Zealand, if possible.
- APEC Financial Requirements is complicated and not so friendly to our trainers. The facilitators usually had to do lots of preparation for the training prior to the workshop. So, the complicated financial process causes some difficulties for them. Some economies had to self sponsored for the GCP inspection workshop
- The setting and content of the project are so effective and useful. Therefore, I recommend this project should be re-conducted for other member of APEC

Part B for Speakers

Number of respondents was 4 among 4 speakers.

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

- The project achieved its objectives
- We could exchange current situations and philosophy of each regulatory agency
- The project has provided the information and experience
- This workshop provided a good environment for informed discussion of regulatory best practice in the area of clinical trial regulation as well as global perspectives of the current state of regulation in a number of APEC economies
- A number of real world examples were used which fostered good discussion between attendees

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

- The attendees were the most appropriate target group
- The attendees seemed to be well matched to the curriculum and provided good insight of discussion as well as representing their economies well

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

- Excellent
- Tried our best to meet their needs
- While difficult to assess it appeared that there was good dialogue between participants between participants and speakers
- Building understanding of the approaches in various jurisdiction and providing a platform for harmonization seem to be progressing well

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

- More specific topic and bring the real case from each country to discuss in the next meeting
- Through this feedback form from participants' perspectives
- Might have more of an involvement of participants in the planning stages of the workshop (or more time on issues brought up by participants)

(e): Any other suggestions?

- None