

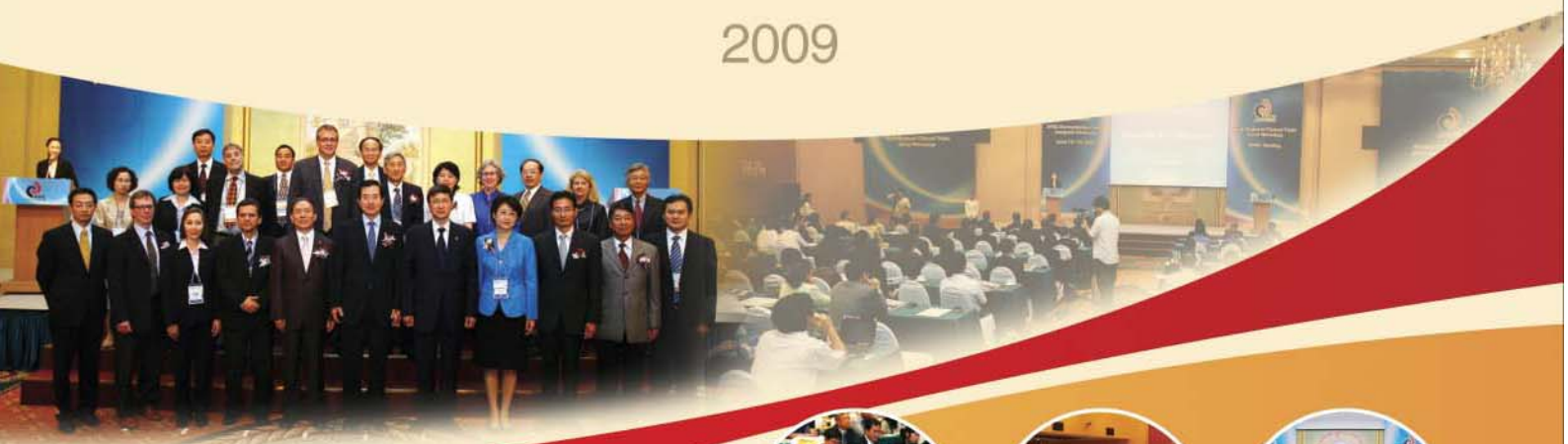


Asia-Pacific
Economic Cooperation

Multi-Regional Clinical Trials Seoul Workshop

Inaugural Workshop of the APEC Harmonization Center

2009



APEC Life Sciences Innovation Forum





MULTI-REGIONAL CLINICAL TRIALS SEOUL WORKSHOP

Inaugural Workshop of the APEC Harmonization Center

2009



APEC Harmonization Center

APEC Life Sciences Innovation Forum
APEC Harmonization Center

Prepared By
APEC Harmonization Center Secretariat
Korea Health Industry Development Institute (KHIDI)
57-1 Noryangjin-dong, Dongjak-gu, Seoul, 156-800, Korea
Tel : (822) 2194-7323, Fax : (822) 822-8811,
Email : ahckorea@khidi.or.kr, Website : www.apec-ahc.org

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

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I. Executive Summary

1. Summary of Proceedings

'Multi-Regional Clinical Trials Seoul Workshop', the inaugural workshop of the APEC Harmonization Center, was hosted by Korea Food and Drug Administration (KFDA), organized by the Korea Health Industry Development Institute (KHIDI), and supported by APEC Life Sciences Innovation Forum (LSIF). A total of 562 participants attended the workshop from 15 APEC economies (Australia, Canada, P.R. China, Chinese Taipei, Hong Kong, Japan, Korea, Malaysia, Mexico, Peru, Philippines, Singapore, Thailand, the United States, and Vietnam) and 2 non-APEC countries (France and the United Kingdom).

The workshop benefited from the technical expertise of invited persons from the following organizations including government, industry, and academia: 1) Center for Drug Evaluation, Chinese Taipei, 2) COFEPRIS, Mexico, 3) Health Canada, Canada, 4) KFDA, Korea, 5) PMDA, Japan, 6) SFDA, China, 7) ThaiFDA, Thailand 8) USFDA, United States 9) Industry (Bayer, GSK, Merck, Pfizer, PhRMA, Wyeth) 10) University (University of Western Ontario).

The workshop was divided into six plenary sessions and four breakout sessions.

Session One. *The Value and Challenges of Multi-Regional Clinical Trials*. The session dealt with the presentations on: 1) The Values and Challenges of Multi-Regional Clinical Trials, 2) Values and Challenges of MRCT: A Regulatory Perspective.

Session Two. *Intra-Regional Efforts to Streamline the Conduct of Clinical Trials: The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group*. Four presentations were made on: 1) Perspective for Global Clinical Trials, 2) Current Regulatory Situation in Korea, 3) Tri-party Clinical Initiatives and Its Prospective, 4) Intra-Regional Efforts to Streamline the Conduct of Clinical Trials: The ASEAN Pharmaceutical Products Working Group.

Session Three. *ICH Overview*. Speakers shared their views on: 1) Industry Perspectives on the Adoption of ICH Guidelines in Asia, 2) ICH Overview & Impacts of Efficacy Guideline in Global Drug Development.

Session Four. *Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in order to Succeed*. The Presentations were on: 1) Interpreting Subgroup Analyses in Clinical Trials, 2) Issues with Design and Analysis in MRCT, 3) Statistical/Operational Considerations When Designing and Implementing a Multi-Regional Clinical Trial.

Session Five. *Operational Aspects*. The presentations in this session focused on: 1) Selected Topics in the Operational Aspects of Multi-Regional Clinical Trials, 2) Operational Aspects based on Korean Experience, 3) Aspects on the Planning & Implementation the GCP & QA for MRCTs.

Session Six. *Regulatory Guidance/ Perspectives/ Issues*. The session dealt with issues on: 1) Implementation/Adaptation of ICH Clinical Guidelines into "Good Review Practice and Regulatory Partnership" in Chinese Taipei, 2) Regulatory Guidance/Issues - A Company Perspective.

Breakout Sessions. The Participants were divided into the following four breakout sessions. 1) Regional Specific Issues, 2) Site Management, Data Management and Good Clinical Practice, 3) Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in order to Succeed, and 4) Specific Therapeutic Areas.

2. Summary of Findings and Recommendations

Findings

A. Regional Specific Issues

- Different requirements from countries, e.g., numbers of patients required in clinical trials in the country
 - Develop guidance for scientific basis to look at the data from multiple countries
 - Better understand/develop statistical methodologies and techniques for multi-regional trials
 - Better understanding of the differences regulations in different countries
 - Create a repository of regulations
- Select an appropriate therapeutic area or disease to pilot how we can deal with and develop guidance for multi-regional trials
- Mechanism to solicit and collect input from stakeholders on an ongoing basis
- Broader participation; specific plan with defined timelines
- Training
 - Mechanism for assessing needs, identifying priorities, qualifying trainers, developing curriculums, certification, etc.
 - "RHSC training subcommittee"
 - Workshop on " Good Review Practice", science-based review
 - Case studies
 - Long-term investment, e.g., academia education and training

B. Site Management, Data Management and Good Clinical Practice

- Develop a Better Understanding of Inter-Regional Variability
 - Initiate a prospective collection and archiving of MRCT data sets to enable scholarship on inter-regional variability
 - Identify key (clinically relevant with the potential to affect trial outcomes) variables causing inter-regional variability.
 - ICH E-5 intrinsic and extrinsic factors
 - Impacts on Quality variation
- Enable Greater Science-Based Decision-Making
 - Provide a forum to increase collaboration among industry, academic and regulatory scientists to enhance awareness of the issues specifically related to MRCT design
 - Focus on the scientific rationale on the appropriateness of regional participation rather than merely local participation (e.g., pre-specified minimum numbers or enrollment percentages do not appear to be science based, and are a significant deterrent to MRCT.
 - Promote appropriate scientific tools (e.g., biostatistical theory) to enable regulators and industry across the APEC region to better understand MRCT design and execution.
 - Encourage participation by small/medium sized companies.

- Enhance the Capabilities of Physician-Investigators (PIs) Involved in MRCT Execution
 - Provide an education forum for PIs
 - Focus on the important role they play in MRCT design, and the unique obligations they must fulfill in MRCT execution
 - Encourage PIs to participate in the development of common self-assessment tools (e.g., quality of life assessments)
 - Promote common terminology for AE/SAE reporting - (e.g., MedDRA terminology).
 - Increase PI awareness that they are subject to oversight by multiple drug regulatory authorities.
 - Increase attention to the Informed Consent Process - (staff training, documentation, translations).

Recommendations

A. Training

- Create RHSC subcommittee on training
- Survey / assess areas of interest / needs
- Consider dedicated mailbox
- Prioritize needs
- Identify quality trainers
- Develop metric/reporting mechanism for determining benefits
- Face-to-face programs, webinars, modules
- Involve regulators, industry, academia

B. Develop 'guidance' for MRCT

- Prospective Research and Data Collection
- Create Principles Document

C. Repository of Information

- Industry to identify critical areas with significant impact of disharmony
- Common Language (translation issues)
- Clearinghouse of events and information related to harmonization
- Network of experts

D. Promote dialogue on MRCT

- Promote dialogue on MRCT
- Establish for a for further discussion

E. Develop Templates for Reporting and Reviewing

3. Summary of the Workshop Evaluation

Evaluation forms were given to participants and resource persons to provide their ratings on following categories: 'general evaluation', 'contents of the workshop', and 'speakers'.

80.3% of the participants who completed the evaluation rated the seminar either “very satisfied” or “satisfied” of the workshop in general. When asked to rate the value of the workshop in improving the professional knowledge of the participants, 82% of those who completed the evaluation selected either “very satisfied” or “satisfied”. Other highly rated elements of the seminar included the interaction with speakers, the materials provided, and the usefulness of information.

Participants were also asked to provide suggestions on future seminars including the workshop agendas. The most common response received was a request for small group breakout sessions. Some comments are as follows:

- It would be good to have more practical sessions instead principles ex. case reviews, etc.
- Short presentations (30 mins) at each breakout session are needed as an overview and guidance for the participants to express view/opinions on the topics discussed.
- The break out session of workshop should really be divided into smaller groups
- Shorter workshop. Smaller breakout sessions to and discussion. Better instruction on flow of activities.
- To have smaller breakout sessions using smaller groups and rooms. Supplemented with focus group. To get more involvement from other health authorities.
- Direction/ focus "discussion" are necessary to take it further. Need better integration in science among regulator, scientists from industry and academic.

Suggested Workshop Agendas

- Electronic system / GCP comparison among Korea/Japan/China.
- Ethics consideration in Multi-regional Clinical Trials.
- More detailed of the same topics will be more appreciated.
- Good regulatory practice and review. Realizing simultaneous global development.
- More specifics on certain topics and have a thorough discussion about issues and potential solutions. Action plan has to come out from the session.
- MRCT on biomilar and/or bioproduct. Possible way of small size pharmaceutical company can do MRCT.
- Evaluation of MRCT.
- Sharing good practice of successful clinical trials.
- The experiences in good review practices or the assessment and evaluation of the CT documents.

II. Multi-Regional Clinical Trials Seoul Workshop

1. Participants

- VIPs

APEC economies	
	<p><i>Kohei Wada (Japan)</i> Co-Chair ICH GCG</p>
	<p><i>Mike Ward (Canada)</i> Chair APEC LSIF Regulatory Harmonization Steering Committee</p>
	<p><i>Victor Alejandro Dongo Zegarra (Peru)</i> Director General DIGEMID-MINSA</p>
	<p><i>Werawan Tangkeo (Thailand)</i> Deputy Secretary General Thailand Food and Drug Administration</p>
Korea	
	<p><i>Jae-Hee Jeon</i> Minister Ministry for Health, Welfare, and Family Affairs</p>
	<p><i>Ung Jun Byun</i> Chair Health, Welfare, and Family Affairs Committee The National Assembly of Republic of Korea</p>
	<p><i>Young Hak Yoo</i> Vice Minister Ministry for Health, Welfare, and Family Affairs</p>

	<p><i>Yeo Pyo Yun</i> Commissioner Korea Food and Drug Administration</p>
	<p><i>Sang Yong Lee</i> Deputy Commissioner Korea Food and Drug Administration</p>
	<p><i>Seung Hee Kim</i> Director, APEC Harmonization Center President, National Institute of Food and Drug Safety Evaluation</p>
	<p><i>Bup Wan Kim</i> President Korea Health Industry Development Institute (KHIDI)</p>

▪ **Speakers & Moderators**







	<p>Plenary I, Breakout Session 2 <i>Mark Paxton (United States)</i> Associate Vice President, International Regulatory Affairs, PhRMA</p>
	<p>Plenary I, III, Breakout Session 1 <i>Toshi Kobayashi (Japan)</i> Technical Advisor, PhRMA-Japan</p>
	<p>Plenary I, IV, VI, Breakout Session 3 <i>James Hung (United States)</i> Director of Division of Biometrics I Office of Biostatistics, US Food and Drug Administration</p>
	<p>Plenary II <i>Justina A. Molzon (United States)</i> Associate Director, International Programs US Food and Drug Administration</p>
	<p>Plenary II <i>Haruo Akagawa (Japan)</i> Associate Center Director, Center for Products Evaluation Pharmaceuticals and Medical Devices Agency</p>
	<p>Plenary II, VI <i>Kyung Won Seo (Korea)</i> Director Drug Evaluation Department, KFDA</p>
	<p>Plenary II, VI <i>Jian-hua Ding (China)</i> Director, Division of American and Oceania Affairs, Dept of International Cooperation State Food and Drug Administration / ICH GCG representative</p>
	<p>Plenary II, V, VI <i>Yuppadee Javroongrit (Thailand)</i> Assistant Director, Drug Control Division, Thai FDA</p>

	<p>Plenary III <i>Yoshiaki Uyama (Japan)</i> Review Director, Office Of New Drugs III, PMDA Coordinator, ICH Steering Committee</p>
	<p>Plenary III, VI, Breakout Session 2 <i>Martha A. Brumfield (United States)</i> Senior Vice-President, Worldwide Regulatory Affairs & QA Pfizer Inc</p>
	<p>Plenary IV, V, Breakout Session 1 <i>Ling Su (China)</i> Vice President, Clinical Research and Development Wyeth Asia Pacific Region</p>
	<p>Plenary IV, Breakout Session 4 <i>Allan Donner (Canada)</i> Professor, Department of Epidemiology and Biostatistics University of Western Ontario</p>
	<p>Plenary IV, V, Breakout Session 3 <i>William Wang (China)</i> Department of Biostatistics and Research Decision Sciences (BARDS) Merck Research Laboratories, Merck & Co, Inc.</p>
	<p>Plenary V, Breakout Session 4 <i>Yil Seob Lee (Korea)</i> Director, Medical and Regulatory GlaxoSmithKline Korea</p>
	<p>Plenary VI <i>Heng-Der Chern (Chinese Taipei)</i> Director Taiwan Center for Drug Evaluation</p>
	<p>Plenary VI <i>Min Irwin (China)</i> Medical Director of Medical and Regulatory Affairs Bayer Schering Pharma China</p>
	<p>Plenary VI <i>Marco Antonio Llanas Blanco (Mexico)</i> Sanitary Authorization Commission Federal Commission for the Protection against Sanitary Risks</p>

- **Delegates**

<p><i>Yam Pei Ching (Malaysia)</i> Assistant Director, Clinical Research and Compliance Section National Pharmaceutical Control Bureau, Ministry of Health</p>
<p><i>Zaril Harza Zakaria (Malaysia)</i> Senior Assistant Director, Clinical Research and Compliance Section National Pharmaceutical Control Bureau, Ministry of Health</p>
<p><i>Elizabeth Carmelino (Peru)</i> Executive Director, Director of Control and Sanitary Surveillance, DIGEMID</p>
<p><i>Maria Vargas (Peru)</i> Member, Pharmacovigilance and Pharmacoepidemiology Team, DIGEMID</p>
<p><i>Liza S Pajarillo (Philippines)</i> Food-Drug Regulation Officer III, Bureau of Food and Drugs, Department of Health</p>
<p><i>Wenzel C. Asprec (Philippines)</i> Food-Drug Regulation Officer III, Bureau of Food and Drugs, Department of Health</p>
<p><i>Thongchai Thavichachart (Thailand)</i> Senior Expert Advisor, Thailand Center for Excellence for Life Sciences Ministry of Health</p>
<p><i>Wilai Bundittanugula (Thailand)</i> Senior Expert in Drug Standard, Thailand Food and Drug Administration</p>
<p><i>Hai Doan Ngoc (Vietnam)</i> Secretary for Vice Minister, Department of Science and Training, Ministry of Health</p>

▪ **Committee - Special Thanks**

	<p><i>Barbara Norton (United States)</i> Chair, APEC LSIF Planning Group Director, Industry Office of United States Trade Representative (USTR)</p>
	<p><i>Kate Clemans(United States)</i> APEC LSIF Technical Advisor Director, C&M International</p>
	<p><i>Mike Ward (Canada)</i> Chair APEC LSIF Regulatory Harmonization Steering Committee</p>
	<p><i>Justina A. Molzon (United States)</i> Associate Director, International Programs US Food and Drug Administration</p>
	<p><i>Mark Paxton (United States)</i> Associate Vice President, International Regulatory Affairs PhRMA</p>
	<p><i>Henry Pistell (United States)</i> APEC LSIF Task Force Consultant, C&M International</p>

2. Proceedings of the Workshop

2.1 Workshop Program

Day One

Monday, June 15, 2009	
09:00 – 10:30	RHSC Preparatory Meeting
10:30 – 11:00	Registration and Check-in
11:00 – 12:00	Inauguration Ceremony (Grand Ballroom)
12:00 – 13:00	Luncheon (Triangle Foyer)
13:00 – 13:30	<p>Welcome and Introduction</p> <p>Seung Hee Kim, APEC Harmonization Center Director Mike Ward, APEC LSIF Regulatory Harmonization Steering Committee Chair</p>
13:30 – 15:00	<p>Plenary I: The Value and Challenges of Multi-Regional Clinical Trials (Grand Ballroom)</p> <p><i>Description:</i> Large-scale clinical trials, conducted on a global scale, are often the basis for regulatory approval of new drug therapies. While these trials offer access to broad, diverse patient populations, they are not without logistical challenges, including issues related to the quality of trial conduct. Furthermore, the diversity of patients and medical practice patterns open a host of questions on how to interpret trial results and their applicability to both the broad and the specific trial populations. These issues can result in significant debate when it comes to product approval and labeling.</p> <p><i>Session Chair/Moderator: Mark Paxton, PhRMA</i></p> <p><i>Speakers:</i> <i>Toshi Kobayashi, PhRMA-Japan</i> <i>Jim Hung, US FDA</i></p>
15:00 – 15:30	Refreshment Break
15:30 – 17:00	<p>Plenary II : Intra-Regional Efforts to Streamline the Conduct of Clinical Trials: The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group (Grand Ballroom)</p> <p><i>Description:</i> There are many differences within and between regions that can have an impact on the conduct and design of clinical trials. Recognizing that Asia has been rapidly gaining importance as a venue of world wide drug development, the Ministers of Health of Korea, Japan, and China have affirmed the significance of <i>clarifying ethnic factors in clinical data</i>, in order to facilitate drug development. This session will focus discussion on the clinical concerns leading to the Tripartite Agreement entered into by the Ministers of Health for Korea, Japan, and China, and the resulting work plan intended to resolve some of these concerns. This session will also serve to provide an update on the ASEAN Pharmaceutical Product Working Group and its efforts to harmonize compliance requirements in the conduct of clinical trials within the ASEAN region.</p>

	<p><i>Session Chair/Moderator:</i> <i>Justina Molzon, US FDA</i></p> <p><i>Speakers:</i> <i>Haruo Akagawa, PMDA (Japan)</i> <i>Kyung Won Seo, KFDA (Korea)</i> <i>Jian-hua Ding, SFDA (China)</i> <i>Yuppadee Javroongrit, TFDA (Thailand)</i></p>
	Short Break – Please remain seated
17:00 – 18:30	<p>Plenary III: ICH: Overview (Grand Ballroom)</p> <p><i>Description:</i> ICH has produced an extensive series of guidelines that together provide a solid framework for guiding drug development and registration. A proper understanding of ICH guidelines is essential to ensuring the appropriate design, conduct, monitoring and assessment of clinical trials that meet the expectations of regulatory bodies. In addition to defining an international standard for GCP (E6), ICH guidelines address trial design (E8), statistical considerations (E9), choice of controls (E10) and special populations (E7 and E11). The development of the CTD has also been important in structuring information in a consistent format within marketing applications, thereby providing a basis for enhanced regulatory communication.</p> <p><i>Session Chair/Moderator: Toshi Kobayashi, PhRMA-Japan</i></p> <p><i>Speakers:</i> <i>Yoshiaki Uyama, PMDA</i> <i>Martha Brumfield, Pfizer</i></p>
18:30 -	Opening Night Reception (Hosted by KFDA-Diamond Hall)

Day Two

Tuesday, June 16, 2009	
8:00 – 8:30	Registration
8:30 – 10:15	<p>Plenary IV: Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed (Grand Ballroom)</p> <p><i>Description:</i> Multi-regional trials pose important statistical challenges with regard to study design, appropriate methods of analysis, and interpretation of results. This session will consider aspects such as the importance of a quality protocol, issues of study design including challenges and opportunities involving endpoint selection, choice of appropriate analysis methods, presentation of trial results, investigation of the level of consistency of results across regions, and the implications of trans-cultural factors on these issues.</p>

	<p><i>Session Chair/Moderator: Ling Su, Wyeth</i></p> <p><i>Speakers:</i> <i>Allan Donner, University of Western Ontario</i> <i>Jim Hung, US FDA</i> <i>William Wang, Merck</i></p>
10:15 – 10:45	Refreshment Break
10:45 – 12:00	<p>Plenary V: Operational Aspects (Grand Ballroom)</p> <p><i>Description:</i> This session will cover the importance of planning and implementation aspects for Multi-Regional trials, training and certification of institutions, investigator sites, investigators and staff, Good Clinical Practice, Quality Assurance (Monitoring/QC/Audits of sites); Data Management issues, CRO interfaces, etc...</p> <p><i>Session Chair/Moderator: William Wang, Merck</i></p> <p><i>Speakers:</i> <i>Ling Su, Wyeth</i> <i>Yil Seob Lee, GSK Korea</i> <i>Yuppadee Javroongrit, TFDA</i></p>
12:00 – 13:00	Luncheon
13:00 – 15:00	<p>Plenary VI: Regulatory Guidance/Perspectives/Issues (Grand Ballroom)</p> <p><i>Description:</i> Regulatory Agencies within APEC will discuss their views on the <i>implementation</i> of ICH clinical guidelines, including adaptations of those guidelines. Topics relevant to this session include implementation of ICH E5, placebo-controlled trials, and other clinical aspects of drug development. This session will also present the perspective of industry on challenges to international clinical development.</p> <p><i>SessionChair/Moderator: Martha Brumfield, Pfizer</i></p> <p><i>Speakers:</i> <i>Herng-Der Chern, CDE, Taiwan</i> <i>Jian-hua Ding, SFDA</i> <i>Min Irwin, Bayer</i></p> <p><i>Additional Panelists:</i> <i>Jim Hung, US FDA</i> <i>Yuppadee Javroongrit, TFDA</i> <i>Antonio Blanco, COFEPRIS</i> <i>Kyung Won Seo, KFDA</i></p>
15:00 – 15:30	Refreshment Break

<p>15:30 – 17:30</p>	<p>Breakout Sessions (Grand Ballroom)</p> <p><i>Description:</i> The focus of the Breakout Sessions will be to cover selected topics (listed below) in more depth in an interactive setting, where Session Facilitators will provide additional insights into the topics and also invite active participation from the audience to allow for issues to be further discussed. Ideally “value-added” proposals would be identified from the dialogue, such as best practices or recommendations for further action. These ideas will be shared in plenary session with the entire workshop. These reports are also expected to serve as input into the Next Steps parts of the workshop and discussions within the Regulatory Harmonization Steering Committee meeting that follows this workshop.</p> <p>Session 1: Regional Specific Issues</p> <p><i>Description:</i> Data supporting biopharmaceutical product development have typically been generated from clinical trials conducted in the US, Western European countries, and Japan, with contributions from a few other countries with similarly developed research and development infrastructure and effective regulatory processes. Data from emerging and developing countries have generally been minimal. However, industry is rapidly globalizing product development with increasingly more clinical trials being conducted in the nontraditional regions/countries. While such globalization of clinical trials presents tremendous opportunities, many unique and challenging region-specific issues need to be addressed to allow data generated from one region to be readily usable in another region.</p> <p>This breakout session will discuss these issues, highlighting best practices based on participants' varied experiences. The session will also make recommendations for further action on the more challenging issues. Specifically, the session will focus discussion on region-specific scientific, regulatory and operational issues, among others.</p> <p><i>Moderators:</i> <i>Toshi Kobayashi, PhRMA-Japan / Ling Su, Wyeth</i></p> <p>Session 2: Site Management, Data Management and Good Clinical Practice</p> <p><i>Description:</i> Multi-regional trials pose operational challenges including the appropriate site management of centers, data handling and other issues addressed by GCP. This session addresses:</p> <ul style="list-style-type: none"> ▪ Successful center selection, appropriate training and how to best monitor and control diverse study centers. Guidelines from regulators about minimum criteria for study site quality will be discussed. Recommendations are given as to what types of training are best suited for multinational study centers. ▪ Day-to-day data management issues associated with Multi-Regional trials, specifically, situations around AE and SAE reporting norms, translations and challenges with Pan-Asian trials.
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	<ul style="list-style-type: none"> Current ethical issues fundamental to multi-country clinical trials, focusing on attaining practical solutions through audience interaction and discourse. <p><i>Moderators:</i> Mark Paxton, PhRMA Martha Brumfield, Pfizer</p>
17:30 – 18:30	Group Photo Session/ Break
18:30 -	Hospitality Reception/ Dinner

Day Three

Wednesday, June 17, 2009	
8:00 – 8:30	Registration
8:30 – 10:00	<p>Breakout Sessions (Continued – Grand Ballroom)</p> <p>Session 3: Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed</p> <p><i>Description:</i> This session will provide an opportunity for more in-depth discussion of topics raised during the plenary session, as well as new related topics that the audience would like to bring up. The focus will be on issues related to design and analysis of global trials from a statistical perspective, such as the impact of regional treatment differences on sample size and the interpretation of test/estimation results.</p> <p>This session will also examine the numerous factors that can result in differences in endpoints for different regions, including regional differences in healthcare systems and medical practice, culture, disease prevalence, compliance and perceptions of patients and physicians. Discussions will focus on regional differences, particularly in patient reported outcome (PRO) measures and possible steps to address them. In particular, quantitative and qualitative interactions of treatment and region in terms of PRO measures will be discussed, in addition to potential inconsistency in PRO domain scores. Finally, logistical and statistical approaches to address regional differences in regulatory requirements for endpoints in global programs will be discussed.</p> <p><i>Moderators:</i> William Wang, Merck Jim Hung, FDA</p> <p>Session 4: Specific Therapeutic Areas</p> <p><i>Description:</i> This breakout session will invite the audience to brainstorm about the challenges involved in conducting global clinical trials, using vaccines as an example. Participants will be asked to identify the key scientific, operational, ethical, and regulatory issues that pose hurdles to the success of these trials. The group will then identify current best practices to address these issues and suggest next steps to improve these solutions.</p>

	<i>Moderators:</i> <i>Allan Donner, University of Western Ontario</i> <i>Yil Seob Lee, GSK Korea</i>
10:00 – 10:30	Refreshment Break
10:30 – 11:30	Plenary- Feedback from Breakout Sessions (Grand Ballroom)
11:30 – 12:00	Summary/ Next Steps/ Meeting Adjourned
12:00 – 13:00	Luncheon
13:00 – 15:00	RHSC (Regulatory Harmonization Steering Committee) Meeting (Grand Ballroom)
15:00 – 15:30	Refreshment Break
15:30 – 18:30	RHSC Meeting (Grand Ballroom)
18:30 -	Dinner

Day Four

Thursday, June 18, 2009		
8:30 – 10:00	RHSC Meeting (Grand Ballroom)	
10:00 – 10:30	Refreshment Break	
10:30 – 12:00	RHSC Meeting (Grand Ballroom)	
12:00 – 13:00	Luncheon	GMP Pharmaceutical Ware Visit
13:00 –	RHSC Meeting (Closed-Flamingo)	

2.2 Presentations from the Workshop

- Plenary I: The Value and Challenges of Multi-Regional Clinical Trials

Industry Efforts to Resolve International Regulatory Barriers to Simultaneous Global Development



Session Chair/Moderator

Mark Paxton (United States)

Associate Vice President

International Regulatory Affairs

PhRMA

Contents

- Defining SGD
- Why is SGD important?
- On-going efforts by drug regulatory authorities and industry to address SGD
 - Recent efforts by regulators
 - Industry Efforts: Formation of the SGD Committee
 - PhRMA - identified SGD Barriers
 - A Work-in-Progress: Barriers to SGD in the APEC Region
 - What NOW?
 - Drug Lags - 2005
 - Regulatory Requirements and Review Times
 - Review Times and Drug Lags



Industry Efforts to Resolve International Regulatory Barriers to Simultaneous Global Development

Mark Paxton, MS, JD

Simultaneous Global Development

PhARMA

Overview:

- Defining SGD.
- Why is SGD important?
- On-going efforts by drug regulatory authorities and industry to address SGD.

Defining SGD



- The generation of sufficient data in multiple regions/countries with the same pivotal trial protocol for the purpose of achieving simultaneous global filings and ultimately approval (the "SGD Trial")
- Note: Initial focus is presently on simultaneous global trial initiation and submission . . . with simultaneous global approval as an ultimate goal.

The Importance of SGD



- **Wholly inadequate patient access** to new therapies to address unmet medical needs
 - Industry and regulators must collaborate to avoid disadvantaging patients in the future
- Varying drug lags across the globe:
 - Internal organizational structure (industry)
 - Substantial "regulatory variability" across regions and countries
- Costly sequential/duplicative studies

Recent efforts by regulators

PhRMA

- **ICH E-5 "Ethnic Factors in the Acceptability of Foreign Clinical Data"** (February, 1998) and **ICH E-5 Q&A** (Clarifying E-5: June, 2006)
- MHLW Finalizes "**Basic Principles on Global Clinical Trials**" (September, 2007)
- FDA/PhRMA CLC **Multi-Region Clinical Trial Workshop** Washington (November, 2007)
 - Provided a forum to discuss ICH E-5 implementation issues (e.g., clinical relevance of ethnic factors)
 - But also raised awareness of several regulatory impediments
- **Tripartite Health Ministers Agreement (China, Korea, and Japan)** and the East Asia Pharmaceutical Regulatory Symposium (EAPRS: Tokyo April, 2008)
- Three (3) ICH-GCG recognized **regional harmonization initiatives** within APEC

Industry Efforts: Formation of the SGD Committee

PhRMA

- Recommended by the Global Heads of R&D of PhRMA member companies
- Comprised of Global Heads for Regulatory Affairs and Clinical Development and other experienced experts (Inaugural Meeting March, 2008)
- Vision is:
 - "To provide a framework to guide simultaneous global development with acceptance of GCP-compliant clinical trial data to support global product registration for **expedient** global patient access to meaningful new therapies."
- To facilitate SGD, PhRMA member companies are committed to engaging drug regulatory authorities in open, transparent and science-based dialogs.

PhRMA –identified SGD Barriers

PhRMA

- Systematic identification, categorization, evaluation, and prioritization (what can readily be resolved, what cannot).
- **Categories** include:
 - Regulatory Requirements (e.g. Country-specific dossier requirements)
 - Operational Barriers – (e.g., GCP compliance, clinical infrastructure, internal company structure, etc.)
 - Extrinsic and Intrinsic Clinical Factors (rigorously expands upon ICH E-5)
 - Legal and Statutory Structure

A Work-in-Progress: Barriers to SGD in the APEC Region

PhRMA

Barrier List	Regional/Country Relevance					
	CH	JP	KO	TVV	AP	India
1.1. Regulatory Requirements – Dossier Content						
- Requirement for country-specific Phase I (PK) study	x	x		x		
- Requirement for bridging study			x	x		
- Requirement for local registration study	x	x	x	x	x	
- Requirement for data showing optimal dose(s) for local patients		x				
- Requirement for minimum number of patients from country	x					
- Requirement for source country approval to complete Dossier	x		x	x	x	
- CMC and GMP requirements beyond ICH (Q1A) and/or CPP requirements (e.g., in lieu of having the capability of conducting PAs)	x		x		x	
- Other Differing Regulatory Standards					x	

What NOW??

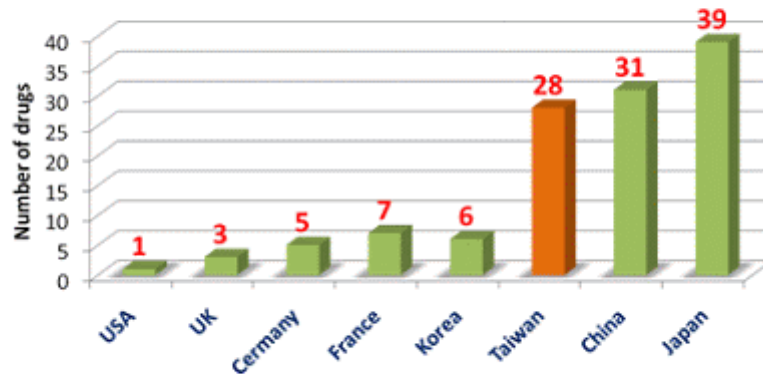
ERWA

- Continued assessment of observed barriers to differentiate administrative, regulatory, organizational barriers from scientific/clinical issues
 - We must conduct a critical review for medical relevance of any observed barrier - this is paramount to advancing SGD
- In addition, regulators must implement risk-based practices not only for achieving adequate regulatory assurance, but also for enhancing early access for patients without compromising safety and efficacy.
 - **Enhanced collaboration among and between regulatory authorities is absolutely necessary!**

Drug Lags - 2005

ERWA

Number of unapproved drugs among world's top selling 99 in 2005

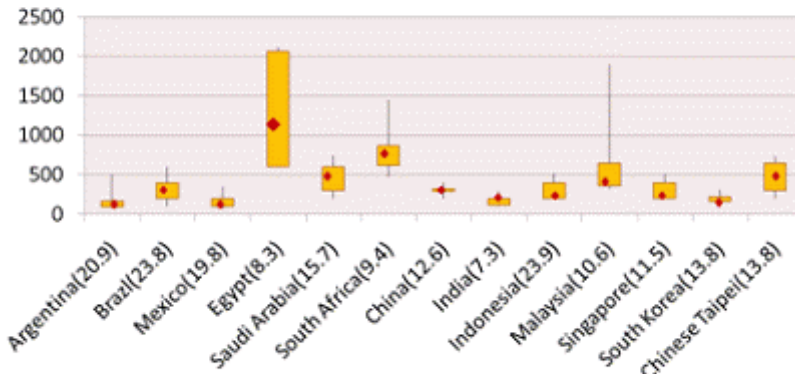


Source: Journal of Health Care and Society (Vol. 43, 2005)

Regulatory Requirements and Review Times

ERWA

Regulatory approval times from date of submission to date of approval for New Active Substances approved between 2004-2006



(n) = number of NCEs. Box: 25th and 75th percentiles. Whiskers 5th and 95th percentiles. Diamond = median

Data Source: Presentation by Professor Stuart Walker & Dr. Neil McAuslane, CMR International, in the IFPMA Regulatory Symposium held at Kuala Lumpur in March 2008.

Review Times and Drug Lags

ERWA

- **Where Review times are within reasonable norms (comparatively), and there is a drug lag, what is the cause?**
 - (i.e., where you cannot blame any portion of the drug lag on review times, what is the cause)?
- **Does industry have a responsibility? Absolutely**
- **But what about Regulatory Requirements?**
 - Throughout this workshop, I ask you to consider: What are the clinically relevant requirements that justifies an impediment to SGD?

- Plenary I: The Value and Challenges of Multi-Regional Clinical Trials

The Value and Challenges of Multi-Regional Clinical Trials



Speaker:

Toshi Kobayashi (Japan)

Technical Advisor

PhRMA-Japan

Contents

- Introduction
- Environment
 - Worldwide Pharmaceutical Market
 - Why Asia is important in Drug Development
 - R&D Investments
 - Less Products - Drug approved has been declining
 - Total Healthcare Costs
 - Consultation and Review at PMDA
- Challenge
 - The R&D Process: Long, Complex, and Costly
 - Multi-Regional CTs
 - Total Multi-Regional Clinical Trials in Japan
 - Regulatory Cooperation in Asia
- Doing it

Multi-Regional Clinical Trials Seoul Workshop

Inaugural Workshop of the APEC Harmonization Center

“The Values and Challenges of Multi-Regional Clinical Trials”

June 15th, Monday Seoul, Korea

Toshi Kobayashi, Ph.D.

Japan Technical Representative

PhRMA (USA) - Japan

IP reserved

[<toshi.kobayashi@phrma-jp.org>](mailto:toshi.kobayashi@phrma-jp.org)



07K/ym

1

INTRODUCTION

Advancing through “Life Science
Harmonization”

Science



Enhancing

Life



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2

Evidence of Enhancing Life : Discharged Patients



amkym

PRMA

3

Talking Outlines.....

Perspectives from Benefits to Patients

1. Environment
2. Matters concerned
3. Challenges
4. Doing it !

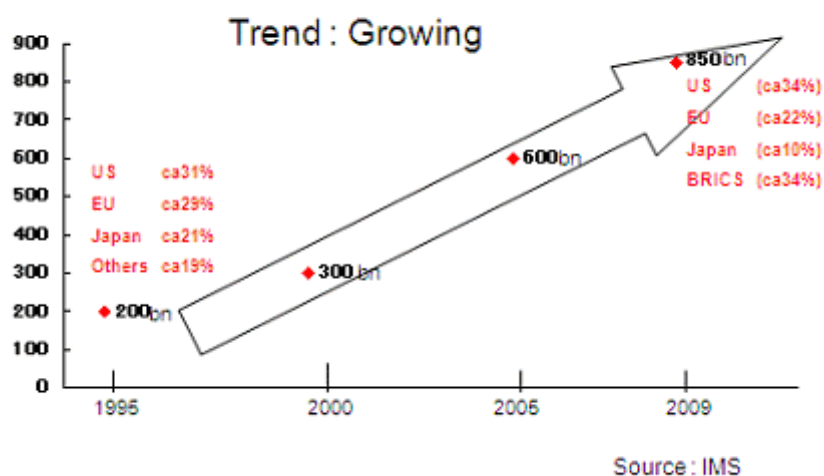
amkym

PRMA

4

1. Environment

Worldwide Pharmaceutical Market



09K0ym

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1. Environment (2)

Why Asia is important in Drug Development

- Largest portion of global population
 - Approximately 30% of the World Population
- Most exploding drug market
- Good drug R&D environment (speed, cost, quality, motivation, etc.)



Positive impacts on Global Drug Development

09K0ym

PRMA

Dr. S.Toyoshima, PMDA

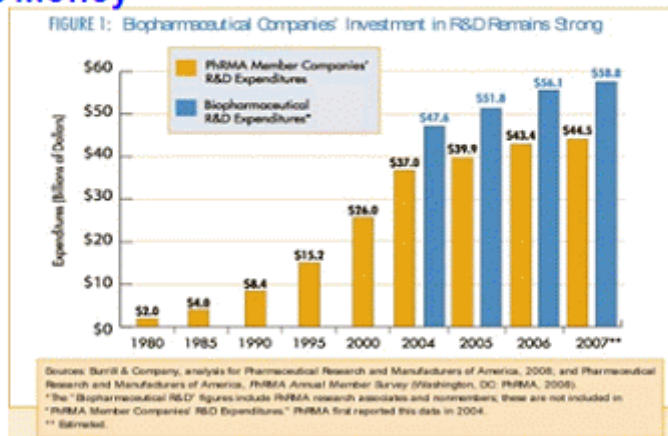
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1. Environment (3)

R&D Investments

Trend : Innovation Crisis

More Money

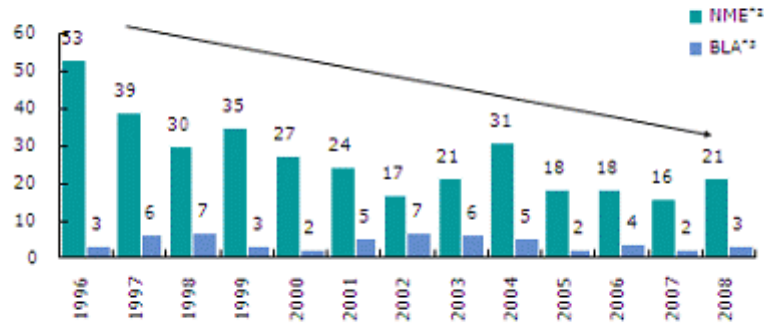


1. Environment (4)

Trend : Innovation Crisis (2)

Less Products Drug approved has been declining

= of drugs approved by FDA^{*1}



*1 FDA <http://www.fda.gov/cder/rdmt/NMEapps93-06.htm>
<http://www.fda.gov/cder/rdmt/Internet/NME07.htm>
<http://www.fda.gov/cder/rdmt/Internet/NME08.pdf>

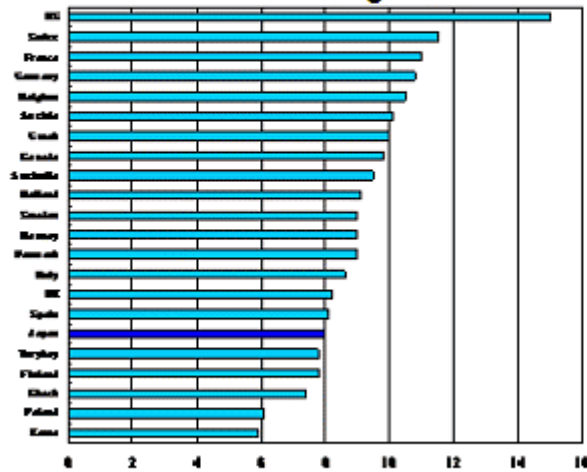
**2 NME: new molecular entity
 **3 BLA: biologic license applications



1. Environment (5)

Total Healthcare Costs

Trend : Increasing



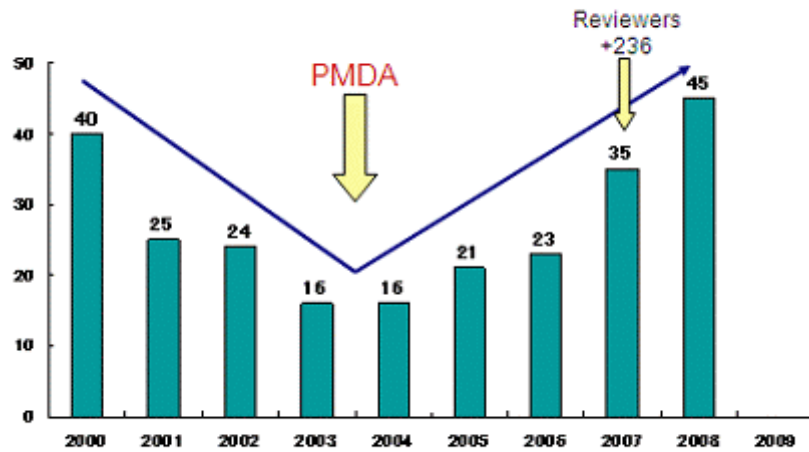
However, instead,
 Japan/Asia
 needs More
 Increase!



2.Matters concerned (3)

B. Consultation and Review at PMDA

a. PMDA established in 2004 – Right Thing at Right Timing



2.Matters concerned (4)

B. Consultation and Review at PMDA (2)

b. PMDA and Industry commitment toward 2011 FY

New targets : Total review time (April, 2007)

		Fiscal 2006*	Fiscal 2007	Fiscal 2008	Fiscal 2009	Fiscal 2010	Fiscal 2011
Ordinary products (median)	Total review time (months)	21	21	20- 21	19	16	12
	Government review time (months)	13	13	12- 13	12	11	9
	Applicant review time (months)	8	8	8	7	5	3
Priority products (median)	Total review time (months)	13	12	12	11	10	9
	Government review time (months)	6	6	6	6	6	6
	Applicant review time (months)	6	6	6	5	4	3

* For fiscal 2006 the results upto January 2007

2.Matters concerned (5)

B. Consultation and Review at PMDA (3)

C. Approvals of NDAs (2004~2007)

		Fiscal 2004	Fiscal 2005	Fiscal 2006		As of the end of January 2009		Agreement
				Applications from fiscal 2004	Applications from fiscal 2005**	Applications from fiscal 2006***	Applications from fiscal 2006***	
Priority + Standard	No. of Approvals Authorities (Median)	49 [694]	69 [694]*	24 [234]	77 [294]*	49 [294]	31 [294]*	
	Total Review Time	13.8 weeks	12.4 weeks	16.2 weeks	21.7 weeks	19.2 weeks	20.1 weeks	
Priority	No. of Approvals Authorities (Median)	22 [294]	19 [294]*	9 [294]	24 [294]*	19 [294]	20 [294]*	6 weeks
	Total Review Time	4.5 weeks	10.4 weeks	4.9 weeks	15.6 weeks	13.7 weeks	12.3 weeks	12 weeks
Standard	No. of Approvals Authorities (Median)	27 [494]	42 [494]*	16 [734]	63 [234]*	29 [494]	61 [494]*	13 weeks
	Total Review Time	13.4 weeks	12.4 weeks	18.1 weeks	27.4 weeks	20.3 weeks	22.0 weeks	21 weeks

Note : The percentage in [] is the number of reviews completed within +2 months of application for "Total" and "Ordinary products" and within 6 months for priority review products.

* : The figures include applications filed prior to March 2004, which were excluded from the Midterm Plan target.

** : NDAs since April, 2004.

2. Matters concerned (5)

B. Consultation and Review at PMDA (4)

However,

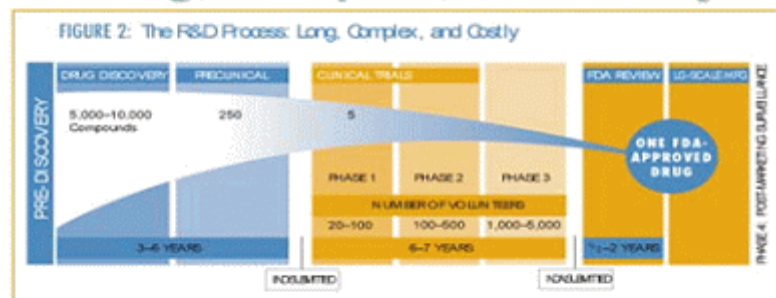
- Neither PMDA or the industry are satisfied with this,

Because

- The product – candidates reviewed at PMDA are not the same as overseas.

3. Challenge

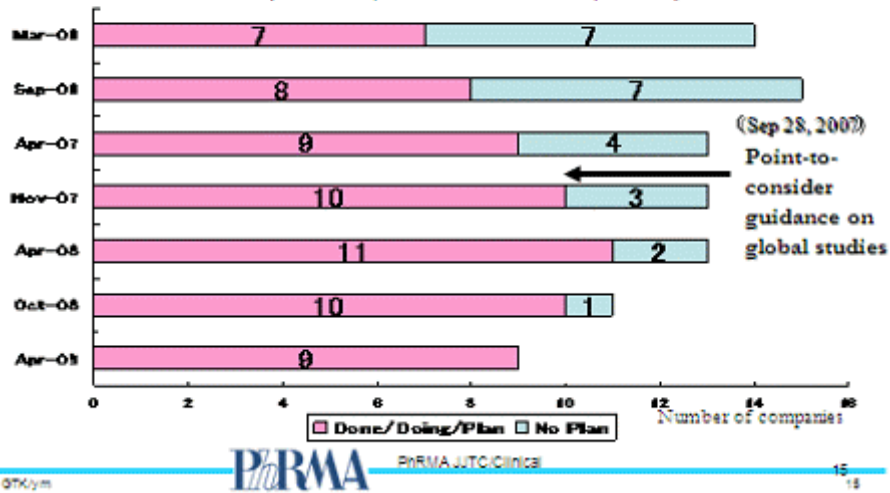
**The R&D Process :
Long, Complex, and Costly**



3. Challenge (2)

A. Multi-Regional CTs (PhRMA-Japan companies)

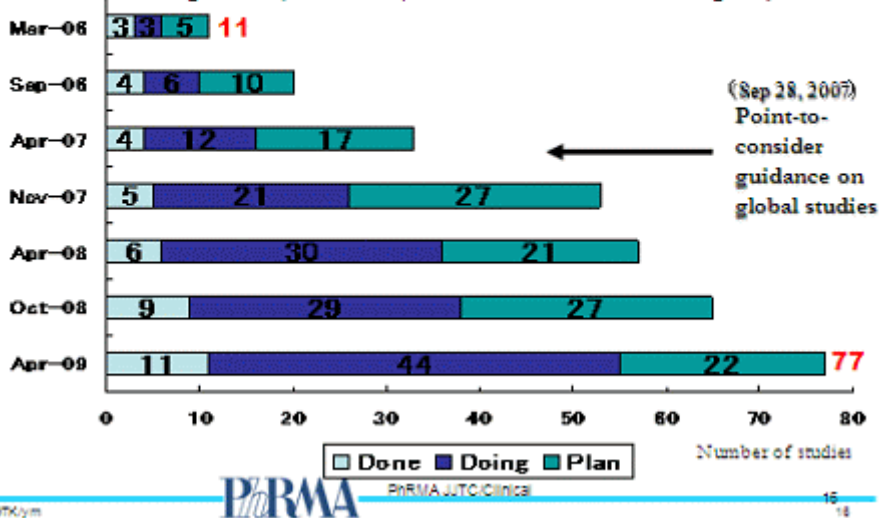
a. Stance on Multi-Regional (National) Clinical Trials among PhRMA companies (US-subidiaries) in Japan.



3. Challenge (3)

A. Multi-Regional CTs (PhRMA-Japan companies)(2)

b. Multi-Regional (National) Clinical Trials including Japan



3. Challenge (4)

A. Multi-Regional CTs (PhRMA-Japan companies) (3)

c. Scale of Multi-Regional CTs – Completed Trials –

Number of countries	Approved (YY/MM)	T.Patient	Japanese (J/T :%)	Asian		Therapeutic Area	Phase
28	2006/4	1513	96 (6.3)	124	N	Urology	III
2	2006/4	608	293 (48)	315	N	Urology	III
7		160	15(4.4)	-	N	Oncology	II/III
17**		243	6(2.5)	11	E	Oncology	II
3		480	320 (67)	160	E	Osteoporosis	II/III
33		7500	344(4.6)	-	E	Osteoporosis	III
-		-	-	-	E	cardiovascular	III
10*	Under Review	400	25(6.3)	few	E	cardiovascular	II/III
9	Prepn. CSR*	1200	230(19.2)	1006 (80.8)	E	Oncology	III
20*		1300	130	0	N	CNS	II/III
3*		35-45	40	30-45	E	CNS(Mental Illness)	II

*: Up-dated

PhRMA J/JTC/Clinical



N: New Molecular Entity E: Line Extension

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3. Challenge (5)

A. Multi-Regional CTs (PhRMA-Japan companies) (4)

c. Scale of Multi-Regional CTs – Ongoing Trials 1/4 – 1-11

Number of countries	Period (Months)	T.Patient	Japanese (J/T :%)	Asian (%)		Therapeutic Area	Phase
40	84	500	-	-	E	Oncology	III
-	48	15000	-	-	N	CV	III
50	156	8000	140(1.8)	420(5.3)	E	Oncology	III
42	60	8200	60(0.7)	135(1.6)	E	Oncology	III
15	4Y	600	40	-	E	Oncology	II/III
5	36	260	80	180	E	Oncology	II/III
14	54	255	30(11.8)	25	N	Oncology	II/III
14	48	876	50	60	N	Oncology	III
20	36	15000	300	1500	N	CV	III
-	12	400	300	100	E	CNS	III
5	6	480	100	420	E	Neuro-psychiatic	III

PhRMA



PhRMA/JTC/Clinical

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3. Challenge (6)

A. Multi-Regional CTs (PhRMA-Japan companies) (5)

c. Scale of Multi-Regional CTs – Ongoing Trials 2/4 – 12-22

Number of countries	Period (Months)	T.Patient	Japanese (J/T :%)	Asian		Therapeutic Area	Phase
20	36	709	72	150	N	Oncology	III
22	24	1500	100	0	N	Neuro-psychiatic	III
4	16	500	320()	240	E	Urology	III
-	Long	-	-	-	E	CV	III
4	12	-	-	-	N	Urology	II/III
-	22	-	-	-	N	Oncology	II/III
-	48	1200	-	-	E	Oncology	II/III
-	-	-	-	-	E	Oncology	II/III
-	-	-	-	-	N	RA	II/III
-	24	176	-	-	N	Oncology	II/III
-	60	290	-	-	N	Oncology	II/III

PhRMA



PhRMA/JTC/Clinical

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3. Challenge (7)

A. Multi-Regional CTs (PhRMA-Japan companies) (6)

c. Scale of Multi-Regional CTs – Ongoing Trials 3/4 – 23-33

Number of countries	Period (Months)	T.Patient	Japanese (J/T :%)	Asian (%)		Therapeutic Area	Phase
-	24	160	-	-	N	Oncology	II/III
-	24	540	-	-	N	Oncology	III
-	-	-	-	-	N	Osteop	II
24	18	1400	140	300	N	Oncology	III
4	12	540	270	0	N	Respio	III
32	24	1500	150	150	N	Oncology	III
32	12	600	70	200	N	Oncology	III
5	30	260	40	0	N	Oncology	II
22	36	19500	-	-	N	CV	III
10	36	10000	-	-	N	CV	III
-	-	16000	-	-	N	Osteop.	III

3. Challenge (8)

A. Multi-Regional CTs (PhRMA-Japan companies) (7)

c. Scale of Multi-Regional CTs – Ongoing Trials 4/4 –

34-44(1)

Number of countries	Period (Months)	T.Patient	Japanese (J/T :%)	Asian (%)		Therapeutic Area	Phase
-	-	800	-	-	N	Respio	II
2	-	250	-	-	N	Respio	II
18	39	8044	450	?	N	Infection	III
2	12	250	50	-	N	Insomnia	IIb
26	66	660	50	?	E	Oncology	III
4	23	54	40?	15?	N	Oncology	II
-	35	740	60	?	N	Oncology	III
2	12	700	350	-	N	CNS	III
35	60	1000	100	-	N	Oncology	III
-	24	400	20	-	N	CV	III
15	24	500	100	-	N	CV	II
25	8(JAN)	1300	50		N	UC	II/III

3. Challenge (9)

A. Multi-Regional CTs (PhRMA-Japan companies) (8)

Conclusion

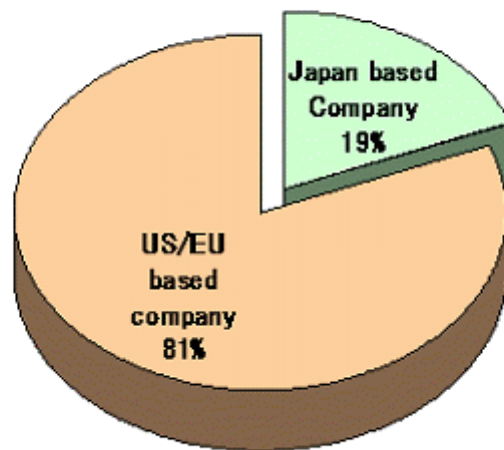
■ Current Situation

(1) The number of Multi National Trials has been increased

-- Point-to-consider guidance on global studies (Sep 28, 2007) --

3. Challenge (10)

B. Total Multi-Regional Clinical Trials in Japan



As of Jan. 30th

Dr. S.Toyoshima, PMDA

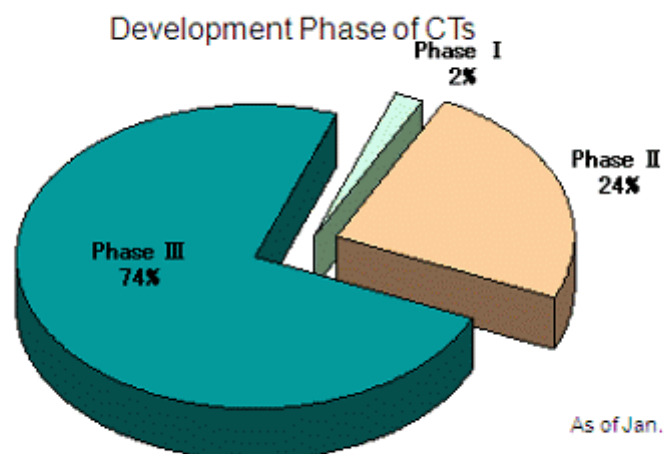
PRMA

PRMA

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3. Challenge (11)

B. Total Multi-Regional Clinical Trials in Japan (2)



As of Jan. 30th

Dr. S.Toyoshima, PMDA

PRMA

PRMA

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3. Challenge (10)

C. Regulatory Cooperation in Asia

- April 2007 1st Tripartite **Health Ministries** Meeting (China/Korea/Japan)
- April 2008 1st Tripartite **Director-Generals** Meeting (China/Korea/Japan)
- April 2008 1st East Asian **Regulatory Symposium** (China, Korea, Thailand, Singapore, Japan)
- January 2009 **MOU** (China SFDA & Japan MHLW)

For Strengthening Regulatory Cooperation in Asia

Dr. S.Toyoshima, PMDA

09K0ym



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3. Challenge (10)

C. Regulatory Cooperation in Asia (2)

China/Korea/Japan Director-General Meeting on Pharmaceutical Affairs (April 14, 2008)

Agreements

1. SFDA, KFDA and MHLW agree to promote scientific research cooperation under the legal background of each country in the Joint Research Project on Ethnic Factors in Clinical Data with a view to encouraging global development and sharing clinical data.
2. 3 Authorities initiate Information Exchange Scheme on general pharmaceutical affairs.
3. Working group (WG) is to be established to promote the Joint Research Project, the information exchange and other preparation works. The 1st WG meeting will be held in November 2008 in Japan.

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3. Challenge (11)

C. Regulatory Cooperation in Asia (3)

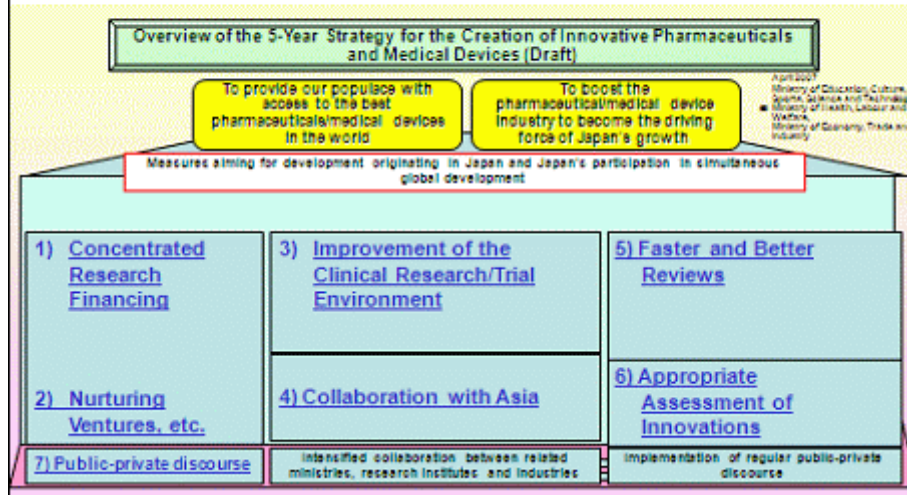
Dr. Tokin / Dr. Kawata WG in NIHW (Japan)

● PK Study

- Published database study under progress
- Planning clinical trials in healthy volunteers in China, Korea and Japan / budgeted yen 240m (2009~)
- Japan WG is going to propose plans to China and Korea

4. Doing it

Under collaboration with Worldwide authorities and industries



- Plenary I: The Value and Challenges of Multi-Regional Clinical Trials

Values and Challenges of MRCT: A Regulatory Perspective



Presenter

James Hung (United States)

Director of Division of Biometrics I

Office of Biostatistics

US FDA

Abstract

Multi-regional clinical trial (MRCT) becomes a reality for global development of medical products. Two essential interrelated purposes of MRCT are obtaining a global measure of treatment effect and using the trial results to bridge from global to local or between the local regions. Achieving these purposes is conditional on the ability of MRCT to generate scientific evidence needed. This presentation will refresh the concept of ‘averaging’ and discuss its power and pitfall. The knowledge of such power and pitfall lends itself to understanding where the values and challenges stem from. The values of MRCT include cost effectiveness and statistical efficiency, global harmonization on data/trial quality, ethical standard and regulatory standard. Challenges are also in many dimensions, such as evidence-based on interpretation, ability to study the potential regional differences of real interest, global harmonization on many aspects. Some regulatory experiences in the challenges of MRCT will be shared.

Values and Challenges of MRCT: A Regulatory Perspective

H.M. James Hung, PhD
Division of Biometrics I, OB/OTS/CDER
U.S. Food and Drug Administration

*Presented in APEC MRCT Workshop, Seoul, Korea,
June 15-18, 2009*

Robert O'Neill
OB/OTS/CDER, US FDA

Disclaimer

The view expressed in this presentation are not
necessarily of the US FDA

Outline

- ◆ Essential Framework and 4 scenarios
- ◆ Values of MRCT
- ◆ Challenges of MRCT
- ◆ Concluding Remarks

Two essential tools for generating scientific evidence in clinical trials:

- randomization
- averaging

Randomization \Rightarrow 'comparability'

Averaging \Rightarrow 'measuring treatment effect'

4 'regions'



Scenario 1

BP lowering effect (in mmHg) of a drug (vs. placebo):

(I, II, III, IV) = (4, 4, 4, 4)

Global drug effect estimate = 4

Combining 4 regions maximizes precision of estimate

~~~~~ Power of Averaging ~~~~~

4 'regions'



**Scenario 2**

BP lowering effect (in mmHg) of a drug (vs. placebo):

(I, II, III, IV) = (3.5, 3, 4.5, 3.5)

Global drug effect estimate = 4 (still interpretable)

Combining 4 regions maximizes precision of estimate

~~~~~ Power of Averaging ~~~~~

4 'regions'



Scenario 3

BP lowering effect (in mmHg) of a drug (vs. placebo):

(I, II, III, IV) = (0, 4, 7, 2)

Global drug effect estimate = 4 (*interpretable?*)

Combining 4 regions maximizes precision of estimate

~~~~~ Pitfall of Averaging ~~~~~

4 'regions'



**Scenario 4**

BP lowering effect (in mmHg) of a drug (vs. placebo):

(I, II, III, IV) = (-2, 2, 8, 4)

Global drug effect estimate = 4 (*interpretable?*)

Combining 4 regions maximizes precision of estimate

~~~~~ Pitfall of Averaging ~~~~~

Utilities and Pitfalls of “**averaging**”:

- Handle the precision of estimate
- Average may or may not be interpretable
- When the average is interpretable, informative bridging may be possible, but extra care is usually needed (e.g., Scenarios 2-3)
- *Bridging is much more difficult to handle*

Challenges in practice stem from the fact that at best we can only deal with estimates that are subject to uncertainty and perturbation

Literature suggested 'Bridging clinical trial strategy' is mostly inferior to 'MRCT strategy' in terms of evidence interpretability, statistical efficiency,

MRCT: Simultaneous conduction of trial for multiple geographical regions under the same trial protocol

Multi-regional clinical trial (MRCT) essentially serves two interrelated purposes

- assessment of global treatment effect
- use the trial results to bridge from global to local or between regions



Many factors can possibly cause regional differences in drug effect (**heterogeneity**)

- **intrinsic factors***

race, genetic factors, ...

- **extrinsic factors***

background treatment, social factors, health care system, medical practices, ...

- **quality of trial conduct or data**

*ICH E5

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The regional differences of real interest, if any, are those attributed to intrinsic and extrinsic factors (e.g., ethnic or genetic differences, medical practices and health care systems)

Data quality problem can accentuate or attenuate regional differences in treatment effect in terms of effect estimate, but it will boost variances of the global estimate

Values of MRCT

- ◆ Can yield a global effect estimate with best precision
- ◆ Global estimate may be best for bridging if effect estimates are similar between regions
- ◆ offer opportunity to study regional differences of real interest
- ◆ Stimulate collaborative clinical research among regions for worldwide public health

Vickers et al (1998, CCT)

Table 1 Results of Controlled Clinical Trials of Acupuncture by Country of Research

| Country | Total Trials Analyzed | Favoring Test Treatment | |
|-------------|-----------------------|-------------------------|------------|
| | | Number | Percentage |
| USA | 47 | 25 | 53 |
| China | 36 | 36 | 100 |
| Sweden | 27 | 16 | 59 |
| UK | 20 | 12 | 60 |
| Denmark | 16 | 8 | 50 |
| Germany | 16 | 10 | 63 |
| Canada | 11 | 3 | 27 |
| Russia/USSR | 11 | 10 | 91 |
| Austria | 9 | 8 | 89 |
| Italy | 9 | 8 | 89 |
| Australia | 6 | 1 | 17 |
| France | 6 | 5 | 83 |
| Taiwan | 6 | 6 | 100 |
| Japan | 5 | 5 | 100 |
| Finland | 4 | 2 | 50 |
| Hong Kong | 3 | 3 | 100 |
| Netherlands | 3 | 1 | 33 |
| New Zealand | 3 | 2 | 67 |
| Poland | 3 | 2 | 67 |
| Switzerland | 3 | 1 | 33 |
| Bulgaria | 2 | 2 | 100 |
| Brazil | 1 | 1 | 100 |
| Croatia | 1 | 1 | 100 |
| Israel | 1 | 1 | 100 |
| Nigeria | 1 | 1 | 100 |
| Sri Lanka | 1 | 0 | 0 |
| Vietnam | 1 | 1 | 100 |
| Total | 252 | 171 | 68 |

O'Neill (2007)

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Values of MRCT

- ◆ Raise awareness of concept of 'quality', can enhance trial quality for all local regions
- ◆ Harness global harmonization in trial standard
- ◆ Nurture clinical trial leadership w/ global view
- ◆ Cost effectiveness, ethical standard, regulatory standard, data/trial quality assurance,

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Challenges of MRCT

- ◆ Regional differences of effect estimates appear in many MRCTs
 - causes unknown
 - interpretation difficult
 - unclear about how to tease out real differences of interest from observed differences
 - unclear how to consider them in trial planning
 - how to best inform consumers is unknown

Some regulatory experiences ...

- ◆ Cardio-Renal
 - MERIT-HF, RENAAL
 - 13 of 16 large outcome trials show a small effect in US (Lawrence, RSR work)
- ◆ Psychiatry, Neurology (Research on-going)

RENAAL (quantitative interaction)

| Region | TRT | Control | HR |
|-----------|-------|---------|------|
| I (17%) | 39.2% | 59.1% | 0.55 |
| II (19%) | 38.4% | 35.4% | 0.94 |
| III (19%) | 56.9% | 58.4% | 0.91 |
| IV (45%) | 42.0% | 43.0% | 0.95 |
| Overall | 43.5% | 47.1% | 0.84 |

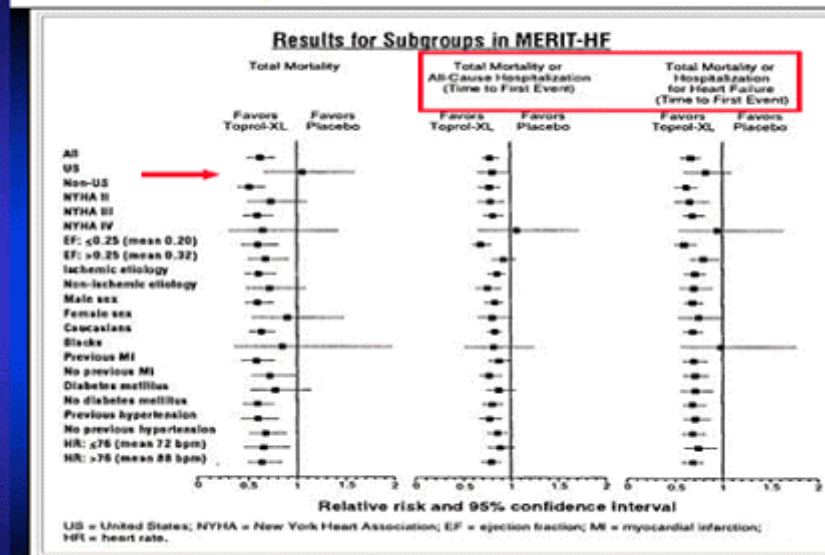
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HR: hazard ratio (TRT/Control) for clinical outcome endpoint multi-national trial of >1500 patients

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Qualitative or quantitative interaction?



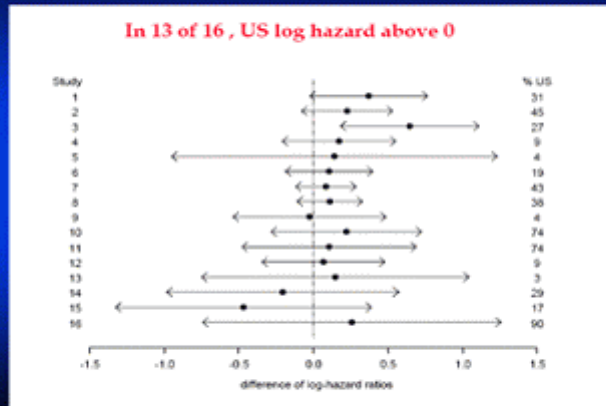
From drug label

J.Hung, 2009 APEC MRCT

21

Lawrence et al (2003-2004, FDA RSR work)

Estimates and confidence intervals for difference between US and Non-US treatment effects for each study



Lawrence

O'Neill (2007)

J.Hung, 2009 APEC MRCT

22

Vickers et al (1998, CCT)

Table 1 Results of Controlled Clinical Trials of Acupuncture by Country of Research

| Country | Total Trials Analyzed | Favoring Test Treatment | |
|-------------|-----------------------|-------------------------|------------|
| | | Number | Percentage |
| USA | 47 | 25 | 53 |
| China | 36 | 36 | 100 |
| Sweden | 27 | 16 | 59 |
| UK | 20 | 12 | 60 |
| Denmark | 16 | 8 | 50 |
| Germany | 16 | 10 | 63 |
| Canada | 11 | 3 | 27 |
| Russia/USSR | 11 | 10 | 91 |
| Austria | 9 | 8 | 89 |
| Italy | 9 | 8 | 89 |
| Australia | 6 | 1 | 17 |
| France | 6 | 5 | 83 |
| Taiwan | 6 | 6 | 100 |
| Japan | 5 | 5 | 100 |
| Finland | 4 | 2 | 50 |
| Hong Kong | 3 | 3 | 100 |
| Netherlands | 3 | 1 | 33 |
| New Zealand | 3 | 2 | 67 |
| Poland | 3 | 2 | 67 |
| Switzerland | 3 | 1 | 33 |
| Bulgaria | 2 | 2 | 100 |
| Brazil | 1 | 1 | 100 |
| Croatia | 1 | 1 | 100 |
| Israel | 1 | 1 | 100 |
| Nigeria | 1 | 1 | 100 |
| Sri Lanka | 1 | 0 | 0 |
| Vietnam | 1 | 1 | 100 |
| Total | 252 | 171 | 68 |

O'Neill (2007)

J.Hung, 2009 APEC MRCT

23

Challenges of MRCT

- ◆ Trial/data quality assurance
 - disparity in concept of 'quality'
 - disparity in trial/data monitoring at local level
 - regulatory enforcement
 - difficulty in trial/data inspection (translation, cultural aspects, resources, ...)

Some experiences from regulatory applications ...

- Trial conduct problems
- Poor record keeping
- Flawed procedure
- Interpretation issues (e.g., translation)
- Measurement procedure
- Subjective assessment
- Compliance to study protocol

All the above will adversely affect *interpretability of trial results*

Challenges of MRCT

- ◆ Global harmonization
 - clinical trial standard (e.g., GCP, data/site managements)
 - clinical trial leadership
 - regulatory standard/guidance
 - infrastructure
 - operational aspects (regional vs. global issues)

Concluding Remarks

- ◆ MRCT has many venues to contributing to worldwide public health – a way to go
- ◆ No all endpoints can be properly studied in MRCT – requires a lot of work ahead to validate sensitivity/specificity of endpoint measurements (FDA raising awareness)
- ◆ Statistical considerations are vital

Concluding Remarks

- ◆ Need statistical work to explore potential regional differences by therapeutic areas
- ◆ MRCT offers many opportunities for between region collaboration by which clinical trial paradigms can be embraced to rise to a higher level to meet the challenges in terms of operational aspects, quality control,

Concluding Remarks

- ◆ Trial conduct or data quality is critical to interpretability of trial results in terms of global effect estimate and ability to bridge
- ◆ Global harmonization in many areas (e.g., clinical trial standard and leadership, regulatory standard) is needed

Selected References

O'Neill (2007, Presentation in PhRMA/FDA workshop)

Hung et al (2003, 2006-2009 presentations in ISS, DIA, ...)

- Plenary II: Intra-Regional Efforts to Streamline the Conduct of Clinical Trials: The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group

Perspective for Global Clinical Trials



Speaker:

Haruo Akagawa (Japan)

Associate Center Director

Center for Products Evaluation

PMDA

Contents

- PMDA's activities
 - "Drug Lag"
 - Improvement of the Consulting Service and review system
 - Promotion of Global Clinical Trial

- East Asia in Global Drug Development
 - MRCTs in Asian countries
 - Necessary discussions
 - Possibility of Ethnic difference
 - Meetings and Agreements
 - Future style of global development (Asia+US+EU)



Perspective for Global Clinical Trials

Pharmaceuticals and Medical Devices Agency (PMDA)

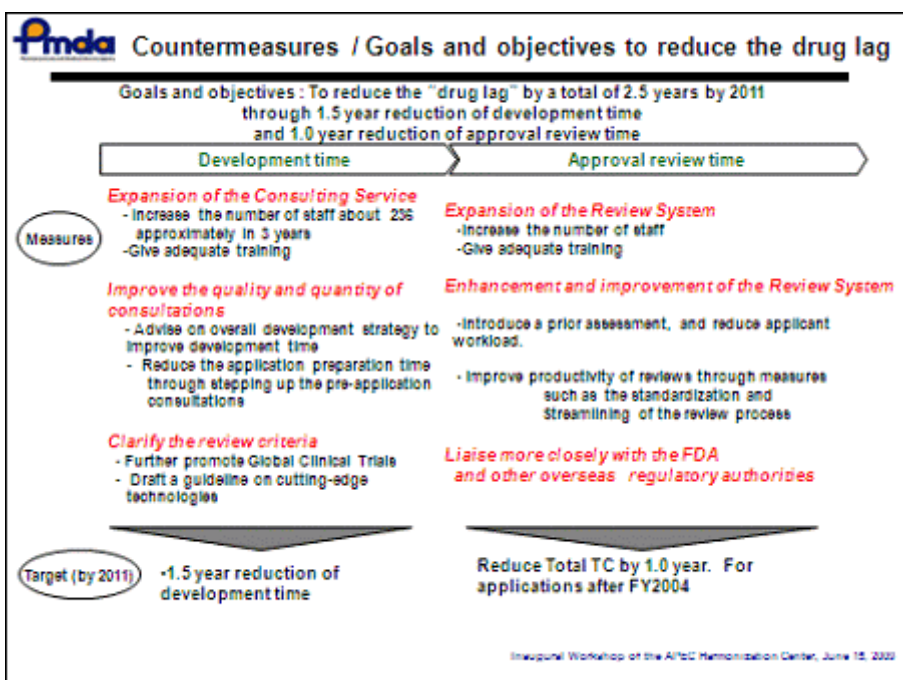
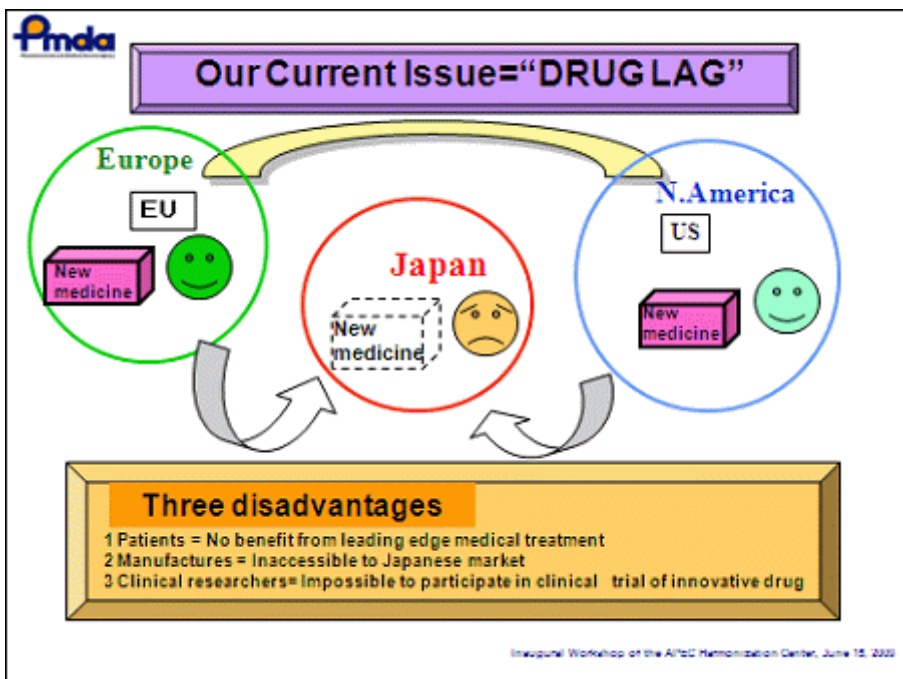
**Associate Center Director,
Center for Products Evaluation
Haruo Akagawa**

Inaugural Workshop of the AP/EC Harmonization Center, June 15, 2009



PMDA's activities

Inaugural Workshop of the AP/EC Harmonization Center, June 15, 2009





1. Improvement of the Consulting Service and review system

- Increase the number of review staff about 236, in 3 years (FY2007-FY2009)
- Give adequate training
- Clarification of review criteria

Inaugural Workshop of the A/TC Harmonization Center, June 15, 2009



Number of Permanent Staff Members

| | April 1, 2004 | April 1, 2005 | April 1, 2006 | April 1, 2007 | April 1, 2008 | April 1, 2009 |
|--------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Total (including executives) | 256 | 291 | 319 | 341 | 426 | 521 |
| Review Section* (included in total) | 154 | 178 | 197 | 206 | 277 | 346 |
| Safety Section** (included in total) | 29 | 43 | 49 | 57 | 65 | 82 |

* The review Section consists of the Director of the Center for Products Evaluation, Deputy Director, Associate Center Directors, Office of Review Administration, Office of Review Management, Office of New Drug I, II, III, IV and V, Office of Biologics I and II, Priority Review Director, Office of OTC/Genetic Drugs, Office of Medical devices, and Office of Conformity Audit.

** The Safety Section consists of the Chief Safety Officer, Office of Safety and Office of Compliance and Standards.

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Clarification of Review Criteria

- PMDA integrates reviewer's conscious mind and review criteria
- PMDA enhances efficient drug development by enabling the consideration from an early stage of drug developments.
- PMDA encourages data acquisition for more appropriate scientific review



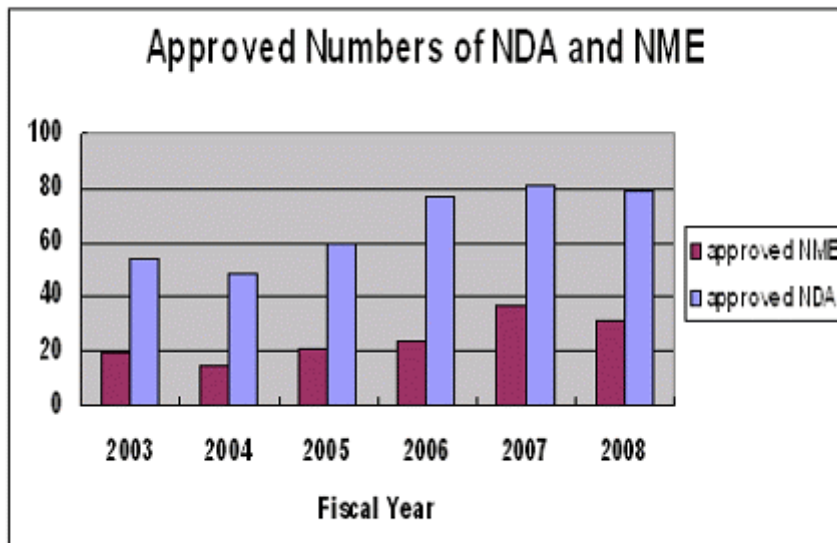
「Points To Consider for Reviewers in New Drug Evaluation」

published in PMDA's website on April 17, 2008

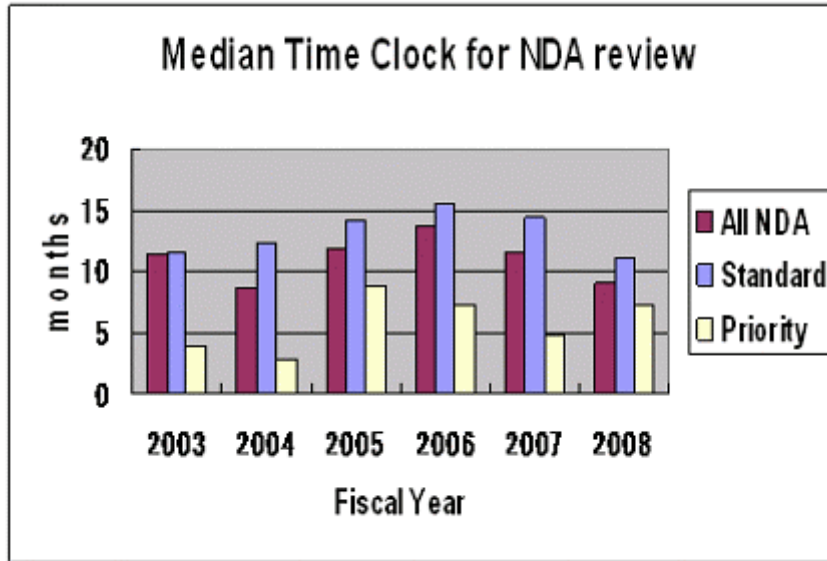
Inaugural Workshop of the A/TC Harmonization Center, June 18, 2009



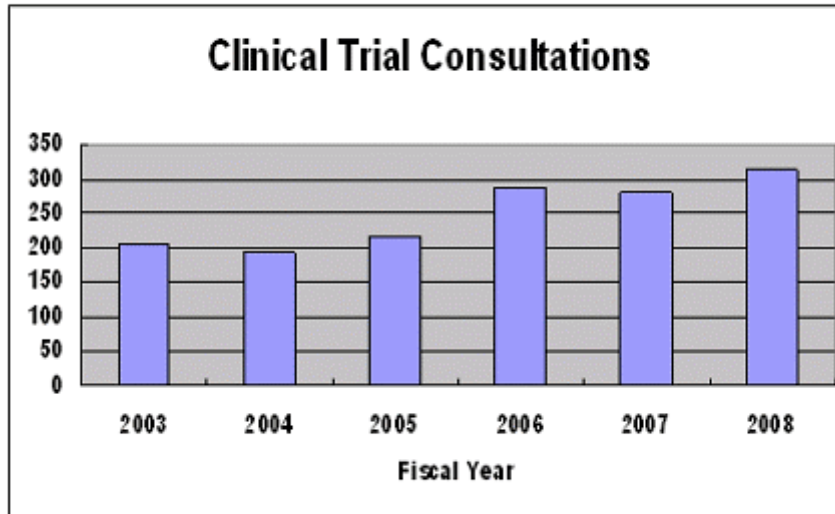
Approved Numbers of NDA and NME



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Inaugural Workshop of the AFCD Harmonization Center, June 18, 2009



Inaugural Workshop of the AFCD Harmonization Center, June 18, 2009



2. Promotion of Global Clinical Trial

Publication of Basic principles on Global Clinical Trials

Inaugural Workshop of the A/TC Harmonization Center, June 15, 2007



Basic principles on Global Clinical Trials

Japanese version

薬食審査発覚0928010号
平成19年9月28日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬食品局審査管理課長

国際共同試験に関する基本的考え方について

従来、我が国においては、ICH-E-Rガイドラインに基づく「外国臨床データを受け入れる際に考慮すべき決裁的要素について（平成19年8月11日医薬審発0742号 厚生省医薬安全局審査管理課長通知）」により、いわゆる「ブラッキング」による海外臨床試験成績を承認申請資料として活用することを認めており、また、欧米諸国における市販後調査等の結果についても必要に応じて承認審査に照して活用しているところである。

Japanese= <http://www.pmda.go.jp/operations/notice/2007/file/0928010.pdf>

English= <http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf>

English version

September 28, 2007
Medication 0928010

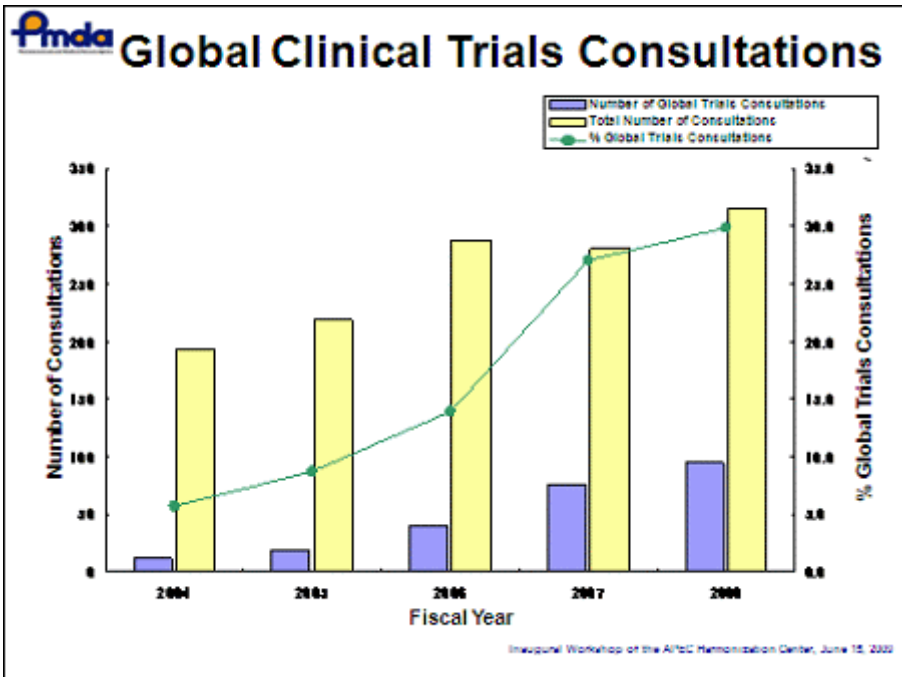
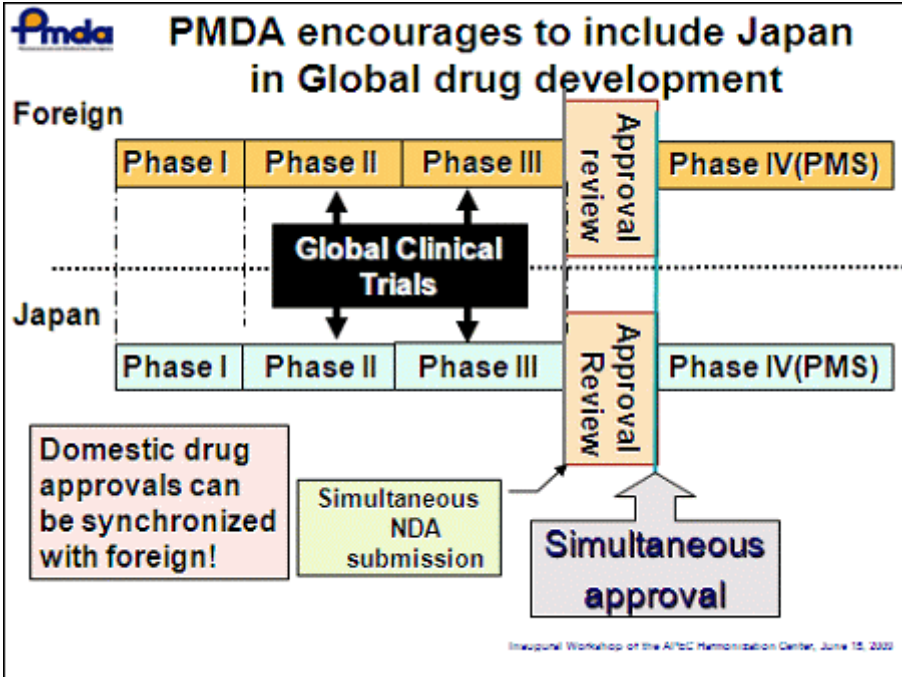
Attention to:
Commissioner of Prefectural Health Supervising Department

From Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

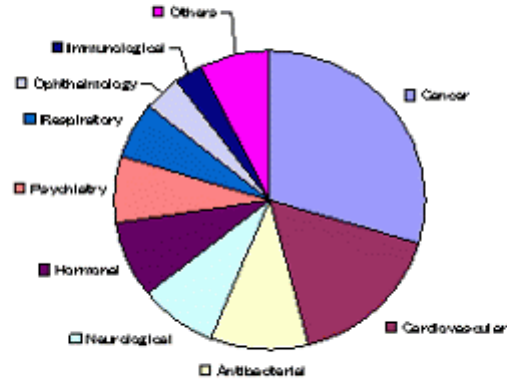
Basic principles on Global Clinical Trials

Up to the present according to "Basic Factors in the Acceptability of Foreign Clinical Data" based on ICH-E-R guideline (Medication, No. 76), Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated August 11, 1998, utilizing foreign clinical trial data in a new drug application what is called "bracketing" has been accepted in Japan, and post-marketing data in USA and EU have been taken into consideration in a case-by-case regulatory approval when necessary.

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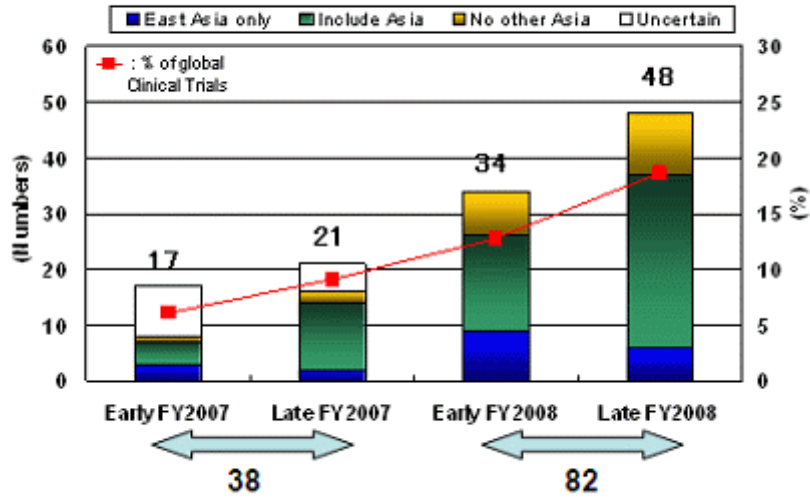


Proportion of Global Clinical Trial Consultations according to Therapeutic Area (FY2008)



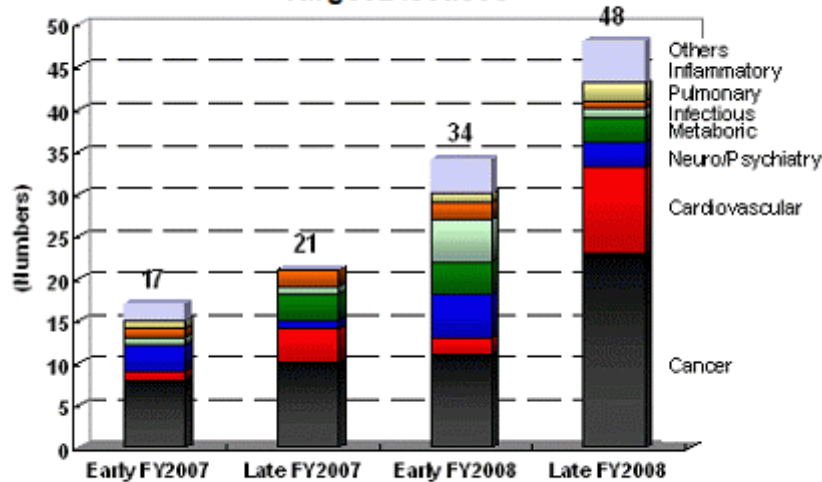
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Trends of Global Clinical Trials including Japan - Operational Regions -



Inaugural Workshop of the APAC Harmonization Center, June 15, 2009

Trends of Global Clinical Trials including Japan - Target Diseases -



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On-going Global Clinical Trials in Japan (by IND notification)

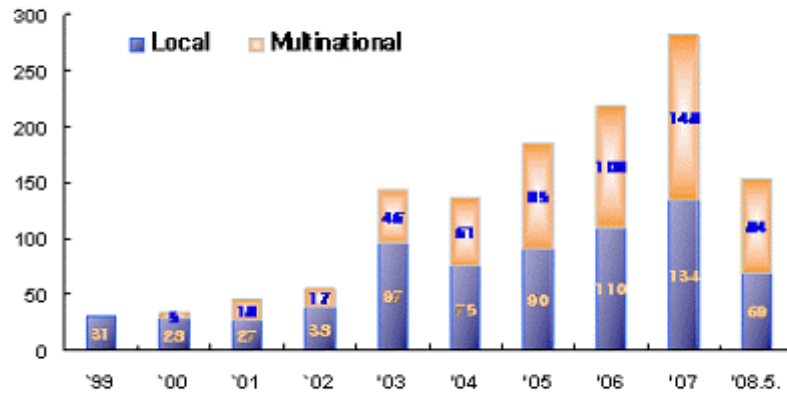
- **FY2008: 524 IND notifications (total)**
- **25 companies notified to conduct 82 global clinical trials (82/524=16%)**
 - Japan based pharma 6 companies 13 protocols
 - **Global pharma 19 companies 69 protocols**
- **Development phase**
Phase-I: 2, Phase-II: 22, **Phase-III: 58**
- **Target diseases**
cancer:33, cardiovascular:17, respiratory:5, central nervous system:3

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Global Clinical Trials in Korea

Clinical Trials approved by KFDA



Kyung Won Seo, KFDA Korea, 5th DIA-Japan, Tokyo, 2008

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Example from approved New Drug Applications

Approved on Apr. 20th 2006

- Tolterodine tartrate
 - Korea-Japan study for bridging (n=600)
 - Medicine for overactive bladder
- Losartan potassium
 - RENAAL study as global study (n=1500)
 - Nephropathy in type 2 diabetic patients

Approved on Feb. 29th 2008

- Trastuzumab
 - HERA study as global study (n=3400, asian=400)
 - Adjuvant therapy for HER2-positive breast cancer

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East Asia in Global Drug Development

Inaugural Workshop of the APAC Harmonization Center, June 15, 2009

MRCTs in Asian countries

- From the beginning of 21st century, East Asian countries took part in the multi-regional clinical trials (MRCTs)
- China, Korea, Chinese Taipei, Hong-Kong, Singapore, etc. have much experience in planning and conducting MRCTs
- Japan is catching up now !

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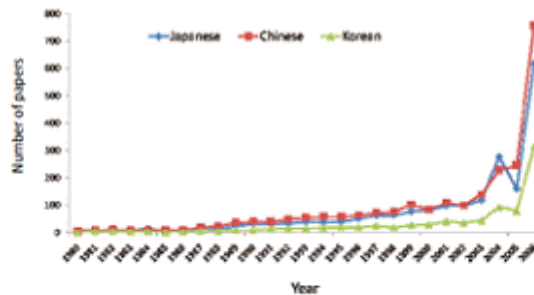
Necessary discussions

- Ethnic similarities
- Ethnic differences
 - Caucasian vs. Asian
 - Within Asian populations
- Various cultures, languages, religions, medical practices (**including drug interaction**)
- Difference in practice between trial sites (hospitals, medical institutes, etc...)

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High Research Activity in Asia!

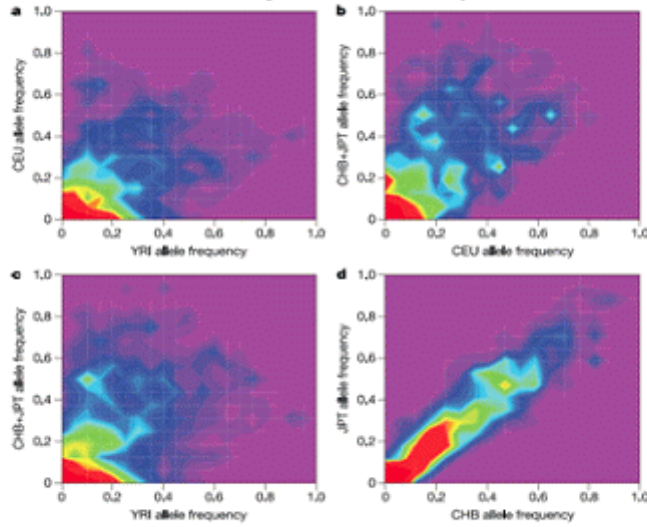
Number of original articles related to clinical pharmacokinetic studies in Japanese, Chinese, and Korean



Dr. Masahiro Tohkin: East Asian Pharmaceutical Regulatory Symposium 2008, April 15, 2008 Tokyo

Inaugural Workshop of the A/TC Harmonization Center, June 15, 2009

Genetic Similarity between Japanese and Chinese

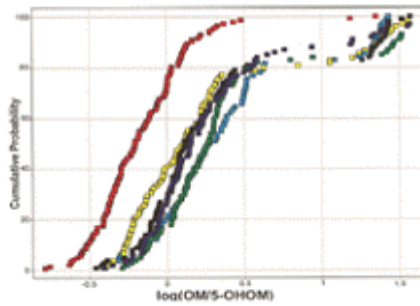


The International HapMap Consortium. A haplotype map of the human genome. *Nature* 2005;437:1299-320

Inaugural Workshop of the A/T/C Harmonization Center, June 15, 2009

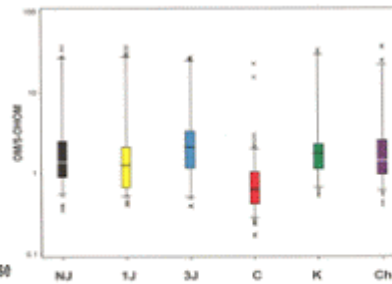
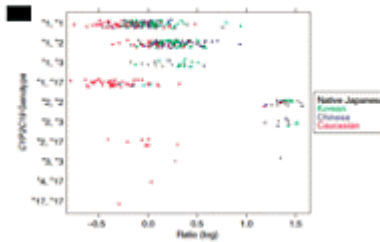
Ethnic Similarity on CYP2C19

- Similar Metabolic Activity in Japanese, Korean and Chinese
- Japanese < Caucasian



■ Native Japanese, ■ 1G-Japanese, ■ 3G-Japanese, ■ Caucasian, ■ Korean, ■ Chinese

Myrand SP et al, *Clin Pharmacol Ther*, 84: 3, 347-361, 2008



Inaugural Workshop of the A/T/C Harmonization Center, June 15, 2009

Possibility of Ethnic difference

Rosuvastatin

| Population | Dose (mg/day) | n | C _{max} (ng/mL) | AUC (ng·h/mL) | Reference |
|------------|---------------|----|--------------------------|---------------|--|
| Japanese | 10 | 6 | 7.87 | 126 | Rinsho'yaku, 21, 187-203, 2005 |
| | 20 | 6 | 20.5 | 209 | |
| | 40 | 6 | 41.5 | 404 | |
| White | 20 | 6 | 10.7 | 103 | |
| | 40 | 6 | 38 | 291 | |
| Chinese | 10 | 20 | 11 | 122 | |
| White | 40 | 36 | 25 | 216 | Clin Pharmacol Ther, 78, 330-341, 2005 |
| Chinese | 40 | 35 | 59.1 | 500 | |
| Malay | 40 | 35 | 50 | 412 | |
| Indian | 40 | 35 | 42 | 352 | |

PGx can not explain the difference at this stage.

Dr. Masahiro Tokin: East Asian Pharmaceutical Regulatory Symposium 2008, April 15, 2008 Tokyo

Inaugural Workshop of the A/TC Harmonization Center, June 18, 2009

Possibility of Ethnic difference

Tolterodine (sustained release capsule)

| | Parent Compound | | | Active Metabolite | | Free Form | |
|------------|-----------------|------------------------|-------------|------------------------|-------------|---------------------|----------|
| | Dose mg | C _{max} ng/mL | AUC ng·h/mL | C _{max} ng/mL | AUC ng·h/mL | C _{max} nM | AUC nM·h |
| Japanese | 2 | 1.12 | 13 | 0.76 | 8.77 | 1.07 | 12.5 |
| Caucasian* | 2 | 2.53 | 40.3 | 1.28 | 13.7 | 1.31 | 15.2 |
| Korean | 2 | 1.48 | 18.2 | 1.18 | 15 | 1.61 | 20.5 |
| Japanese | 4 | 1.3 | 14.8 | 1.68 | 19.2 | 2.07 | 23.9 |
| Caucasian | 4 | 2.57 | 26.8 | 2.27 | 25.1 | 2.7 | 30.3 |
| Korean | 4 | 2.83 | 33.2 | 2.12 | 27.4 | 2.65 | 33.9 |
| Japanese | 6 | 2.87 | 26.7 | 3.34 | 34.8 | 4 | 42.8 |
| Caucasian | 6 | 2.03 | 15.5 | 3.19 | 33 | 3.52 | 40.1 |
| Korean | 6 | 4.38 | 45.5 | 3.85 | 41.6 | 5.15 | 55.7 |

* Contains 2 poor metabolizers

PMDA Review report (2006)

PGx of CYP2D6 can not explain the difference between Japanese and Korean.

Dr. Masahiro Tokin: East Asian Pharmaceutical Regulatory Symposium 2008, April 15, 2008 Tokyo

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- More experience & scientific research
- Net-working & collaboration in Asian region
- Develop best fit drugs for Asian populations

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Health Ministers' Joint Statement among China, Korea & Japan (April 8, 2007)



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Director-General Meeting

China/Korea/Japan Director-General Meeting on Pharmaceutical Affairs was held on April 14, 2008 in Tokyo

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Agreements

- SFDA, KFDA and MHLW agree to promote scientific research cooperation under the legal background of each country in the Joint Research Project on Ethnic Factors in Clinical Data with a view to encouraging global development and sharing clinical data.
- Three Authorities initiate Information Exchange Scheme on general pharmaceutical affairs.

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East Asian Pharmaceutical Regulatory Symposium

- East Asian Pharmaceutical Regulatory Symposium was held in Tokyo on April 14 and 15, 2008.
- Co-hosted by PMDA and MHLW
- Asian regulators:
China, Korea, Singapore, Thailand, Japan

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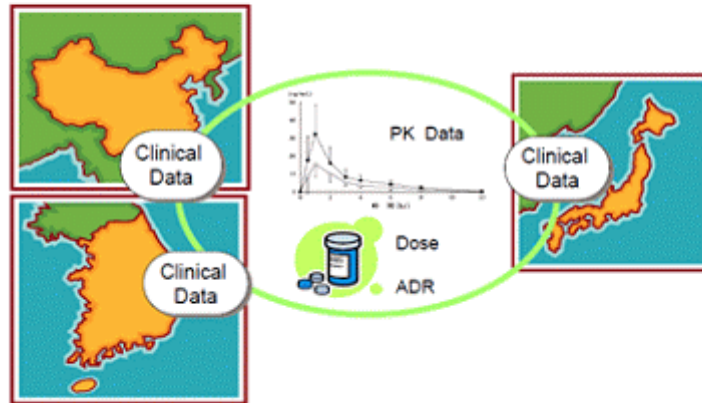


Regulator's View for Global Drug Development

- Clinical Trials in Asia are growing
- Timely Discussion between Industry and Regulatory Agency are important to maximize efficiency of drug developments
- Encourage to include Asia in Global Drug Developments from an early stage of drug developments **(Moving from Sequential Bridging to Simultaneous Developments)**
- International Regulatory Harmonization and more collaboration among regulatory agencies are necessary

Inaugural Workshop of the APAC Harmonization Center, June 18, 2009

China/Korea/Japan Joint Research Project
on Ethnic Factors in Clinical Data



Inaugural Workshop of the A/TC Harmonization Center, June 18, 2009

A Plan for FY2009, Prospective PK study

Prospective PK study

Including Chinese, Korean and Japanese

- Budget: approximately 200M Yen (=2M \$)
- PK for several marketed drugs is planned to measure
- PK will be measured by use of validated methods



Prospective PK comparisons
among populations more precisely

Inaugural Workshop of the A/TC Harmonization Center, June 18, 2009

Very near future style of Global Development (Asia + US + EU)

- Asian drug development as a part of global development is very important
- Positive dialog about Asian Clinical Trial Network for information/experience exchange
- Challenge to conduct **Asia+EU+US** Study
- Let's try for a win-win situation

Inaugural Workshop of the A/CCT Harmonization Center, June 15, 2009

All the players in good harmony

for the welfare of patient!



Thank you for your attention

Inaugural Workshop of the A/CCT Harmonization Center, June 15, 2009

**- Plenary II: Intra-Regional Efforts to Streamline the Conduct of Clinical Trials:
The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group**

Current Regulatory Situation in Korea



Speaker:

Kyung Won Seo (Korea)

Director

Drug Evaluation Department

KFDA


Contents

- Organization of KFDA
 - KFDA Organization
 - Activities of Center for Drug Development Assistance
 - Regional KFDA Organization
 - Pharmaceutical Safety Bureau
 - Biopharmaceuticals and Herbal Medicine Bureau
- Regulatory System - NDA
 - Scheme of NDA Approval
 - KiFDA Online System
 - Implementation of ICH CTD
 - Transparency
 - Example
- Regulatory System -IND
 - IND Process
 - Approval/Dossier
 - Clinical Trials
 - Pre-IND Consultation
 - Why it is attractive?

Current Regulatory Situation in Korea

Kyung Won Seo
Korea Food & Drug Administration

KFDA 식품의약품안전청
Korea Food & Drug Administration



CONTENTS

- 1 Organization of KFDA**
- 2 Regulatory System – NDA**
- 3 Regulatory System – IND**



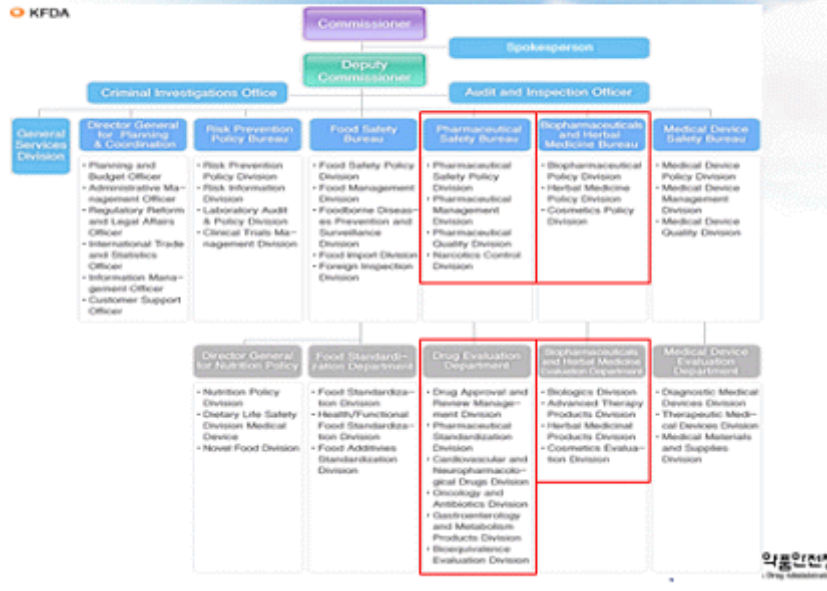
I. Organization of KFDA



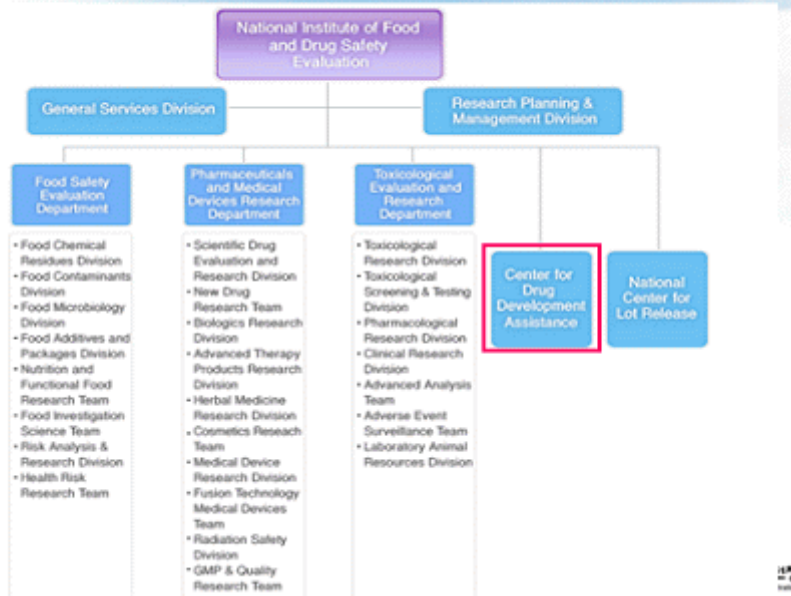
KFDA Organization

- Central Office of Korea Food and Drug Administration
- National Institute of Food and Drug Safety Evaluation
- Regional KFDA Organizations

KFDA Organization



NIFDS Organization



Activities of Center for Drug Development Assistance

- ❖ Providing sponsors with assistance to resolve challenges faced during the drug approval process
 - Customized support which meets each customer's need in the drug development
 - Regulatory consultation regarding documentations to ensure the quality, safety, and efficacy of drugs
- ❖ Operation of online training programs for sponsors and CRO
- ❖ Operating the APEC harmonization center



KFDA 식품의약품안전청
Korea Food & Drug Administration

Regional KFDA Organization

| Seoul Regional KFDA | Busan Regional KFDA | Gyeongin Regional KFDA | Daegu Regional KFDA | Gwangju Regional KFDA | Daejeon Regional KFDA |
|--|--|--|--|--|--|
| <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Import Management Division • Hazardous Substances Analysis Division | <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Import Management Division • Center for Food & Drug Analysis <ul style="list-style-type: none"> – Hazardous Substances Analysis Division – Imported Food Analysis Division | <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Import Management Division • Center for Food & Drug Analysis <ul style="list-style-type: none"> – Hazardous Substances Analysis Division – Imported Food Analysis Division | <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Hazardous Substances Analysis Division | <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Hazardous Substances Analysis Division | <ul style="list-style-type: none"> • Customer Support Division • Food Safety Management Division • Medical Products Safety Division • Hazardous Substances Analysis Division |
| | <ul style="list-style-type: none"> • Jaseongdae Imported Food Inspection Center • Shinseondae Imported Food Inspection Center • Yangsan Imported Food Inspection Center • New Port Imported Food Inspection Center | <ul style="list-style-type: none"> • Ulsang Imported Food Inspection Center • Incheon International Airport Imported Food Inspection Center • Pyeongtaek Imported Food Inspection Center | | | |

KFDA 식품의약품안전청
Korea Food & Drug Administration

Pharmaceutical Safety Bureau

| Pharmaceutical Safety Bureau | Drug Evaluation Department |
|---|---|
| <ul style="list-style-type: none"> • Pharmaceutical Safety Policy Division • Pharmaceutical Management Division • Pharmaceutical Quality Division • Narcotics Control Division <div style="background-color: #0070C0; color: white; padding: 5px; margin-top: 10px;"> <p>129 government officials
100 contract workers</p> </div> | <ul style="list-style-type: none"> • Drug Approval and Review Management Division • Pharmaceutical Standardization Division • Cardiovascular and Neuropharmacological Drugs Division • Oncology and Antibiotics Division • Gastroenterology and Metabolism Products Division • Bioequivalence Evaluation Division |

식품의약품안전청
Food & Drug Administration

Biopharmaceuticals and Herbal Medicine Bureau

| Biopharmaceuticals and Herbal Medicine Bureau | Biopharmaceuticals and Herbal Medicine Evaluation Department |
|--|---|
| <ul style="list-style-type: none"> • Biopharmaceutical Policy Division • Herbal Medicine Policy Division • Cosmetics Policy Division <div style="background-color: #0070C0; color: white; padding: 5px; margin-top: 10px;"> <p>83 government officials
10 contract workers</p> </div> | <ul style="list-style-type: none"> • Biologics Division • Advanced Therapy Products Division • Herbal Medicinal Products Division • Cosmetics Evaluation Division |

식품의약품안전청
Food & Drug Administration

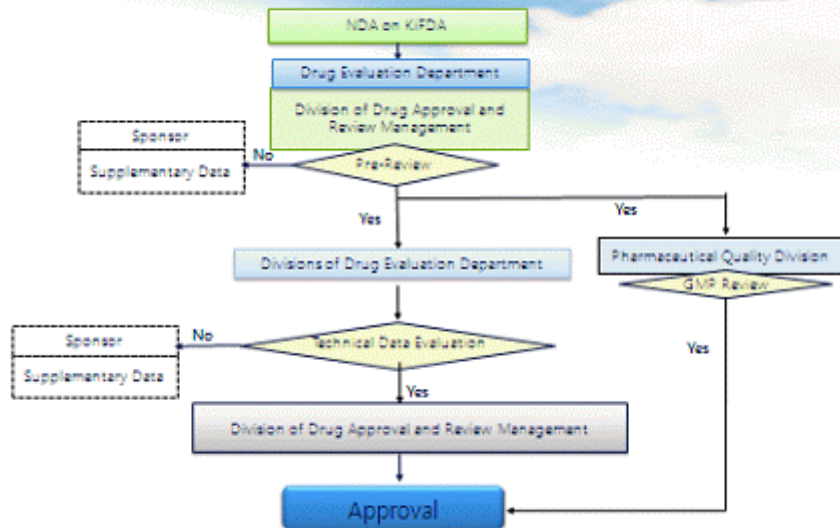
Pharmaceutical Safety Bureau

Scope of activities are

- ✓ Marketing authorization
- ✓ Clinical trial authorization
- ✓ Regulation of advertising
- ✓ Post-Marketing Surveillance
- ✓ Sample Analysis

II. Regulatory System – NDA

Scheme of NDA Approval



KiFDA Online System

KiFDA Online System

- The purpose of KiFDA on-line system is to improve the transparency and publicity (from Oct., 2, 2006)
- The sponsor can
 - submit their dossiers on-line
 - check the reviewers who are taking the charge of review of his/her product
- KiFDA alerts reminds the reviewer of the due date to complete the review.

Implementation of ICH CTD

ICH CTD

- From March of 2009, it is mandatory to submit the application for new chemical entities in the ICH CTD format.
- Module 2 should be written in Korean.
- KFDA is preparing the 'Guidance for Industry - Preparing drug approval application in the CTD format'.

Transparency

KFDA posts the reviews report on the website

- ✓ Indications
- ✓ Conditions of approval
- ✓ The legal basis
- ✓ List and summary of studies conducted
- ✓ Decision-making criteria
- ✓ Review reports

Example

The screenshot displays the KFDA (Korea Food & Drug Administration) website interface for a New Drug Application (NDA) submission. The main content area shows the '신약신제품허가신청서' (New Drug Application) form. A specific section titled '전임상·유효성 검토서' (Pre-clinical Test Results) is expanded, revealing a table of test results and a list of test methods.

| 검사항목 | 시험대상제제 | 시험방법 | 시험결과 |
|--------|--------------------------------|--------------------------------|--------------------------------|
| 1. 안전성 | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg |
| 2. 유효성 | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg |
| 3. 품질 | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg | 신약신제품(제제명) 100mg, 200mg, 400mg |

Below the table, there is a list of test methods (시험방법) and their results (시험결과):

- 1. 안전성: 신약신제품(제제명) 100mg, 200mg, 400mg
- 2. 유효성: 신약신제품(제제명) 100mg, 200mg, 400mg
- 3. 품질: 신약신제품(제제명) 100mg, 200mg, 400mg

Fee for Review Application

| Category | Before Oct. (US\$) | After Oct. 2008(US\$) | |
|-------------------------------------|--------------------|-----------------------|-------|
| | | Visit | KiFDA |
| NCE | 50 | 4000 | 3800 |
| Line extensions (e.g. salt changes) | 30 | 1200 | 1100 |
| Generics | 30 | 1000 | 900 |
| Minor modification | 0 | 120 | 100 |

Approval Time

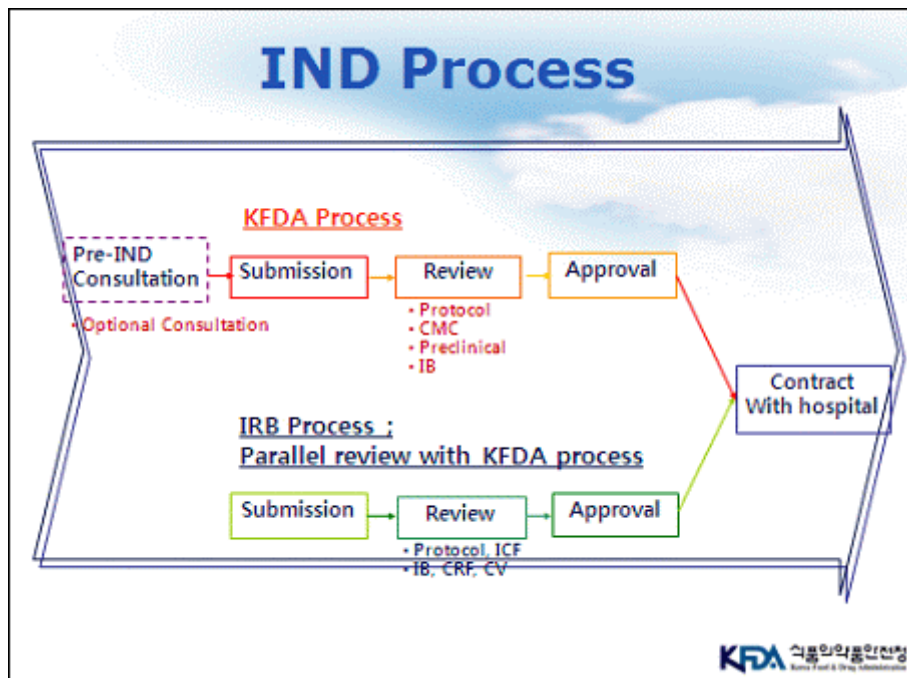
New Drug Application

- New chemical entity : 85 working days
 - 60 days for scientific review
 - 25 days for administrative review
- Major line extension : 60 working days
- KFDA can request supplement data only twice during one review cycle.
- Sponsor response time
 - The First request : 60 calendar days
 - The Second request : 10 working days
 - Sponsor can extend their response time.

Dossier for NDA



III. Regulatory System – IND



Approval Time - IND

IND Application

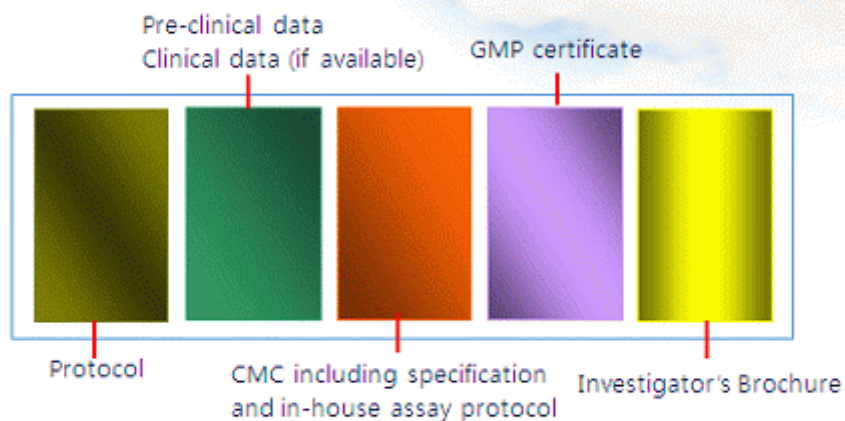
- 30 working days
 - 25 days for scientific review
 - 5 days for administrative review
- Sponsor response time is 30 calendar days.

Supplement data frequently requested

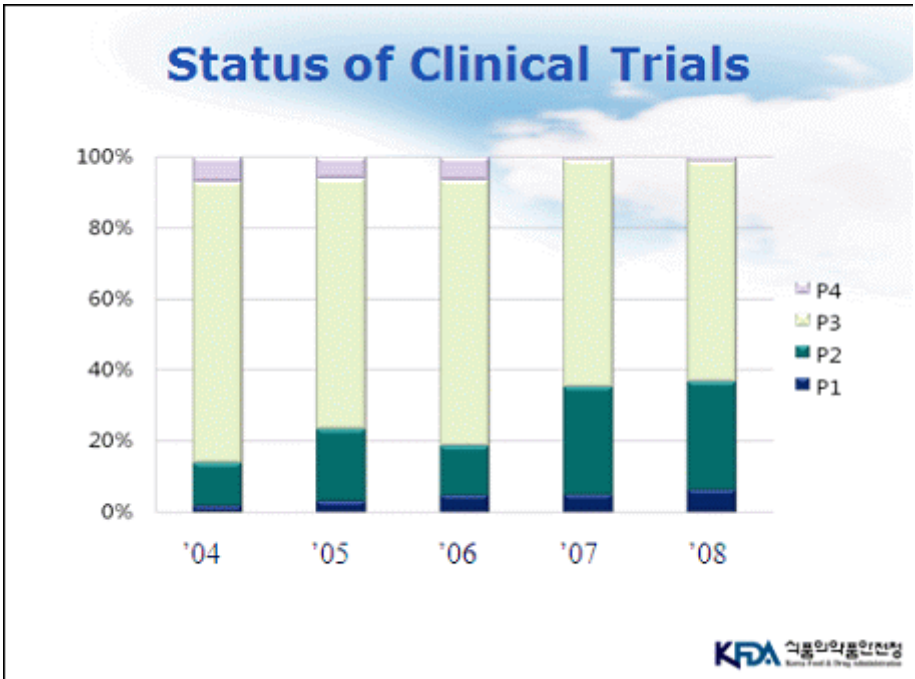
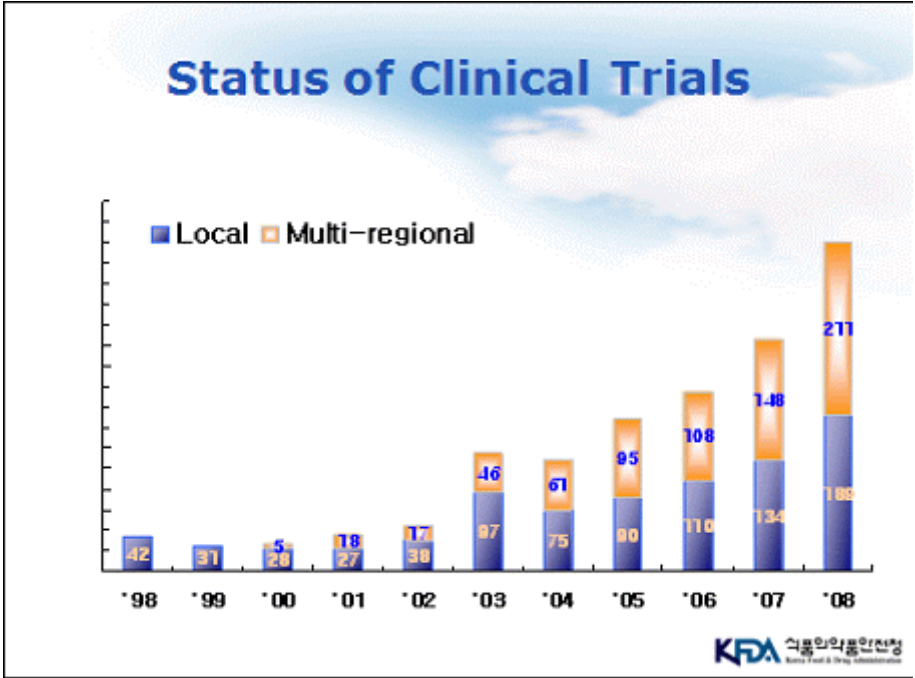
- Information about investigational drugs and placebo
- Stability data to assure the stability of investigational drug during clinical trials
- Patient inclusion and exclusion criteria, etc

KFDA 식품의약품안전청
Korea Food & Drug Administration

Dossier for IND



KFDA 식품의약품안전청
Korea Food & Drug Administration



Regulatory Hierarchy



Clinical Trials

Essential Elements

- The protocol approved by KFDA
- Only at the accredited clinical trial sites
- Qualified investigator
- Protection of the right and safety of subjects
- Informed consent before enrollment of subjects

Clinical Trials

Protocol

- ICH- E6 6. Clinical trial protocol and protocol amendments
- Added Features
 - Informed consent form(s)
 - Separate informed consent form for pharmacogenomic study
 - Agreement for Compensation of Clinical Trial
 - Information about payments and compensation available to subjects

Accredited Clinical Institutes

Accredited Clinical Sites

- Unique System in the World
- Number of Accredited Clinical Institutes
: 127 training hospitals

Accredited Clinical Institutes

Inspection Program

- Check-list for Inspection of facilities
- Categories
 - Routine : every other year
 - Directed
 - Reports of severe adverse events
 - At the time of completion of a clinical trial
 - Untrustworthy clinical reports in the NDA

Clinical Trial Notification

Procedures (Draft)

- Submitted directly to IRB
 - responsible for scientific evaluation on trial design and the safety and efficacy of the medicine
 - responsible for assessment on ethical acceptability
- Notification to the KFDA

Clinical Trial Notification

Scope of Clinical Trial Notification

- Bioequivalence studies based on pharmacokinetics for incrementally modified drugs e. g., salt changes
- Phase 3 trials which have been approved in ICH – member nations (EU, United States, Japan)
- Sponsor-investigator trials of marketed anticancer products
- Amendments of approved protocol

Pre-IND Consultation

30-day Approval Clock for INDs

- Application of the Pre-IND consultation by sponsors
- Legal-binding by official letter from KFDA
- Submission of IND according to results of Pre-IND consultation
- If there are no objections by KFDA within 30 days, the trial may be started

Pre-IND Consultation

Pre-IND Consultation

- **Timing of Submission**

At least 4 weeks prior to the intended date for meeting

- **Content of Packages**

A brief statement of the purpose of the meeting

A list of specific questions

The summary of pre-clinical and clinical data

IND content (if applicable)

Why it is attractive?

- **Attractive Pharmaceutical Market**

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

- **Efficient Regulatory Agency**

- > Open communication with KFDA officer
- > Clear review timeline of 1 month
- > Clear requirement for review & approval
- > Operation of APEC Harmonization Center

- **Qualified Investigator and Institution**

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

- **Strong Support from Government**

- > 60M USD government investment by 2010 for 15 regional Clinical Trial Centers
- > Korea National Enterprising of Clinical Trial (KoNECT)

- Plenary II: Intra-Regional Efforts to Streamline the Conduct of Clinical Trials: The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group

Tri-party Clinical Initiatives and Its Prospective



Speaker:

Jian-hua Ding (China)

Director

Division of American and Oceania Affairs,
Department of International Cooperation

State Food and Drug Administration

ICH GCG representative

Contents

- Past Activities
- 2009 activities
- MOU of KFDA-SFDA
- MOU of MHLW-SFDA
- MOU Conclusion
- Something for Tri-party in CT?
- Cooperative with ICH?
- Conjunction with Ideas as Simultaneous Development?
- Suggestions

Tri-party Clinical Initiatives and Its Prospective

MULTI-REGIONAL CLINICAL TRIALS SEOUL WORKSHOP, Inaugural Workshop of the APEC Harmonization center.

Ding Jianhua
State Food And Drug Administration
April 15, 2009, Seoul

Past Activities

- 2005, MOU between three Health Ministers of Korea, China and Japan in Seoul. Established the milestone for clinical trial cooperation within that region, in considering the possibility that its population differences might be very small.
- 2007, the first Tri-party meeting with public symposium on clinical trial followed in Tokyo.
- Some academic actions taken placed on some disease, initiated by Japan

2009 activities

- Working group need to be established
- Working group meeting should be held as soon
- Second Symposium on clinical trials could be hold in China after working group meeting.

MOU ofKFDA-SFDA

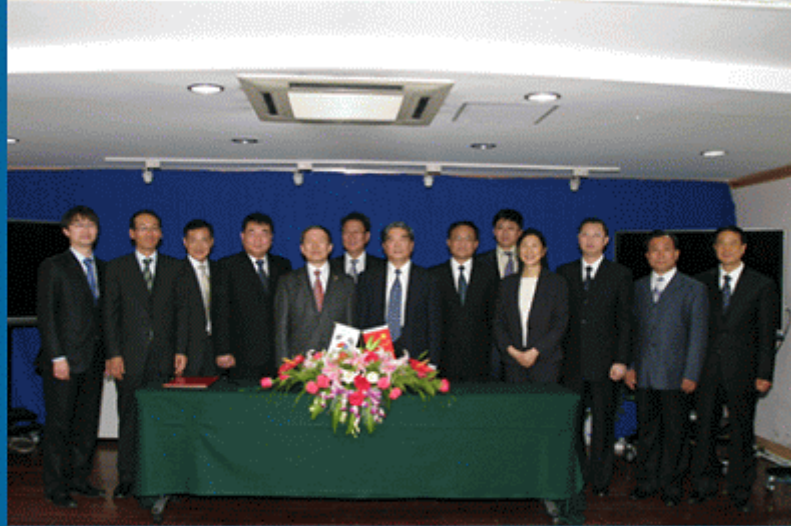
- Signed April 27, Beijing, SFDA office by Yun, YeoPuo, KFDA commissioner, and Shao Mingli, SFDA commissioner
- Effective in Korean, Chinese and English
- Cover area: food (health food), drug (nature product), medical device, cosmetics
- Mechanism: high-level annual meeting rotating by country
- Workgroup: 4 groups, food, drug, medical device, cosmetics, working-level meeting annually on rotation base, industry and third party could be invited upon consent

Cooperation Area - KFDA-SFDA MOU

- Exchange of information: regime, legislation, regulatory approval, other relevant policy.
- Mutual exchange of product safety information: imported and exported pharmaceutical products concerned
- Inspection support: for safety problem, facilitate inspections to each other
- Joint Symposium
- Joint Training course
- Promoting exchange of information on exported products



Yun, YeoPuo, KFDA Commissioner, and Shao Mingli, SFDA Commissioner, photo after MOU signature ceremony in Beijing April 27, 2009



Group photo of KFDA and SFDA after signature ceremony in April 27, 2009

MOU of MHLW-SFDA

- **Signed March, by fax signature, between SFDA Commissioner and MHLW vice-Minister**
- **Effective in Chinese and Japanese**
- **Cover area: drug , medical device, cosmetics**
- **Mechanism: annual meeting rotating by country,**
- **Workgroup: 2 groups, drug, medical device. More working group could be set up. Qualified association could be invited to attend working group meeting upon consent of two sides.**

Cooperation Area - MHLW-SFDA MOU

- Achieve and maintain safe and health for the people of both country, by establish bilateral understanding and trust of each other.
- Constructive discussion on laws, regulation and other related regulatory issues, including the current status, and the development in relation to its administrative measure and implementation.
- Respect international responsibilities of each other in the area of drug and medical device.
- Contribute to a health development of China-Japan relationship by drug and medical device cooperation activities.

MOU Conclusion

- Mainly focus on information exchange, communication, understanding, cooperation
- Annual meeting, working groups as mechanism
- Third party could be invited as agreed by two side
- However, no specific objective related to **CLINICAL TRIAL**.
- A **Tri-party MOU** could be very useful to cover specifically on regional CT



Something for Tri-party in CT ?

- **Objectives:** need to be more clarified and indentified.
- **Organizational structure:** some structure need to be established based on objectives. Such as working group composition, decision making group and its structure, the participation of regulatory body and industry representatives. (ICH a model)
- **Plan:** activities better to be planed in advance
- **Openness:** third party participation and support, such as ICH, APEC LSIF, WHO, general public, to keep transparent.
- **Importance:** legal base need to be early established if there is any result coming out in future
- **Minority population diversification:** China along has 56 minorities.

Cooperative with ICH ?

- **A goal of ICH?** (if ICH taking this regional efforts as its guideline implementation input?)
- **A result of ICH?** (If ICH guidelines E5, workable during procedure?)
- **Any support from ICH ?** (whether issues considered by ICH and the role of issue within ICH ?)
- **Any further influence on ICH?** (whether its result can make some effect on ICH output?)

Conjunction with Ideas as Simultaneous Development ?

Simultaneous Development: good idea for early availability of treatment of patients with great health needs.

- How this regional effort will be seen by Europe, US as valuable to its R&D?
- How this regional effort will be seen by Regulatory body of Europe, US when CT data produced by the region is used for submission?
- How this regional effort will be seen by pharmaceutical company as influential factor to its multi-center clinical trials strategy globally?

Suggestions

- APEC LISF, ICH, industry, third party, could be invited to listen to, or observe the progress.
- ICH should pay good attention on this issue
- The issue could be taken more formally under the framework of APEC LISF.
- Priorities should be decided on disease three parties felt important.
- A new MOU between KFDA, SFDA, and WHLW should be early established to stimulate the progress.
- Academic conclusion should be worked out for some area of indication as technical basis to facilitate decision making.

**- Plenary II: Intra-Regional Efforts to Streamline the Conduct of Clinical Trials:
The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group**

The ASEAN - PPWG



Speaker:

Yuppadee Javroongrit (Thailand)

Assistant Director

Drug Control Division

Thailand Food and Drug Administration

Contents

- The ASEAN-PPWG
 - Background
 - ACCSQ/PPWG
 - The PPWG - Lead country & Assignment
 - The PPWG – Agreements
 - ACT

- Efforts to streamline the conducts of CTs
 - Adoption of the same relevant ICH Tech.gls.
 - Joined the same Training (APEC-LSIF)
 - The achievement & the future



Plenary II : Intra-Regional Efforts to Streamline
the Conduct of Clinical Trials

The ASEAN – PPWG

by

Yuppadee JAVROONGRIT, Ph.D.

Drug Control Division, FDA, THAILAND

The Multi-Regional Clinical Trials Seoul Workshop

Inaugural Workshop of the APEC Harmonization Center

Grand Hilton Hotel, Seoul, Korea

15-18 June 2009

Yuppadee_AHC Inaugural WS-Korea-15-18 Jun 09

1




Topics

- the ASEAN-PPWG (background, obj., outcome, status)
- efforts to streamline the conducts of CTs
 - adoption of the same relevant ICH Tech.gls.
 - joined the same Training (APEC-LSIF)
 - the achievement & the future


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2



ASEAN

Association of Southeast Asian Nations




Member

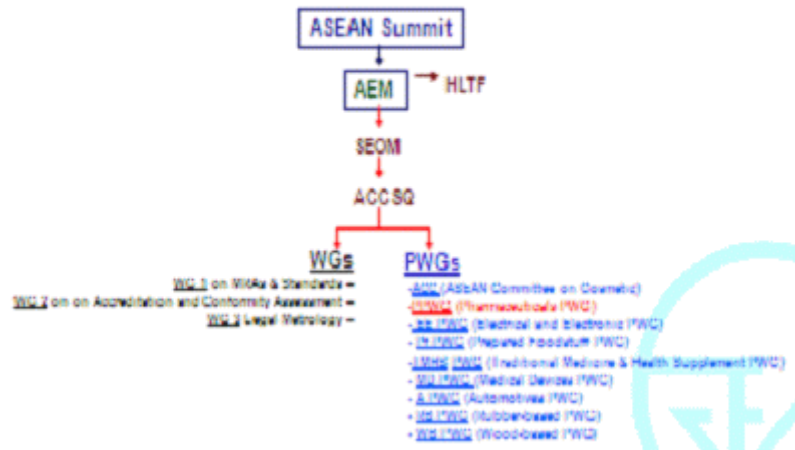
- Brunei Darussalam
- Cambodia
- Indonesia
- Lao PDR
- Malaysia
- Myanmar
- Philippines
- Singapore
- Thailand
- Vietnam

Total population ~ 550 million

Vagstad_AIRC Inaugural WS-Korea-15-18 Jun 09



Economic Cooperation in ASEAN



```

graph TD
    AS[ASEAN Summit] --> AEM[AEM]
    AEM --> SEOM[SEOM]
    SEOM --> ACCSQ[ACCSQ]
    ACCSQ --> WGs[WGs]
    ACCSQ --> PWGs[PWGs]
    
    WGs --- WGL1[WGL 1 on WTA & Standards]
    WGs --- WGL2[WGL 2 on Accreditation and Conformity Assessment]
    WGs --- WGL3[WGL 3 Legal Metrology]
    
    PWGs --- ACC[ACC (ASEAN Committee on Cosmetic)]
    PWGs --- ITC[ITC (Intellectual Property)]
    PWGs --- ELETWG[ELETWG (Electrical and Electronic)]
    PWGs --- FFWG[FFWG (Food and Feed)]
    PWGs --- TCMWG[TCMWG (Traditional Medicine & Health Supplement)]
    PWGs --- MEDWG[MEDWG (Medical Device)]
    PWGs --- AUTWG[AUTWG (Automotive)]
    PWGs --- AEWG[AEWG (Agriculture)]
    PWGs --- WWTWG[WWTWG (Wood-based)]
  
```

Vagstad_AIRC Inaugural WS-Korea-15-18 Jun 09



Ultimate Goal of the ASEAN

ASEAN Summit

ASEAN Leader

ASEAN Economic Community (AEC)

"by the year 2015..... ASEAN will be
Single Market and Single Production Base

(Free flow of Goods, of Services, of Investment, of Capitals, of Skilled Labour)

Mandate/Facilitation towards AEC

- AEC Blueprint
- AEC Scorecard
- ASEAN Charter
- ASEAN Trade Facilitation Work Programme
- ASEAN Trade in Goods Agreement (ATIGA)





ACCSQ/PPWG

A SEAN Consultative Committee
for Standards and Quality /
Pharmaceutical Product Working Group

Objective:

to develop harmonization scheme of Pharmaceuticals regulations of the ASEAN member countries, to complement and facilitate the objective of AFTA, particularly, the elimination of Technical Barriers to Trade posed by the regulations, *without compromising on drug quality, efficacy, and safety*"



The ASEAN – PPWG (2)

- Establishment → 1999
- Aim & Target :
 - for Generic, Modified, and NCEs & Bio. products
 - after achieved 'ASEAN Harmonized Product'
 - ↓
 - 'Trial Implementation'
 - ↓
 - Full Implementation by 31 Dec. 2008 !



The PPWG – Lead country & Assignment (1)

Chair country : Malaysia

Co-Chair country : Thailand

- **ACTR**: *Quality* → Indonesia
Safety → Philippines
Efficacy → Thailand
- **ACTR-Guidelines**: *Analytical Validation* → Thailand
BA/BE Studies → Malaysia
Process Validation → Singapore
Stability Study → Indonesia





The PPWG – Lead country & Assignment (2)

- **ACTD**: Overall *ACTD & ACTD Organization* → Thailand
Administrative & Glossary → Malaysia
Quality → Indonesia
Non-Clinical → Philippines
Clinical → Thailand
- **IWG**: Singapore (*Chair*)
Indonesia (*Co-Chair*)
- **MRA-GMP**: Singapore / Malaysia (*Co-Chairs*)
- **MRA-BA/BE**: Malaysia / Indonesia (*Co-Chairs*)
- **Vaccine Chapter**: Thailand / Indonesia
- **Training**: Philippines
- **Variation Guideline**: Malaysia

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The PPWG– Agreement

- Harmonized Key Areas
- Format for ACTR & ACTD
- Content of ACTR/ACTD/Glossary of Term
- ASEAN Harmonized Products
(ACTR + ACTD + Glossary of Term + Technical Guidelines)
- Implementation – Trial period (July 04 onwards)
- Full Implementation **by 31 Dec. 08**

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10



PPWG – Agreement on Technical Guidelines

“Guideline – Quality”

- based on *International Tech. gls.*
- drafted 4 ASEAN Quality gls.
 - (1) Analytical Validation guideline
 - (2) BA/BE Studies guideline
 - (3) Process Validation guideline
 - (4) Stability Study guideline

“Guideline – pre-Clinical/Safety”

- adopted 15 ICH-Safety guidelines

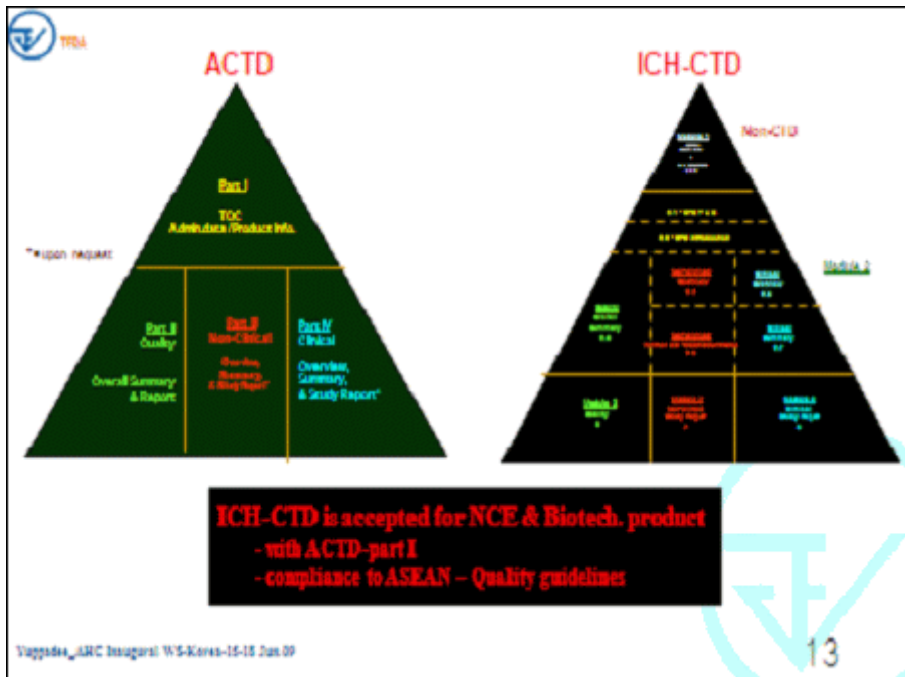
“Guideline – Clinical/Efficacy”

- adopted 11 ICH-Efficacy guidelines



ACTD

The part of
marketing authorization application dossier
that is common to
all ASEAN member countries



- Adoption of the same relevant ICH-E Guidelines**
- E1 → The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
 - E2A → Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
 - E2C → Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drug
 - E3 → Structure and Content of Clinical Study Reports
 - E4 → Dose-Response Information to Support Drug Registration
 - E6 → Good Clinical Practice: Consolidated Guideline
 - E7 → Studies in Support of Special Populations: Geriatric
 - E8 → General Consideration for Clinical Trials
 - E9 → Statistical Principles for Clinical Trials
 - E10 → Choice of Control Group and Related Issues in Clinical Trials
 - E11 → Clinical Investigation of Medicinal Products in the Pediatric Population
- TGA
- ASEAN
- 14



Adoption of the same relevant ICH-S Guidelines

- S1A → Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals
- S1B → Testing for Carcinogenicity of Pharmaceuticals
- S1C → Dose Selection for Carcinogenicity Studies of Pharmaceuticals
- S1C(R) → Addendum to S1C: Addition of a Limit Dose and Related Notes
- S2A → Guidance on Specific Aspects of Regulatory Tests for Pharmaceuticals
- S2B → Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals
- S3A → Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies
- S3B → Pharmacokinetics: Guidance for Repeated Dose Time Distribution Studies
- S4 → Single Dose Toxicity Tests
- S4A → Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
- S5A → Detection of Toxicity to Reproduction for Medicinal Products
- S5B(M) → Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products
- S6 → Safety Studies for Biotechnological Products
- S7A → Safety Pharmacology Studies for Human Pharmaceuticals
- M3 → Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals



Joining the Same Training

"APEC-L-SIF Training Project" in Thailand

| Title: Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice | | | | |
|--|---|--|--|--|
| Major Phase | Set 1
Review of Drug Development in Clinical Trial | | Set 2
GCP/Clinical Research Inspection | |
| | Preliminary WS
(17-21 Mar 09) | Advance WS
(02-09 Feb 09) | Basic WS
(27-30 May 09) | Advance WS
(02-06 Mar 09) |
| Trainers | <ul style="list-style-type: none"> -Dr. Gella LORENZO (USA) -Dr. Junia SATO (PHIL) -Mr. Sam D'AMICO (PHIL) -Dr. Norman STEVENSON (USA) -Dr. Olem NORDY (USA) <p><i>Staff: -OE - Health Canada
- PHILIP - Toronto</i></p> | <ul style="list-style-type: none"> -Dr. Norman STEVENSON (USA) -Dr. William STEVENS (USA) -Dr. Junia SATO (PHIL) -Dr. Sudichai CHOKKICHAI (PHILIP-Health Thailand) | <ul style="list-style-type: none"> -Dr. David LEFAY (USA) -Dr. Jean TOUW-ALLEN (USA) | <ul style="list-style-type: none"> -Dr. David LEFAY (USA) -Dr. Martin K. YAU (USA) <p>Managers</p> <ul style="list-style-type: none"> -Mr. Sam D'AMICO (USA) -Ms. Gella LORENZO (USA) -Ms. Sam D'AMICO (PHIL) -Ms. Gella LORENZO (PHIL) -Ms. Sam D'AMICO (PHIL) -Ms. Gella LORENZO (PHIL) |
| Trainees | = 20 regulators:
(USA - SPH, IN, NY, AZ, TX, VA)
(PHIL - CCG, ABRAC) | = 16 regulators:
(USA - SPH, IN, NY, AZ, TX, VA)
(PHIL - CCG, ABRAC) | = 22 regulators:
(USA - SPH, IN, NY, AZ, TX, VA)
(PHIL - CCG, ABRAC) | = 30 regulators:
(USA - SPH, IN, NY, AZ, TX, VA)
(PHIL - CCG, ABRAC) |
| Course | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Mock Inspection |

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The Trainers & Trainees Preliminary WS- Review of DD in CT



Yuggesha_AHC Inaugural WS-Korea-15-18 Jun 09



The Trainers, Trainees, and ThaiFDA Basic WS- GCP/Clinical Research Inspection



Yagadee_LRC Inaugural WS-Korea-15-18 Jun 09

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Joined the Same Training

“the Achievement & the Future”

- **Same Learning & Understanding** → “similar/same” implementation
 - Lectures → gave “Great Information”
 - Case Studies, Exercise & Mock Exercises → provided “Know-how”
 - Ref.Link/Info. → support “further Understanding”
 - Regulator-Trainer → provided “details + interpretation + applicable approaches”
 - Industry R&D-Trainer → provided in depth knowledge on Drug Dev.
- **Supporting Networking & Cooperation, further**
- **Encouraging a closer regional cooperation on CTs**

- Training & Working together is an essential Key to SUCCESS !

**- Together, ICH & non-ICH could collaborate on CTs
→ sharing “MRCTs Approval & Inspection”**



Thank you !!!

- Plenary III: ICH Overview

ICH Overview & Impacts of Efficacy Guideline in Global Drug Development



Presenter

Yoshiaki Uyama (Japan)

Review Director

Office of New Drugs III, PMDA

Coordinator, ICH Steering Committee

Contents

- ICH overview
 - Background
 - Membership / Structure
 - Steps in the ICH Process
 - Outcomes
 - Keys to success

- Introduction of ICH Efficacy Guideline
 - ICH Efficacy Guideline
 - E3/E4/E5/E6/E8/E9/E10 & E11
 - Other Efficacy-related guideline

- Key Message
 - Cooperation/collaboration, Harmonization
 - Common understanding for proper implementation

ICH Overview & Impacts of Efficacy Guideline in Global Drug Development

Yoshiaki Uyama, Ph.D.
Pharmaceuticals & Medical Devices Agency (PMDA)
Japan

Pharmaceuticals & Medical Devices Agency

Outline

- ICH overview
- Introduction of ICH Efficacy Guideline
- Key Message

Pharmaceuticals & Medical Devices Agency

ICH Overview

Pharmaceuticals & Medical Devices Agency

ICH

**INTERNATIONAL CONFERENCE ON
HARMONIS/ZATION
of
Technical Requirements
for the Registration of
Pharmaceuticals for Human Use**

<http://www.ich.org>

Hosted by ICH Secretariat
IFPMA, Geneva, Switzerland

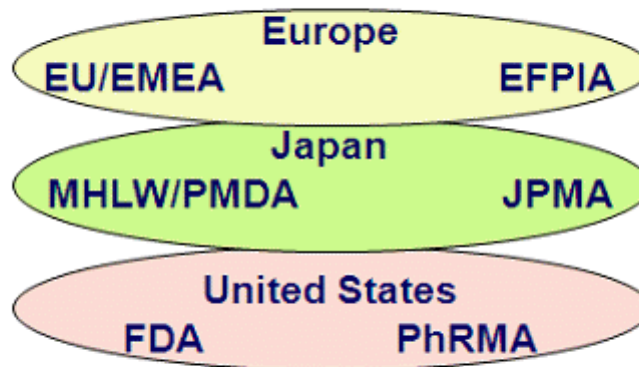
Pharmaceuticals & Medical Devices Agency



ICH Background

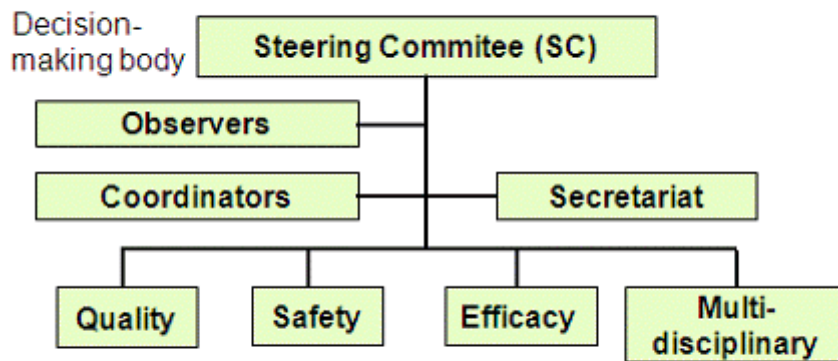
- Unique harmonisation project involving the regulators and research-based industries of US, EU and Japan
 - Started in 1990 (20 year Anniversary Next Year)
 - WHO, Canada, and EFTA are observers
- Well-defined objectives:
 - To improve efficiency of new drug development and registration process
 - To promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonised guidelines and standards

Pharmaceuticals & Medical Devices Agency



Observers: WHO, Canada, EFTA

ICH Structure



EWG(Expert Working Groups): Development

IWG(Implementation Working Group): Q&A, Implementation

Pharmaceuticals & Medical Devices Agency

Steps in the ICH Process

*After adoption
of a topic by
the Steering
Committee*



Pharmaceuticals & Medical Devices Agency



ICH Outcomes

- Over 50 guidelines on technical requirements on: Quality, Safety and Efficacy
- Examples:
 - E2B: Electronic Standards for the Transfer of Regulatory Information (ESTRI)
 - CTD & eCTD: (electronic) Common Technical Document (M4 & M2)
 - MedDRA: Medical dictionary for adverse event reporting and coding of clinical trial data

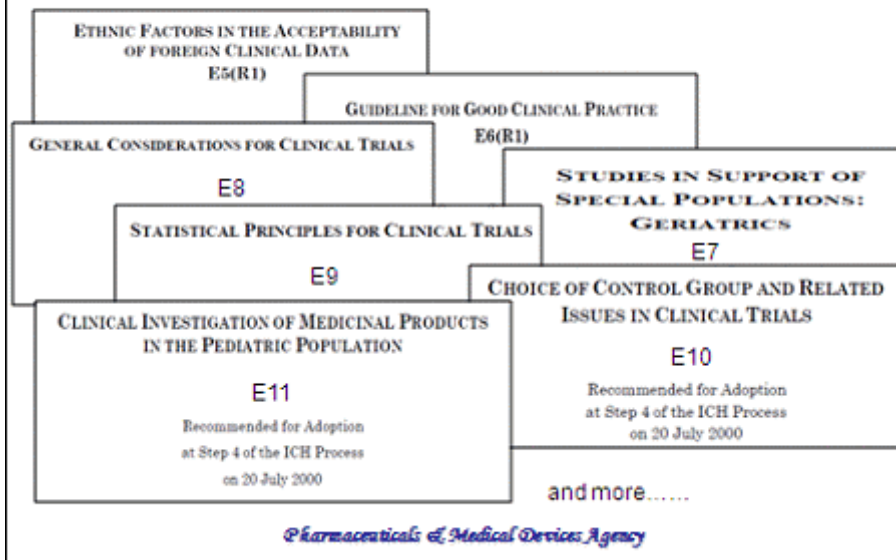
Pharmaceuticals & Medical Devices Agency

- Effective management and administration
 - Through ICH Secretariat and Steering Committee
- Joint participation of regulators and industry
- Science based and consensus driven
- Frequent, regular basis, concurrent meetings of SC and Working Groups that are outcomes based
- Commitment of all parties to implement harmonized guidelines
- Well-defined process and procedures

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A Introduction of ICH Efficacy Guideline

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- Cover the wide-range of issues relating to clinical efficacy and safety of a drug
 - e.g.
 - E5: Ethnic Factors
 - E4, E8, E9, E10: Clinical Trial Designs
 - E6: GCP
 - E7, E11: Special Population
 - And More
- Q&A maybe provided for more detailed explanation, if necessary (e.g.; E5 Q&A)
- Guideline maybe also updated or new Q&A maybe added to catch up with the latest science, if appropriate (e.g.; E5, E7(on going))

E3: Structure and Content of Clinical Study Reports

- Objectives
 - Allow the compilation of a single core **clinical study report** acceptable to all regulatory authorities of the ICH regions.
 - STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

E6: Guideline for Good Clinical Practice

- Objectives
 - Good Clinical Practice (GCP) is an international ethical and scientific quality standard for clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
 - Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected.
 - The objective of this ICH GCP Guideline is to provide a unified standard for the ICH regions to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

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Globalization of Clinical Trials

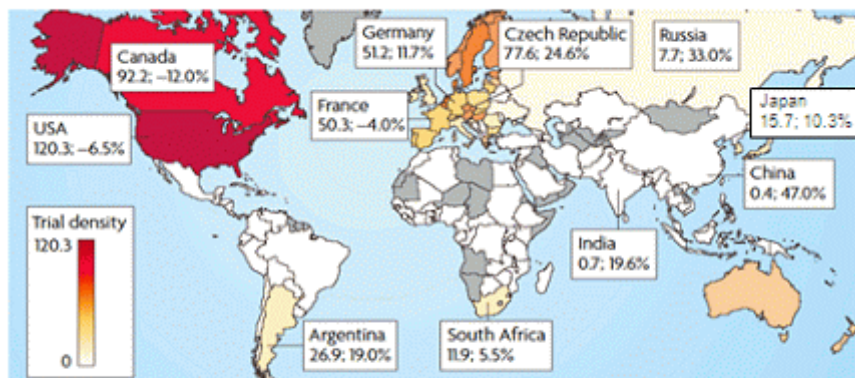


Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.

Nature Rev Drug Discovery, 7: 13, 2008

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E4: Dose-Response Information to Support Drug Registration

- Objectives
 - To describe the importance of **Dose-Response Information** in drug development
 - Minimum effective dose, maximum useful dose
 - To describe **trial designs** to obtain dose-response information
 - Parallel/Cross-over/Titration

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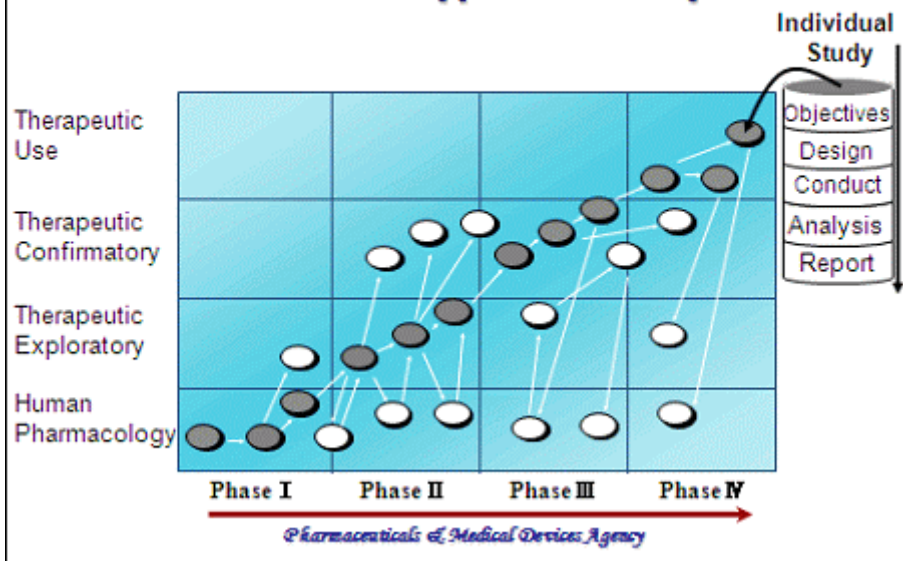
E8: General Considerations for Clinical Trials

- Objectives
 - Describe **internationally accepted principles and practices** in the conduct of both individual clinical trials and overall development strategy for new medicinal products
 - Facilitate **the evaluation and acceptance of foreign clinical trial data** by promoting common understanding of general principles, general approaches and the definition of relevant terms.
 - Present an overview of the ICH clinical safety and efficacy documents and **facilitate the user's access** to guidance pertinent to clinical trials within these documents.
 - Provide a separate glossary of terms used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain them.

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E8: Drug Development: Phases & Types of Study



E9: Statistical Principles for Clinical Trials

- Describe **general statistical principles** for conducting clinical trials: E9
 - Trial design, Endpoint, Minimization of Bias, Sample size, Monitoring etc.

E10: Choice of Control Group and Related Issues in Clinical Trials

- Describe issues for **selecting a control group** in clinical trials: E10
 - Advantage & Disadvantage of each control group

E10: Usefulness of Specific Concurrent Control Types in Various Situations

| Objective | Type of Control | | | | | | | |
|----------------------------|-----------------|------------------------|--------------------|---------------------|-----|-------|-------|---------|
| | Placebo | Active Non-inferiority | Active Superiority | Dose Response (D/R) | P+A | P+D/R | A+D/R | P+A+D/R |
| Absolute Effect Size | ○ | × | × | × | ○ | ○ | × | ○ |
| Existence of Effect | ○ | △ | ○ | ○ | ○ | ○ | ○ | ○ |
| Dose-Response relationship | × | × | × | ○ | × | ○ | ○ | ○ |
| Compare Therapy | × | △ | ○ | × | ○ | × | △ | ○ |
| Assay Sensitivity | ○ | × | ○ | ○ | ○ | ○ | ○ | ○ |

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

- OBJECTIVE
 - To describe the characteristics of **foreign clinical data** that will facilitate their **extrapolation** to different populations and support their acceptance as a basis for registration of a medicine in a new region.
 - To describe regulatory strategies that **minimize duplication of clinical data** and facilitate acceptance of foreign clinical data in the new region.
 - To describe the use of **bridging studies**, when necessary, to allow extrapolation of foreign clinical data to a new region.
 - To describe development strategies capable of characterizing **ethnic factor influences** on safety, efficacy, dosage and dose regimen.

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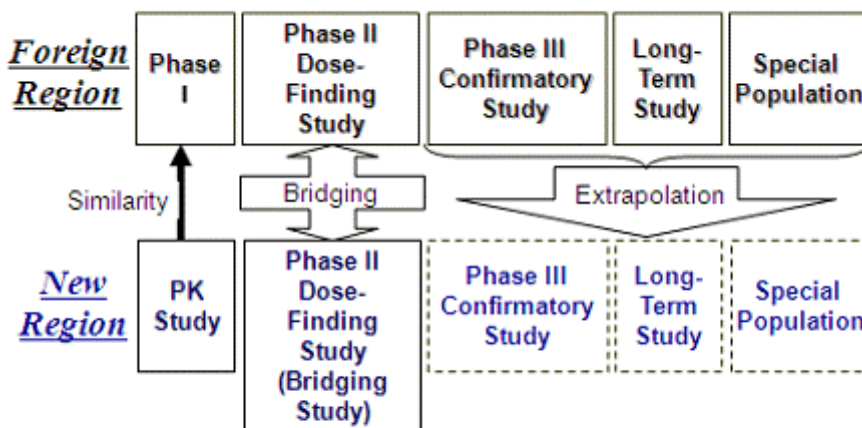
ICH E5 guideline

Classification of intrinsic and extrinsic ethnic factors

| INTRINSIC | | EXTRINSIC |
|---|---|---|
| Genetic | Physiological and pathological condition | Environmental |
| Gender | Height
Body weight | Climate
Sunlight
Pollution
Culture
Socioeconomic status
Educational status
Language |
| | Liver
Kidney
Cardiovascular functions | Medical practice
Disease definition/Diagnostic
Therapeutic approach
Drug compliance |
| | ADME
Receptor sensitivity | |
| Race | | |
| Genetic polymorphism of the drug metabolism | | Smoking
Alcohol |
| | | Food habit
Stress |
| Genetic diseases | Diseases | Regulatory practice/GCP
Methodology/Endpoints |

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E5: Bridging Concept



- No need to repeat a later phase of clinical trials in a new region, if bridging was success.

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- Bridging Concept can be applied in Multi-Regional Clinical Trials
 - A bridging study can be done at the beginning, during or at the end of a global development program
 - Points to consider in Planning, Analysis, Evaluation of the Multi-Regional Clinical Trials are provided
 - Need to include sufficient numbers of subjects
 - Evaluate consistency of effects (e.g.; dose-response) across regions

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- General principles in drug development for special populations
 - Geriatric population: **E7**
 - Patient numbers, Age distribution etc.
 - Pediatric population: **E11**
 - Timing, Formulation, Age, Ethics etc.

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Other Efficacy-related guideline

- **E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs** (May 2005)
- **E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories** (Nov. 2007)
- **E16: Genomic Biomarkers Related to Drug Response: Context, Structure, and Format of Qualification Submissions** (Step 2, June 2009)

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- **Global drug development** will be more increased and more important
- More **cooperation/collaboration** is key to successful global drug development
- **Harmonisation** can reduce duplication and increase shared expertise and promote public health

- **Proper implementation** of ICH guidelines is necessary to conduct scientific and ethical Multi-regional clinical trials
- **Common understanding** of principles and contents of ICH guidelines is important for the proper implementation
- **Training** is key to the proper implementation

- **PMDA HOMEPAGE (English Version)**
<http://www.pmda.go.jp/english/index.html>
(Renewal on March 6, 2009)
- **E-mail:**
uyama-yoshiaki@pmda.go.jp

Thank you for your attention

Pharmaceuticals & Medical Devices Agency

- Plenary III: ICH Overview

Industry Perspectives on the Adoption of ICH Guidelines in Asia



Speaker:

Martha A. Brumfield (United States)

Senior Vice-President

Worldwide Regulatory Affairs & QA

Pfizer Inc.


Contents

- Why is this discussion important?
 - Unmet Medical Need
 - GDP Per Capita Vs Health Expenditure Per Capita
 - Participating in Global Clinical Trials
- Regional Harmonization Initiatives
 - ICH and Regional Harmonization Initiatives
 - Historical Perspective
 - Regional Harmonization Initiatives (RHIs) Brought in New Opportunities
 - ICH Harmonized Guidelines
- Progress in Implementing ICH - One Industry Person's perspective
 - Progress in the Region
 - Identified Challenges in Non-ICH Regions
 - Impact of ICH Quality
 - Good Clinical Practice
 - Indicators of Success in the clinical area
 - Singapore Health Sciences Authority
 - Korean FDA
 - Identified Challenges in Non-ICH Regions
- Success and the future
 - Conclusion
 - Closing thoughts



Industry Perspectives on the Adoption of ICH Guidelines in Asia

MRCT Meeting, Korea
15 June 2009

Martha A. Brumfield, Ph.D. 
Senior Vice President
Worldwide Regulatory and Quality Assurance
Pfizer Inc
New York, NY

DISCLAIMER

Comments in this presentation
reflect the views of the presenter and
not necessarily those of PhRMA
nor of Pfizer Inc.

Outline of Topics

- Why Is This Discussion Important?
- Regional Harmonization Initiatives
- Progress in Implementing ICH - One Industry Person's perspective
- Success and The Future



A reminder.....

Why is this discussion even important?



Asian Unmet Medical Need

Cardiovascular

- Stroke is much more prevalent than coronary artery disease (CAD) in Asia
- In China alone: 800,000 to 1 Million deaths per year from Stroke
Six Million Stroke Survivors

Infectious Disease

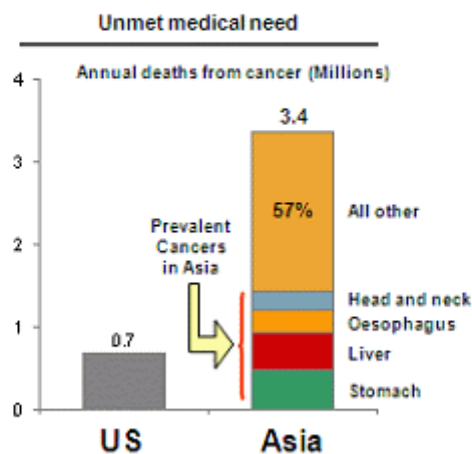
- Hepatitis B affects 2 billion people worldwide
- 360 Million chronically infected
- 25% of chronically affected will die of complications
- No effective treatments: Lamuvidine-resistance; Adenovir- nephrotoxicity

Oncology

- More than half of all cancer deaths worldwide occur in Asia
- Second and Third most common causes of cancer death worldwide are Stomach and Liver Cancer (rare in the West)
- Most Asia Specific Cancers are unmet medical needs with few options



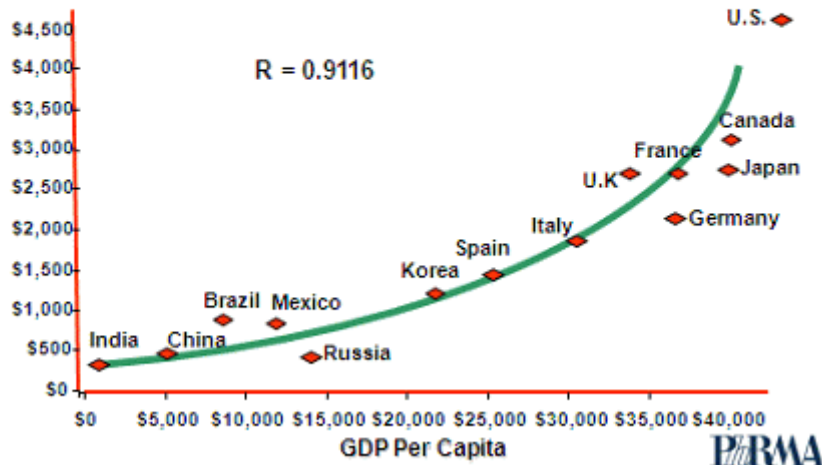
Unprecedented Asian Oncology Unmet Medical Need



Gross Domestic Product (GDP) Per Capita Vs Health Expenditures Per Capita

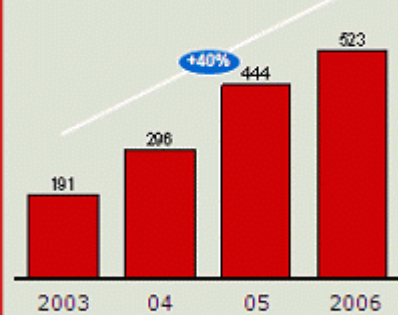
Direct correlation between GDP per capita & healthcare spending

Healthcare Spenditure Per Capita

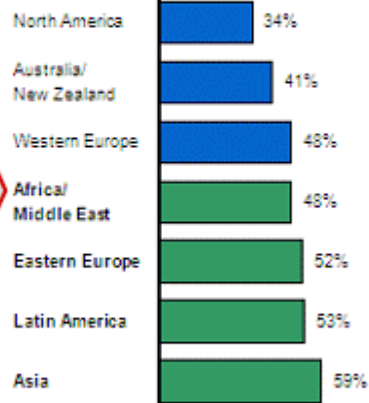


Status of Countries Participating in Global Clinical Trials

Number of Phase III trials sponsored by industry



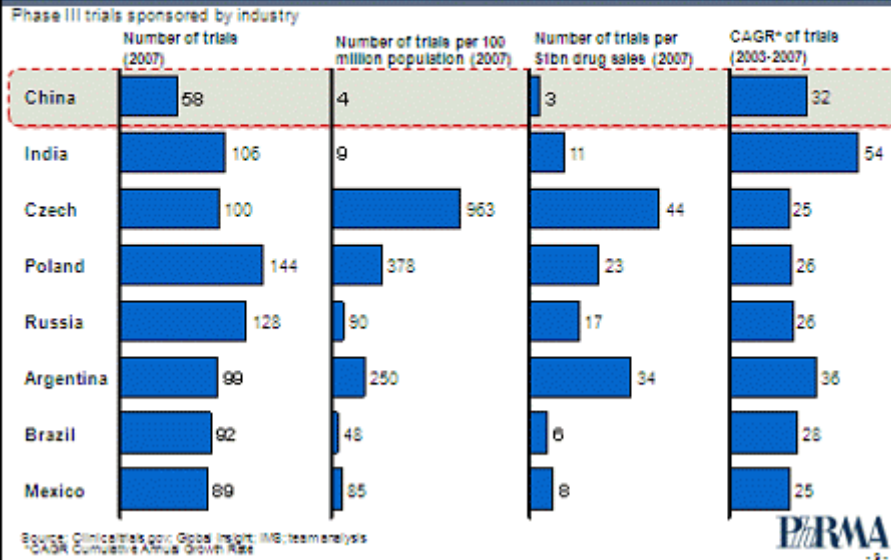
2003-2006 Cumulative Average Growth Rate of Phase III trials by region*



* Trials may contribute to growth in multiple regions
Source: Clinicaltrials.gov, ISTAT, WHO

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CAGR of Phase III Clinical Trials By Country



Participation In Clinical Trials 2005 Versus 2008

| COUNTRY / REGION | Year 2005 | % | Year 2008 | % | Growth |
|------------------|-----------|--------|-----------|--------|--------|
| WORLDWIDE * | 13007 | 100.0% | 16972 | 100.0% | |
| USA | 6469 | 49.7% | 8348 | 49.2% | -1.1% |
| CANADA | 1299 | 10.0% | 1146 | 6.8% | -32.4% |
| GERMANY | 1024 | 7.9% | 1082 | 6.4% | -19.0% |
| UK | 669 | 5.1% | 774 | 4.6% | -11.3% |
| EUROPE | 3348 | 25.7% | 4274 | 25.2% | -2.2% |
| SOUTH AMERICA | 312 | 2.4% | 532 | 3.1% | 30.7% |
| BRAZIL | 182 | 1.4% | 363 | 2.1% | 52.9% |
| CHINA | 141 | 1.1% | 321 | 1.9% | 74.5% |
| INDIA | 139 | 1.1% | 231 | 1.4% | 27.4% |

Source: DIA 21st EuroMeeting: Challenges, Risks and Benefits of Conducting Clinical Trials in Developing Regions

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ICH and Regional Harmonization Initiatives

- Why This Matters
- Regional Harmonization Initiatives
- Progress in Implementing ICH - One Industry Person's perspective
- Success and The Future



ICH

INTERNATIONAL CONFERENCE ON
HARMONIS/ZATION
of
Technical Requirements
for the Registration of
Pharmaceuticals for Human Use

<http://www.ich.org>
Hosted by ICH Secretariat
IFPMA-Geneva, Switzerland

Source: APBC/IBF meeting in Peru in July, 2008



Historical Perspective

- 1990: ICH was created (Regulators and Industry from Europe, Japan, and the US)
 - Canada, EFTA, and WHO as Observers
 - Goal to make regulatory environment for drug development more efficient and to avoid duplication
- 1999: Global Cooperation Group (GCG) formed by ICH
 - Goal to make ICH information available to any requestor
 - Regional Harmonization Initiatives (RHIs) added in 2003
 - Individual Drug Regulatory Authorities invited: Australia, Brazil, China, Chinese Taipei, India, Russia, Singapore, and South Korea
- 2008: Regulators Forum established by ICH



Regional Harmonization Initiatives

Pan American Network on Drug Regulatory Harmonization (PANDRH)
Southern African Development Community (SADC)
Association of Southeast Asian Nations (ASEAN)
Asia-Pacific Economic Cooperation (APEC)
Gulf Cooperation Countries (GCC)



Regional Harmonization Initiatives (RHIs) Brought in New Opportunities

- Establishes two-way dialogue, collaboration
- Provides opportunity to better understand ICH guidelines and process
- Provides opportunity to better understand the needs of other regions
- Provides opportunity for sharing of best practices

*Shifted from information-sharing to
implementation/training*



ICH Harmonized Guidelines

- **Serve as standard** - with regulators in ICH and many non-ICH regions.
- **Define fundamentals of GCP** – e.g., US FDA uses ICH as benchmark on which to base compliance actions (ICH E6)
- **Provide framework** around which to develop good review practices
- **Implementation is the key next step**
– Current focus of ICH activity



Progress in the Region

- Quality
- Good Clinical Practice
- Common Technical Document
- Success and The Future



Identified Challenges in Non-ICH Regions

| <i>Challenge</i> | <i>Relevant ICH Topics</i> | <i>Industry perspective</i> |
|--|---|--|
| Stability testing in special climate zones | ICH Q1A(R2), Q1B, Q1C, Q1D, & Q1E | Good Progress |
| Quality by Design | Newer ICH "Q" topics (Q8/Q8R, Q9, Q10) | Under consideration |
| When to conduct bridging studies | ICHE5 | Some Progress |
| Clinical trials | ICHE6 (GCP), other "E" topics | Good Progress |
| Registration dossier and variations | ICH M4 (CTD) & M2 (eCTD) | Concept being embraced, electronic tools limited |
| Safety reporting | ICHE2A, E2B(R2) & MedDRA | Being embraced |
| Inspections (GMP/GCP/PV) | Not direct ICH topic, but being addressed in ICH Regulators Forum | ICH guidelines provide framework; Regulators to share good practices |



Impact of ICH Quality

| Year | Milestone |
|------|---|
| 1993 | ICH Q1A guideline: <i>Stability Testing of New Drug Substances and Products</i> |
| 2000 | ICH Q1A(R): Revision to expand practical application |
| 2003 | ICH Q1A(R2): Revision as a consequence of Q1F |

Before ICH Q1A: Acceptable storage conditions included uncontrolled room temperature and uncontrolled humidity.
After ICH Q1A was implemented: Carefully controlled storage conditions (e.g., 25 ± 2 °C temperature and 60 ± 5% relative humidity) were instituted to preserve product quality.

NB: Regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions, such as 30°C/75% RH, are acceptable should the applicant decide to use them.



Good Clinical Practice

| Challenge | Relevant ICH Topics | Industry perspective |
|----------------------------------|--------------------------------|----------------------|
| When to conduct bridging studies | ICH E5 | Some Progress |
| Clinical trials | ICH E6 (GCP), other "E" topics | Good Progress |

- Investigators, Regulators, and Sponsors have increased dialogue directed at supporting global clinical trials and understanding when bridging studies/local studies needed
- More global studies are being placed in Asia
 - Increasing capability of investigators and staff
 - Increasing quality of data
 - Increasing drug development capability in country/region
- ANDthere is more to do



Indicators of Success in the clinical area

Indicators of Success:

- The number and sites for clinical trials increase
- Faster approvals to start clinical trials
- Types of trials reflect the innovation a country wants to attract, e.g., multi-national vs local trials or both
- Increased numbers of patients recruited into studies
- Level of quality of data increases
- Level of compliance to regulatory requirements and international best practices increases
- Increased number of applications and approvals for clinical trials
- The review timeline for marketing applications shortens



Singapore Health Sciences Authority

| <i>Challenge</i> | <i>Relevant ICH Topics</i> | <i>Industry perspective</i> |
|-------------------------------------|----------------------------|--|
| Registration dossier and variations | ICH M4 (CTD) and M2 (eCTD) | Concept being embraced, electronic tools limited |

- All new and generic drug applications must conform to either the ICH CTD format or the ASEAN CTD format
- As of December 2008, more than 50% of applications are in ICH CTD format

ICH M4 CTD

Module 1: Local Administrative
 Module 2: Overview & overall summaries
 Module 3: Quality
 Module 4: Non-clinical
 Module 5: Clinical

ASEAN CTD

Part I: Local Administrative
 Part II: Quality
 Part III: Non-clinical
 Part IV: Clinical



Korean FDA

| <i>Challenge</i> | <i>Relevant ICH Topics</i> | <i>Industry perspective</i> |
|-------------------------------------|----------------------------|--|
| Registration dossier and variations | ICH M4 (CTD) and M2 (eCTD) | Concept being embraced, electronic tools limited |

- Adoption of the ICH Common Technical Document (M4) in APEC is also important in structuring information, particularly Quality information, according to global standards.
- Korea has accepted CTDs to date only requiring the local information (Module 1) in Korean.
- New guidance on CTDs for Korea available
- Local promotion of Good Review Practices in Korea are consistent with FDA review practices.



Identified Challenges in Non-ICH Regions

| <i>Challenge</i> | <i>Relevant ICH Topics</i> | <i>Industry perspective</i> |
|------------------|----------------------------|-----------------------------|
| Safety reporting | ICH E2A, E2B(R2) & MedDRA | Being embraced |

- Adoption of the ICH regulatory definitions of seriousness of adverse reactions (ICH E2A) extends far beyond the ICH regions in the interest of protecting patient safety
- Use of the MedDRA terminology to classify adverse reaction terms and other medical concepts is important for best use of medicines
- National pharmacovigilance centers may use either MedDRA or WHO-ART to report ADRs to the WHO Uppsala Monitoring Centre
- Electronic reporting (E2B) of individual case safety reports will improve efficiency as local capacity evolves



Conclusion and The Future

- The geographical face of international drug development and trade is rapidly changing
- ICH guidelines support science and risk-based regulatory decision-making in all regions including non-ICH regions
- Unnecessary duplication of effort in ICH and non-ICH regions is not in the interest of patients
- Sharing of perspectives and experience between ICH and non-ICH regions must continue



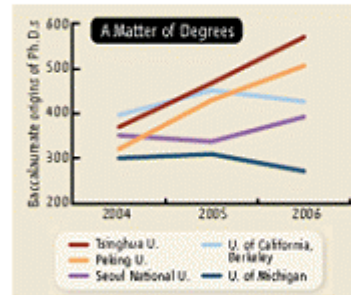
Closing thoughts.....



Expertise In China, India, And Other Countries

Top ten countries of origin of non-US citizens earning doctorates in US universities in 2006

| | | |
|----|----------|------|
| 1 | China | 4774 |
| 2 | India | 1742 |
| 3 | Korea | 1648 |
| 4 | Taiwan | 718 |
| 5 | Canada | 561 |
| 6 | Turkey | 454 |
| 7 | Japan | 322 |
| 8 | Thailand | 268 |
| 9 | Germany | 257 |
| 10 | Russia | 253 |



Leading the pack, Tsinghua and Peking universities top Berkeley in having their graduates complete U.S. doctoral programs.

Reference: Science 11 July 2008: 186. <http://www.sciencemag.org/cgi/content/full/321/5885/186.pdf> Original references can be found at <http://www.nsf.gov/statistics/indycountriesWeb>

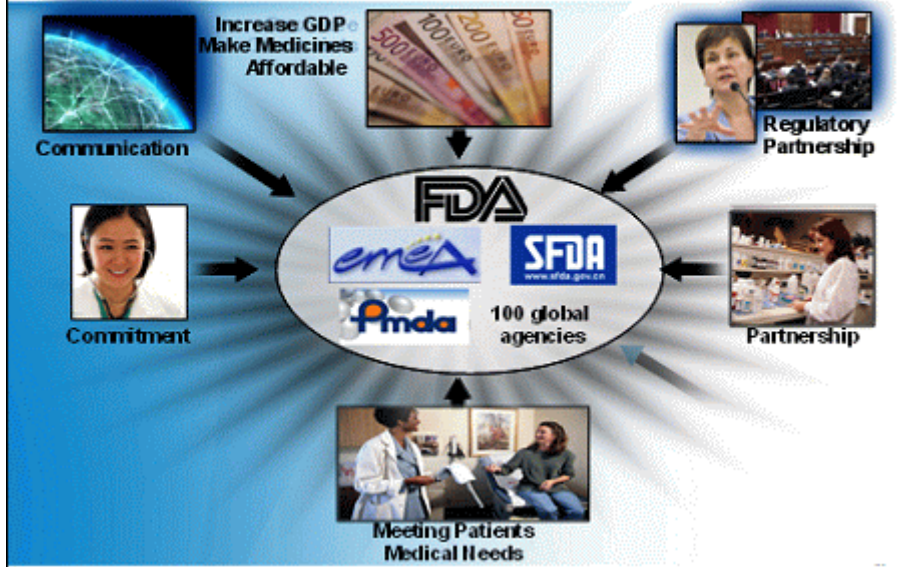
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- 27 -

The Road To Enlightenment...Follow The Lights



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What Success Looks Like



Thank you

- **Plenary IV: Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed**

Interpreting Subgroup Analyses in Clinical Trials



Speaker:

Allan Donner (Canada)

Professor,

Department of Epidemiology and Biostatistics

University of Western Ontario

Contents

- Comparison of Regimens
 - For treating HIV infected patients
 - For treating patients with acute MI
- Interpretational Problems
 - Type I / Type II error
 - Estimation Bias
 - Example 1~4
- Test of Interaction
- Quantitative vs. Qualitative Interaction
 - Bonferroni procedure
- Internal Cross-validation (sample-splitting)
- Bayesian Methods
 - Questions to ask
 - Subgroup analysis by astrological sign
 - "Outcome by Outcome" analyses
- Conclusion

Interpreting Subgroup Analyses in Clinical Trials

Allan Donner,Phd,FRSC
Professor, Department of Epidemiology and
Biostatistics

Director, Biometrics
Robarts Clinical Trials
Robarts Research Institute

University of Western Ontario
London, Canada

Comparison of Regimens for treating HIV infected Patients

Percent of Patients with HIV RNA levels <50 c/ml

| | Raltegravir(n=263) | Efavirenz(n=258) | P |
|------------------|--------------------|------------------|-----|
| Overall | 92% | 89% | .33 |
| Latin America | 91% | 84% | |
| Southeast Asia | 94% | 93% | |
| North America | 90% | 92% | |
| Europe/Australia | 94% | 91% | |

Lennox et al(2009)

EXAMPLE OF A TRIAL SUGGESTING MULTIPLE SUBGROUP ANALYSES

| MORTALITY WITHIN 90 DAYS OF PATIENT ENTRY | | | |
|---|--------------------|-----------------------|------|
| Group | Placebo
(n=697) | Metoprolol
(n=698) | P |
| All Patients | 8.9 | 5.7 | .03 |
| Age 40-69 | 8.1 | 5.1 | .04 |
| Age 70-74 | 15.7 | 11.6 | >.20 |
| Age 40-64 | 5.7 | 4.5 | >.20 |
| Age 65-74 | 14.8 | 8.1 | .03 |
| Definite MI | 13.7 | 9.0 | .05 |
| No Definite MI | 2.1 | 1.3 | >.20 |

Hjalmarson et al.(1981)

INTERPRETATIONAL PROBLEMS

Type I error rates:

Since the number of subgroups of interest may be large, the overall probability of detecting at least one false significant difference may be far greater than nominal.

Suppose separate significance tests are performed within each of G patients subgroups. If each test is performed at the 5% level of significance α and the treatments are identical then the probability of obtaining at least one significant result is:

$$1 - (1 - \alpha)^G$$

e.g., if $\alpha = .05$ and $G=10$, then this probability is 0.40.

Type II error rates:

Since the sample sizes for many subgroup comparisons tend to be small, the probability of failing to detect a substantively important subgroup effect may be high.

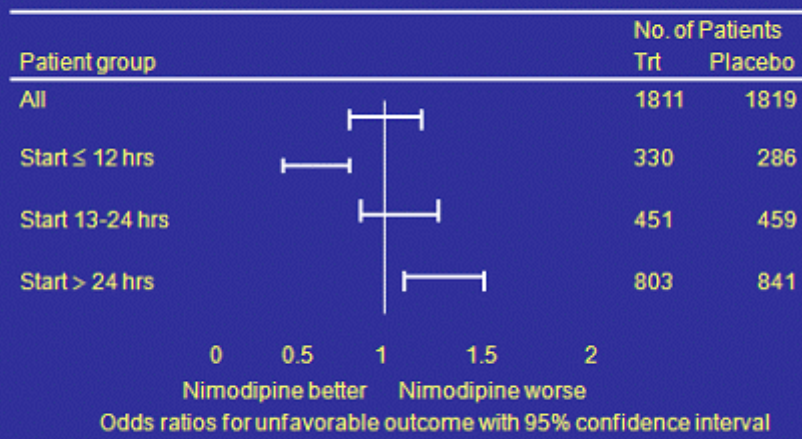
Thus suppose the overall treatment effect is significant while the corresponding effect in a selected subgroup of patients is non-significant.

It is misleading to conclude that the results for this subgroup differ from the overall results.

Estimation Bias

Treatment effects that are reported BECAUSE they are statistically significant (i.e. because they are extreme) will on the average be less extreme when the treatment is applied to a new similar set of subjects.

Example 1: Effect of Nimodipine Treatment on Neurological Outcome After Ischemic Stroke: Subgroup Analyses by Delay to Start of Treatment



"Those starting within 12h showed the strongest beneficial effect. Those starting after 12h showed a slightly negative effect".

J.P. Mohr et al. (1994)

Critique

"Is it biologically plausible that treatment within 12 hours is beneficial but later treatment is harmful? Such qualitative interactions are rare in medicine.

The difference between the effects of early and late treatment may similarly have been due to chance effects. Where the subgroup analyses have not been predefined, even greater caution is needed in interpreting the results".

Counsell et al. (1994)

Example 3:

Do trials sponsored by the pharmaceutical industry show more favorable results?

| | No. of Trials
(No. of Patients) | Relative Odds
of Relapse on
Clozapine | 95% CI |
|-------------------------------------|------------------------------------|---|-------------|
| Trials sponsored
by Industry | 13 (980) | 0.50 | (0.3 – 0.7) |
| Trials Not sponsored
by Industry | 10 (783) | 0.40 | (0.1 – 1.4) |

“Our finding supports the concern that drug company involvement in clinical trials affects the outcome”

Wahlbeck and Adams (1999)

CRITIQUE

“An unequivocal difference in the sponsored trials and an equivocal difference in the unsponsored trials does not establish a difference between the two types of study. To claim that it does amounts to comparing subgroups on the basis of their p-values, and this is known to be flawed”.

Matthews (1999)

TEST OF INTERACTION

The purpose of tests of interaction is to demonstrate that the effect of treatment significantly varies across subgroups.

This approach is to be preferred to performing separate significance-tests within subgroups.

Randomized trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction: Cardiac mortality by sex

| Cardiac Mortality | Men | | Women | |
|-------------------|----------------------|-----------------|----------------------|-----------------|
| | Intervention (n=458) | Control (n=445) | Intervention (n=234) | Control (n=239) |
| Died | 11 (2.4%) | 11 (2.5%) | 22 (9.4%) | 12 (5.0%) |
| Survived | 447 | 434 | 212 | 227 |
| Total | 458 | 445 | 234 | 239 |

“The poor overall outcome for women, and the possible harmful impact of the intervention on women, underline the need for further research”.

Frasure-Smith et al. (1996)

Does the effect of intervention depend on sex?

Test of Interaction:

$$OR_1 = \frac{(11)(434)}{(11)(447)} = 0.97 \quad OR_2 = \frac{(22)(227)}{(12)(212)} = 1.96$$

$$\log_e(OR_1) = .029514 \quad \log_e(OR_2) = 0.67445$$

$$\hat{V}(\log_e[OR_1]) = .18636$$

$$\hat{V}(\log_e[OR_2]) = .13791$$

$$Z = \frac{-.029514 - .67445}{\sqrt{.18636 + .13791}} = \frac{-.70396}{.56945} = -1.24 (p = .21)$$

CONCLUSION: Insufficient evidence exists that effect of intervention depends on sex

QUANTITATIVE VS. QUALITATIVE INTERACTION

Quantitative Interaction:

The magnitude, but not the direction, of the true treatment effect varies across subgroups.

Qualitative Interaction:

The direction of the true treatment effect varies across subgroups. This implies that one treatment is superior for some subsets of patients and the alternative treatment is superior for others.

Bonferroni procedure:

To declare a given subgroup comparison to be statistically significant at level α , require $P < \alpha / G$, where G is the total number of subgroup comparisons performed.

e.g., if $G=10$, then to declare significance at $\alpha=.05$, require $P < .05/10 = .0050$.

This procedure is known to be very conservative, especially if the subgroups are not independent.

Summary

Bonferroni Procedures

- No distributional assumptions
- Require only P-values to implement

Tests of Interaction

- Provide more accurate approximations to true P-value.
- Can be extended through statistical modelling to adjust for covariates.
- Are associated in a natural way with estimates of effect.

A contemporary difficulty created by subgroup analyses: the lay press.

"Why not allow companies to cull the relevant data from existing studies when a certain subgroup is clearly of help?"

Editorial. Wall Street Journal
November 26, 2002

Questions to ask:

- (i) Were the subgroup hypotheses formulated in advance?
- (ii) Are the results biologically credible?
- (iii) Are the results consistent with those from previous trials?
- (iv) Were tests of interaction or other methods of controlling type 1 error rate performed?

Subgroup analysis by astrological sign

| Birth Sign | Percent Reduction in Odds of Death | P |
|------------|------------------------------------|-----------------|
| Scorpio | 48% | < .04 |
| All others | 12% | Not Significant |

Collins, R. et al.(1987)

INTERNAL CROSS-VALIDATION (SAMPLE-SPLITTING)

This technique allows subgroup hypotheses to be generated and tested in the same clinical trial. A portion of the data may be used to formulate hypotheses, with the remaining portion reserved for confirmatory testing.

Advantage: Has intuitive appeal and allows one to use judgement and prior information in selecting subgroups of interest.

Disadvantage: Not very efficient from a statistical point of view.

).

BAYESIAN METHODS

These methods, based on specifying prior probabilities of clinically important interactions, tend to shrink the point estimate of a subgroup effect toward the overall estimate of treatment effect.

Advantage: Prior beliefs concerning the presence of interactions are often based on solid evidence, and Bayesian methods allow these beliefs to formally influence clinical decision-making.

Disadvantage: There will inevitably be disagreements on the appropriate choice of prior probabilities, and thus with respect to the conclusions drawn. These methods, as well, are still in the developmental stage.

Hierarchy of credibility

- (i) Subgroups specified in advance in protocol.
- (ii) Subgroups implied by stratification factors.
- (iii) Subgroups identified by other similar trials.
- (iv) Subgroups identified through trial monitoring and tested in later subjects.
- (v) Subgroups suggested by the data.
- (vi) Subgroups categorized by outcome variables, i.e. events occurring after baseline.

Friedman, Furberg, DeMets
Fundamentals of Clinical Trials (1996)

“Outcome by Outcome” analyses

| Dose Level | Total Group
Number of Patients | Survival Rate |
|------------|-----------------------------------|---------------|
| Full | 78 | 77 |
| Moderate | 222 | 56 |
| Mild | 149 | 48 |
| Total | 449 | 61 |
| Controls | 179 | 45 |

*NEJM*1981; **3**: 10

Survival of Compliant versus Noncompliant HIV Infected Patients Administered Dinitrochlorobenzene (DNCB)

| Subjects | No. of Patients | Progression to AID (%) |
|--------------|-----------------|------------------------|
| Compliant | 13 | 2 (15) |
| Noncompliant | 11 | 5 (45) |

“Patients who discontinued DNCB application appeared to have a higher rate of progression of AIDS”

Stricker et al. (1994)

CRITIQUE:

"The fact that compliant patients who follow instructions may have better whether their treatment works or not has been verified in several studies'

Bigby et al. (1996)

CONCLUSION

"Among women with a history of subfertility, prenatal use of electric blankets was associated with a more than four-fold increase in risk. Despite small numbers and the potential for recall bias, our study indicates that identifying a susceptible population may be required for detecting adverse reproductive effects of electromagnetic fields".

Li *et al.* (1995)

CRITIQUE

"With this sentence and in their Discussion, the authors signal that they would like readers to take this result seriously. Since electromagnetic fields are the exposure under study, attention is bound to be paid. The question is, how much attention is deserved?"

- Overall association is non-significant.
- Definition of compromised reproductive function questionable (history of unprotected intercourse for more than 12 months without becoming pregnant).
- Sparse data (only five exposed cases).
- No test of interaction performed.

Hatch (1995)

- **Plenary IV: Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed**

Issues with Design and Analysis in MRCT



Speaker:

James Hung (United States)

Director of Division of Biometrics I

Office of Biostatistics

US FDA

Abstract

Multi-regional clinical trial poses a great deal of challenge to design, analysis and interpretation of trial results. Issues arise when a global treatment effect of a medical product is interpreted or when the trial results are used to bridge from global to local or between the regions. The potential regional differences in treatment effect of the main interest, i.e., those attributed to intrinsic or extrinsic factors, may be obscured by data quality problems. This presentation will cover analysis consideration and design consideration. Methods of analysis (graphical and analytical) will be discussed. Two inconsistency measures will be introduced. For design considerations, the impact of regional differences on sample size planning will be assessed.

Issues with Design and Analysis in MRCT*

H.M. James Hung, PhD

Division of Biometrics I, OB/OTS/CDER

U.S. Food and Drug Administration

*Presented in APEC MRCT Workshop, Seoul, Korea,
June 15-18, 2009*

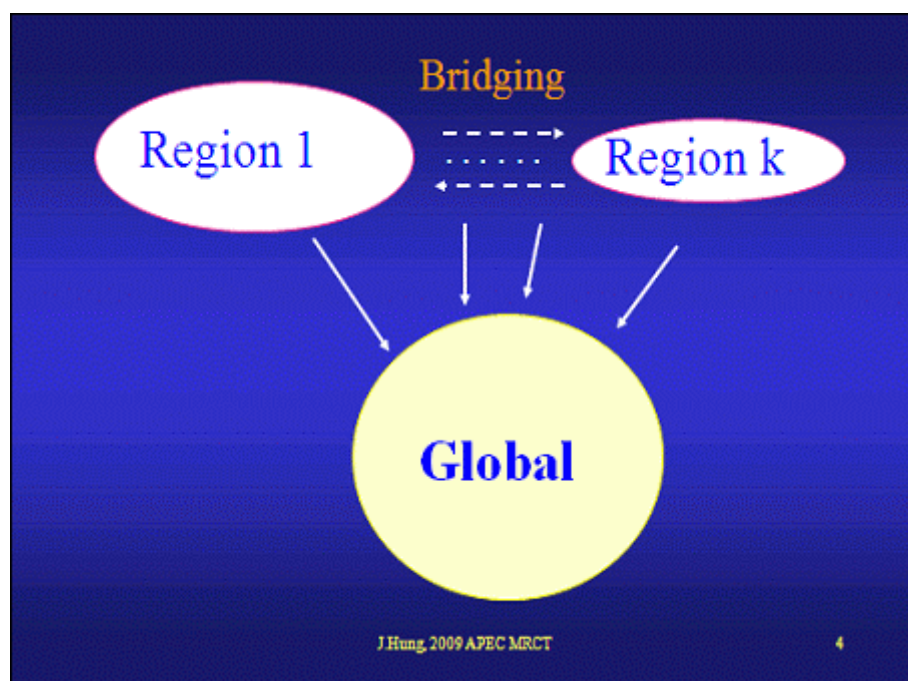
*The views expressed in this presentation are not necessarily of the US FDA

Outline

- ◆ Analysis consideration
- ◆ Design consideration
- ◆ Concluding remarks

Multi-regional clinical trial (MRCT)
essentially serves two interrelated
purposes

- assessment of global treatment effect
- use the trial results to bridge from
global to local or between regions



Many factors can possibly cause regional differences in drug effect (heterogeneity)

- intrinsic factors*

race, genetic factors, ...

- extrinsic factors*

background treatment, social factors, health care system, medical practices, ...

- quality of trial conduct or data

*ICH E5

J.Hung, 2009 APEC MRCT

5

The regional differences of real interest, if any, are those attributed to intrinsic and extrinsic factors (e.g., ethnic or genetic differences, medical practices and health care systems)

Data quality problem can accentuate or attenuate regional differences in treatment effect in terms of effect estimate, and it will boost variances of the global estimate

J.Hung, 2009 APEC MRCT

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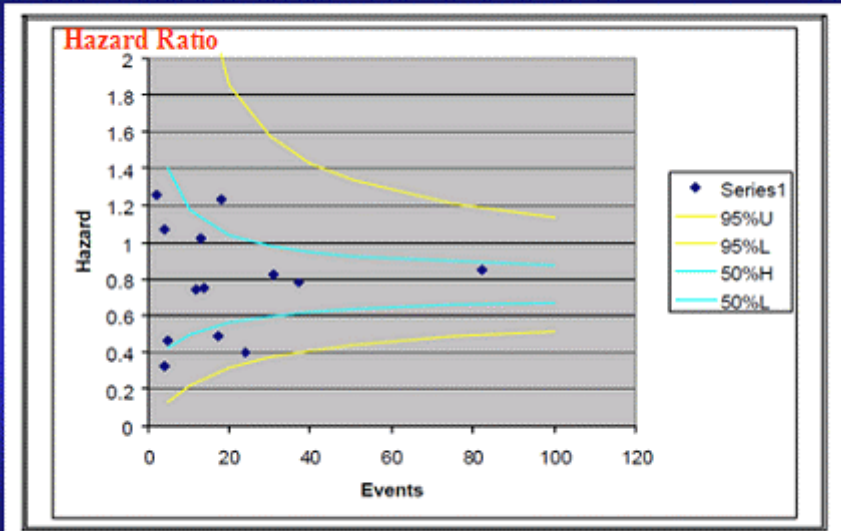
Currently, potential heterogeneity issues in MRCT are still handled in a retrospective or reactive manner in statistical analysis, though awareness of the issues increases in regulatory applications

Analysis Consideration

- ◆ Funnel plot
 - effect size estimate vs. N (or # of events)
- ◆ *Phyp* plot*
 - p-value & p-value quantile curve vs. N (or # of events), given delta
- ◆ Forest plot

*Hung, O'Neill, Bauer, Köhne (1997)

Funnel Plot of hazard ratio by country

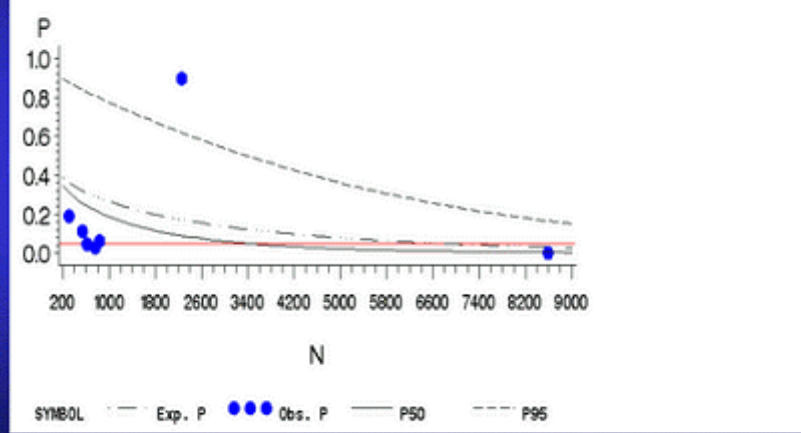


J.Hung, 2009 APEC MRCT

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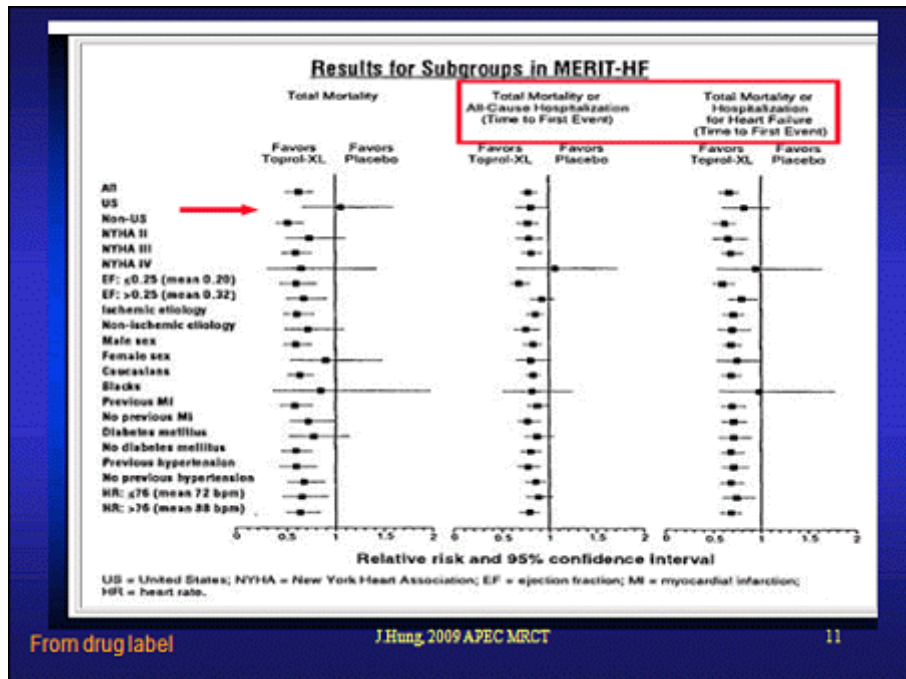
Aspirin – mortality post-MI over 7 trials

Phyp Plot: P vs. N (assuming $\delta=0.04$)



J.Hung, 2009 APEC MRCT

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Analysis Consideration

◆ Analytic approach

- testing treatment by region interaction?
- testing qualitative interaction (Gail & Simon)
- inconsistency assessment

Assessing inconsistency remains a challenge !

Inconsistency Measure

- ◆ Probability of reversal (point est < 0 vs. > 0)

K regions

Total sample size N planned to detect a drug effect δ (standardized) > 0 at level of significance, α , and power $1-\beta$

Sample size for region h : $\lambda_h N$

(assuming equal allocation for treatments)

p: p-value of global trial yielding the overall estimate (d) of treatment effect; $d > 0$

| p | Probability that one region shows a reversal | Probability that two regions show reversals |
|------|--|---|
| .001 | 0.17 | 0.01 |
| .01 | 0.29 | 0.05 |
| .05 | 0.38 | 0.11 |

if true effect size is very close to d

Equal sample size distribution to 4 regions

$\alpha = 0.05$, $\beta = 0.10$, equal variance among regions

p: p-value of global trial yielding the overall estimate (d) of treatment effect; $d > 0$

| p | Probability that one region shows a reversal | Probability that two regions show reversals |
|------|--|---|
| .001 | 0.23 | 0.02 |
| .01 | 0.33 | 0.06 |
| .05 | 0.40 | 0.13 |

if true effect size is very close to d

Sample size allocation to 4 regions = (0.2, 0.1, 0.3, 0.4)

$\alpha = 0.05$, $\beta = 0.10$, equal variance among regions

p: p-value of global trial yielding the overall estimate (d) of treatment effect; $d > 0$

| p | Probability that one region shows a reversal | Probability that two regions show reversals |
|------|--|---|
| .001 | 0.32 | 0.06 |
| .01 | 0.39 | 0.11 |
| .05 | 0.43 | 0.17 |

if true effect size is very close to d

Sample size allocation to 4 regions = (0.1, 0.1, 0.1, 0.7)

$\alpha = 0.05$, $\beta = 0.10$, equal variance among regions

- ◆ Percentage of total variation that is due to heterogeneity rather than chance (Higgins et al)

Cochran's Q test statistic with df degrees of freedom

$$I^2 = \max\left(100\% \times \frac{Q - df}{Q}, 0\right)$$

This was proposed to handle meta-analysis.

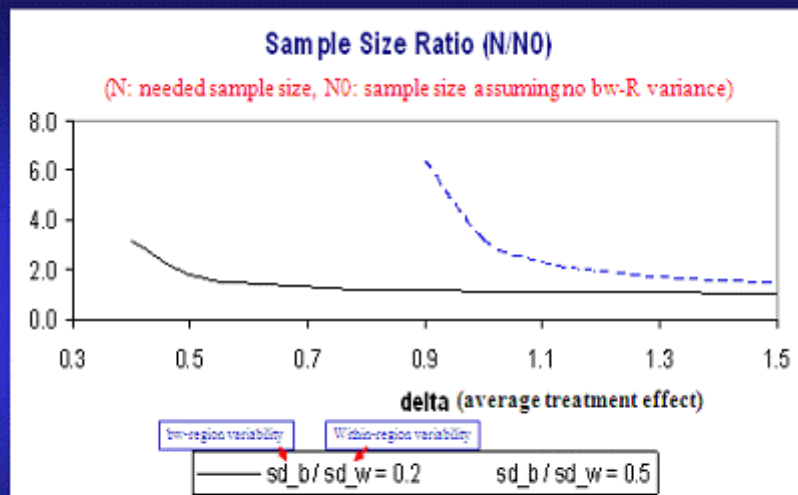
Need to study its statistical properties when it is applied to multi-regional trials.

Question

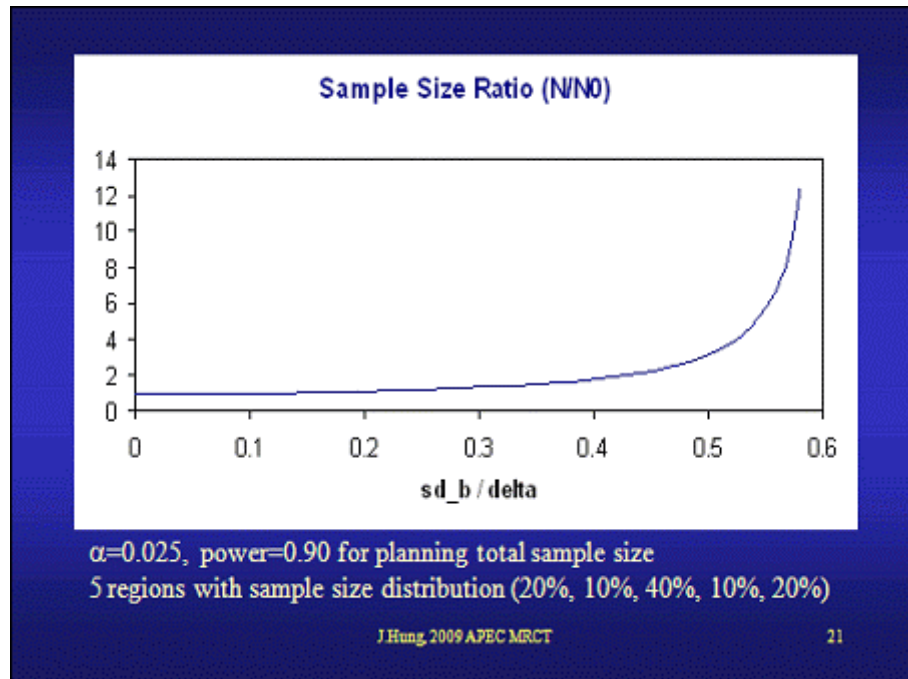
- ◆ If regional differences are suspected, what should the next step be?
 - in-depth extensive work for exploring why
 - for most part, regional differences are myth
 - lay out descriptive statistics for information

Design Consideration

- ◆ key endpoints sensitive to regional differences? (particularly soft endpoints)
- ◆ Define geographical region or 'region' – should be pre-specified (consider intrinsic & extrinsic factors)
- ◆ Quality measure in each region
- ◆ Need of conservative sample size planning



$\alpha=0.025$, power=0.90 for planning total sample size
5 regions with sample size distribution (20%, 10%, 40%, 10%, 20%)



Question

What if we plan sample size conservatively but if in truth there is little regional difference on effect size?

- may entertain group sequential design
- still the more important question:

If regional differences are suspected from analysis, what should be pursued further?

Need to think about this question w/ a plan

Concluding Remarks

If regional differences are caused mostly by trial conduct / data quality among regions, the results of the entire trial might not be interpretable.

Statistical analysis plan should discuss special elements of global trial needing considerations in design and analysis.

Research on quality control needed.

O'Neill (2007, PhRMA/FDA Wkshop)

The Way Forward Some Recommendations to consider

- ◆ For every multi-regional study, create a common template for planning for homogeneity/heterogeneity of regional differences and exploring sample sizing according to assumptions of dropouts, follow-up, compliance, event ascertainment by investigator, degree of internal consistency
- ◆ Enhance all study reports with section that discusses process of quality assurance, data management, quality of data collected, monitoring strategies, important descriptors and outcomes by region/country
- ◆ Improve the statistical analysis plan to specifically address strategies and interpretation of heterogeneity, power, internal consistency of by region results
- ◆ Address the training/certification of investigators and quality checks
- ◆ Auditing strategies, metrics of quality
- ◆ Update the study report for a MRCT to include new issues

Selected References

O'Neill (2007, Presentation in PhRMA/FDA workshop)

Hung et al (2003, 2006-2009 presentations in ISS, DIA, ...)

Gail & Simon (1985, Biometrics)

Hung, O'Neill, Bauer, Köhne (1997, Biometrics)

Galbraith et al (1988, Stat. in Med.)

Higgins et al (2003, BMJ)

Acknowledgment

Robert O'Neill (FDA)

Sue-Jane Wang (FDA)

Appendix

If no regional difference in effect size $\Delta > 0$,
 $P(\text{est. effect } d_h > 0 \mid \Delta)$
 $= \Phi(\Delta\{\lambda_h N\}^{1/2})$

Define $\pi_h = 1$ if $d_h > 0$, and -1 if $d_h < 0$

$$P(\text{m of K regions yield negative effect} \mid \Delta)$$
$$= \sum_{R_m} \prod_{h=1}^K \Phi(\pi_h \sqrt{\lambda_h} \sqrt{N} \Delta),$$

$$R_m = \{(\pi_1, \dots, \pi_K) : \sum_{h=1}^K \pi_h = K - 2m\}$$

- Plenary IV: Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed

Statistical/Operational Considerations When Designing and Implementing a Multi-Regional Clinical Trial



Speaker:

William Wang (China)

Department of Biostatistics and Research Decision Sciences (BARDS)

Merck Research Laboratories

Merck & Co. Inc.

Contents

- Introduction
- Regulatory Guidance Documents
- Statistical Issues
 - Regulatory Guidance
 - Regional Definition
 - Regional Heterogeneity on Power Calculation
 - Sample Size vs. Information
 - Control Group and Non-inferiority Trials
 - Adaptive Design
 - Predefined Analyses
- Operational Issues
 - Quality and Integrity
 - Consistency in Operation
 - Train/Hire the Right Talent
- Concluding Remarks



Statistical/Operational Considerations When Designing and Implementing a Multi- Regional Clinical Trial

William Wang
william_wang@merck.com

Bruce Binkowitz
binkowitz@merck.com
&
William Malbecq
william_malbecq@merck.com

Merck & Co.

MRCT Workshop, Seoul, June 16, 2009



*Views expressed here are those of the author,
not necessarily those of Merck & Co, Inc

Outline



- Introduction
- Regulatory Guidance Documents
- Statistical Issues
- Operational Issues
- Concluding Remarks



2

- Anyone involved in the design and implementation of a multi-regional clinical trial needs to keep five key areas in mind
 - clinical issues
 - ethical issues
 - operational issues
 - regulatory issues
 - statistical issues
- Operational issues can significantly impact the validity and integrity of the statistical analyses
 - Planning at the design stage is imperative to insure the integrity of the trial.

“To understand God’s thoughts we must use statistics, for these are the measure of his purpose.”

- Florence Nightingale, 1898

MRCT Statistical Considerations: Regulatory Guidance



- ICH E3 mentions reporting results by investigator site and suggests examining interactions and outliers.
- ICH E5 talks about regional stand alone results and overall results being reinforced by consistency among regions
- ICH E9 discusses multi-center studies – but don't assume all multi-center issues can be extrapolated to multi-regional issues!!
- EMA strategy paper: Reflection Paper on the Extrapolation of Results from Clinical Studies Conducted Outside Europe to the EU population.
- PMDA Guideline: Sample Size and Ratio of Japanese Subjects
<http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf>



4

MRCT Statistical Consideration: Regional Definition



It is important to predefining the region

- Should region be defined according to the intrinsic factors (eg ethnicity) or extrinsic factors (eg medical practice, economic condition)?
 - Important to collect information on these factors in MRCT
- Interpreting unexpected regional differences and finding will be challenging. Predefining “consistency” among regions could be useful
 - Need to distinguish the between-group difference across region versus the within-group difference across region (less an issue)



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MRCT Statistical Consideration:
Regional Heterogeneity on Power Calculation



- Plan in the protocol for sources of regional heterogeneity
- Variability across region can come from differences in intrinsic and extrinsic factors such as
 - Medical practice
 - Disease definition
 - Population definition
- Consider the minimum # of subjects required by the corresponding regulatory agency.



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MRCT Statistical Consideration:
Sample Size vs Information



It's the statistical information that determines the likelihood of success

- Both the number of subjects and duration of exposure contribute to statistical information
- For event driven trials, the number of events directly impacts the study power
- To evaluate the treatment consistency across region, sufficient information (e.g, # of events in event-driven design) needs to be accrued in each region.



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- Control group selection need to consider the regulatory requirement and availability of control group medication
 - Is the control group approved in all regions?
 - Drug approved in countries with different dosing regimens: can you still use MRCT?
- Acceptability of non-inferiority
 - What if lack of consensus of the non-inferiority margins?
 - What about differences in Health Authority preferences?

Adaption design should consider the regional factors

- Regulatory acceptance of adaptive design by region
- The influence of staggered entry by region
- Implication of regional heterogeneity on stopping decisions
- Feasibility of “timely” adaptation by region

MRCT Statistical Consideration: Predefined Analyses



- Pre-define important subgroup analyses
 - How to discuss/analyze/display regional difference
 - Pre-define consistency of treatment effect (not just by a statistical interaction test).
- Pre-plan the analyses for integrated summaries.
 - Pre-specify how you will integrate the data: Pooling/meta-analysis/modeling/integration of efficacy data.
- Need to think of controlling both Type I error (eg, too many interaction tests or subgroup analyses) or Type II error (eg, low power)



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MRCT Operational Consideration: Quality and Integrity

- Trial operation should ensure quality and integrity of the clinical studies
- Trial integrity requires statistically/clinically valid results that are convincing to a broader scientific community
- Trial Quality includes:
 - Project team and Investigator training
 - Quality Assurance
 - Data management
 - Data Analysis and Reporting



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MRCT Operational Consideration: Consistency in Operation



- Trial Quality Assurance – done the same way in every region? By the same group?
- SOP/Manuals
 - Prepare Global Clinical SOP
 - Prepare Operational manuals for Regional Multinational Studies
- Regional/Local Technological standards and telecommunication bandwidths.
- Language and translations.



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Operational Consideration: Train/Hire the Right Talent



- Investigator Training – standardize across regions
- Educate the clinical development staff to be capable of managing the multinational clinical studies
- Develop talent in the Asia Pacific Region, especially in data management and biostatistics
- Hire or develop CROs with regional experiences and who can collaborate with others



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Concluding Remarks



- **Designing a good multi-regional clinical trial require a broad focus on all areas of clinical trial practice, including clinical, operational, regulatory, statistical, and ethical issues.**
- **It is highly recommended that all these issues be discussed prior to study start among the trial design team.**
- **Multi-regional clinical development requires multi-regional talent development**



- Plenary V: Operational Aspects

Selected Topics in the Operational Aspects of Multi-Regional Clinical Trials



Speaker:

Ling Su (China)

Vice President

Clinical Research and Development

Wyeth Asia Pacific Region

Contents

- Study feasibility
- Site identification
- Regulatory and ethics approvals
- Measurement scales
- Translations
- Training
- Resource and management

Selected Topics in the Operational Aspects of Multi-Regional Clinical Trials

Ling Su, Ph.D.

Vice President, Clinical Research & Development Asia Pacific, Wyeth
Adjunct Professor, Fudan University College of Pharmacy, Shanghai, China

Seoul, June 16, 2009

Outline



- Study feasibility
- Site identification
- Regulatory and ethics approvals
- Measurement scales
- Translations
- Training
- Resource and management

Study Feasibility

- Project/Protocol/Site feasibility
 - Epidemiology
 - Diagnostic criteria
 - Medical practice and standard of care
 - Use of Placebo
 - Comparators and/or concurrent medications
 - Approved indication, availability, dose, etc.
- Timing and process of conducting feasibility
 - Cultural factors

Site Identification

- Site identification and partnership
 - Credential, expertise, experience, resource
 - Competing trials
 - China: SFDA accredited sites (next slide)
 - Develop new sites

China: SFDA Accredited Trial Sites



Source: www.sfda.gov.cn, April 2009, adopted from Lin JY, 2009

Regulatory and Ethics Approvals

- Regulatory dossier requirements
- Regulatory guidelines for study design
- Regulatory expectations and risk-benefit assessment criteria
- Regulatory and ethics approval timelines

Measurement Scales (incl. Patient Report Outcomes)

- Linguistic and cultural considerations
 - Translation and validation
 - Cultural adaptation
 - Pilot testing
 - Rigorous process must be followed
 - Timing
- Training in local language for patients, investigators and coordinators
- Use of electronic devices

Translations

- Translation of protocol may be required for regulatory and ethics committee submissions
- Translation of informed consent to local language
 - Central vs. local translation vendor
 - Quality
- Case Report Forms and/or EDC in local language?
 - Technology
 - Coding

Training

- English is not everyone's language
- Face to face training may be necessary and desirable over "distance" learning
- Protocol related training vs. technology training
- Training is a continuous effort

Resource and Management

- Monitoring resource
 - Monitor study conduct and data early and frequently
- Study management resource
 - HQ, regional, country
- Study supply

Concluding Remarks

- Plan carefully with respect to regulatory, operational and logistical process
- Pay attention to details, communicate regularly and monitor closely
- Close partnership among regulator, sponsor and investigators

Thank You!

- Plenary V: Operational Aspects

Multi-Regional Clinical Trials: Operational Aspects based on Korean Experience



Speaker:

Yil-Seob Lee (Korea)

Vice President

GlaxoSmithKline Korea

Contents

- Objective of ICH

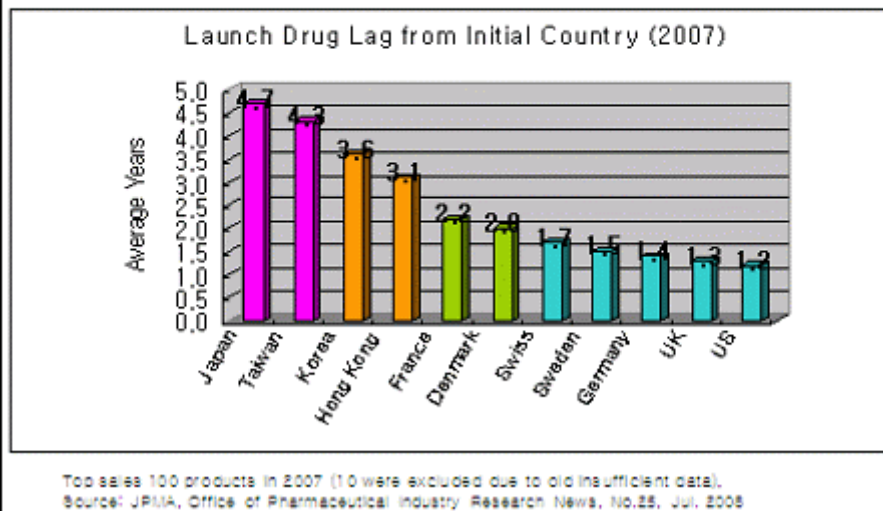
- MRCT
 - Opportunities
 - Challenges

- Changes of Multinational Clinical Trials in Korea

- Factors to increase MRCT in Korea
 - Strong government initiative
 - Excellent sites and investigators
 - Qualified and well operating IRBs
 - Improving quality
 - Availability of CROs
 - Investment from sponsors

- In Summary

Drug Lag in Asian countries



MRCT (Multiregional clinical trial) can be one of solutions to reduce the drug lag

- ◆ Globalization of clinical trials is a reality.
 - ◆ MRCT may cover different ethnic groups and different regions.
 - ◆ MRCT may start simultaneously.
 - ◆ Data from MRCT may be used for regulatory submission of different countries.
 - ◆ Subset data from MRCT may be used as bridging data.
- MRCT has opportunities/benefits and also challenges

Opportunities of MRCT

- ◆ Faster enrolment of subjects
- ◆ Usually cheaper with sites in emerging countries
- ◆ Trial sites in emerging countries have benefits
 - Access to innovative medicine
 - Development and training of staffs at sites
- ◆ Learn each other
- ◆ Improve quality

Challenges of MRCT

- ◆ From Government/Regulatory agency
- ◆ From the Investigator/Trial site perspective
- ◆ From the Patient perspective
- ◆ From the EC/IRB perspective
- ◆ From the Sponsor perspective



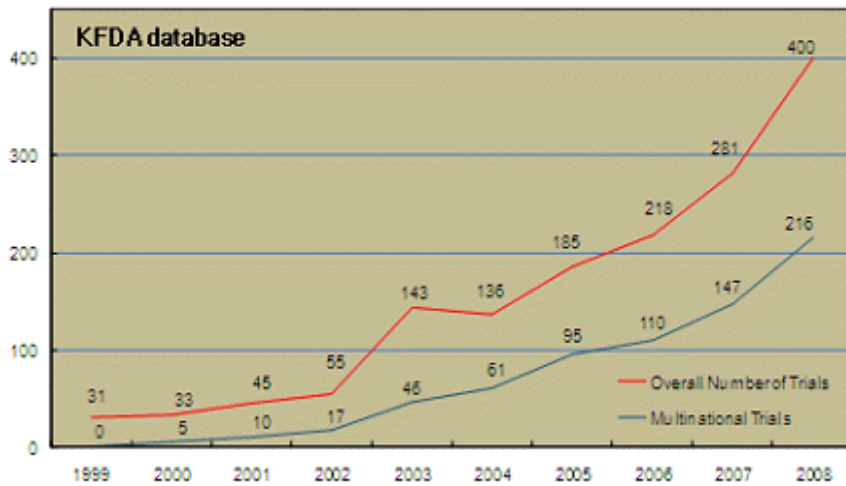
Other types of Challenges

- ◆ Different medical practice and local culture
- ◆ Different life style and diet
- ◆ Different concomitant diseases and medications
- ◆ Variation of regulatory and ethics approvals
- ◆ Relationship between investigators and subjects
- ◆ Central vs Local Lab
- ◆ Way of monitoring / Audit / Inspection
- ◆ Difficulty in supply chain and logistics
- ◆ Language
- ◆

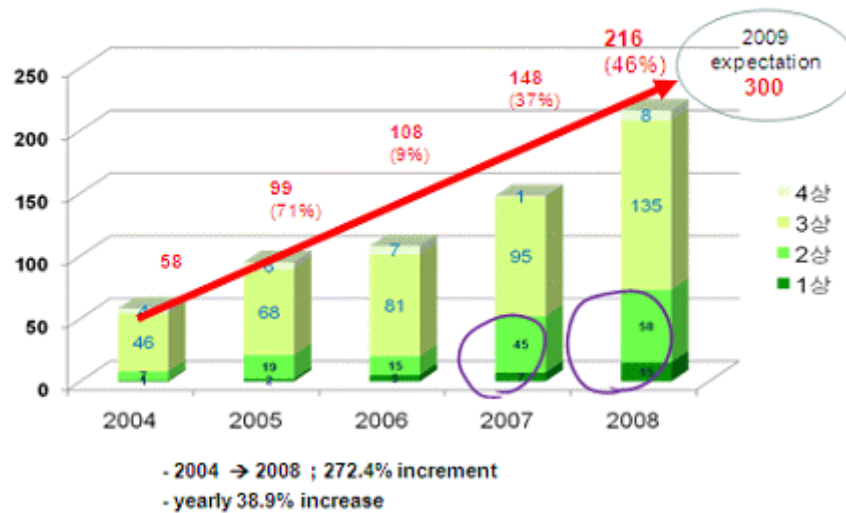
MRCT

- ◆ MRCT including emerging countries are challenging and rewarding
- ◆ Effort for decreasing differences and increasing similarities
- ◆ Better and careful panning with consideration of all related matters
- ◆ More frequent communication and close monitoring
- ◆ MRCT can be managed better with improving some of factors
 - Korean Case

A Korean case : Changes in number of clinical trials in Korea



Changes of Multinational clinical trials in Korea



Oncology Trials

50% + in Asia

167% + in Korea

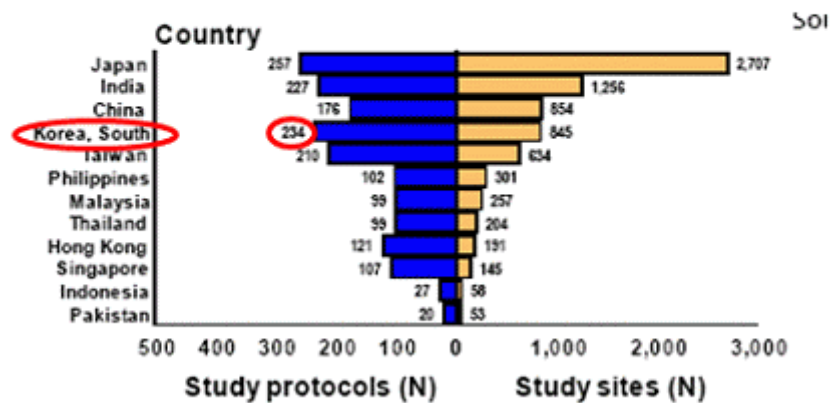
| | Number of trials | | Difference | Percent change |
|----------------|------------------|------|------------|----------------|
| | 2004 | 2007 | | |
| North America | 623 | 794 | 171 | 27% |
| South America | 47 | 51 | 4 | 9% |
| Africa | 23 | 26 | 3 | 13% |
| Eastern Europe | 81 | 84 | 3 | 4% |
| New Zealand | 13 | 9 | -4 | -31% |
| Middle East | 28 | 23 | -5 | -18% |
| Latin America | 33 | 23 | -10 | -30% |
| Western Europe | 338 | 281 | -57 | -17% |
| Asia | | | | |
| Vietnam | 0 | 1 | 1 | ** |
| South Korea | 18 | 48 | 30 | 167% |
| Philippines | 4 | 10 | 6 | 150% |
| China | 16 | 31 | 15 | 94% |
| Japan | 23 | 39 | 16 | 70% |
| India | 18 | 29 | 11 | 61% |
| Malaysia | 5 | 8 | 3 | 60% |
| Pakistan | 2 | 3 | 1 | 50% |
| Singapore | 18 | 25 | 7 | 39% |
| Taiwan | 22 | 29 | 7 | 32% |
| Hong Kong | 19 | 25 | 6 | 32% |
| Thailand | 13 | 12 | -1 | -8% |
| Indonesia | 4 | 2 | -2 | -50% |
| Bangladesh | 1 | 0 | -1 | -100% |
| North Korea | 1 | 0 | -1 | -100% |
| Western Europe | | | | |
| Cyprus | 1 | 3 | 2 | 200% |
| Greece | 12 | 21 | 9 | 75% |
| Spain | 73 | 95 | 22 | 30% |
| Denmark | 26 | 26 | 0 | 0% |
| Iceland | 1 | 1 | 0 | 0% |
| Italy | 84 | 80 | -4 | -5% |
| Ireland | 16 | 14 | -2 | -13% |
| Germany | 123 | 106 | -17 | -14% |
| France | 115 | 99 | -16 | -14% |
| Belgium | 73 | 57 | -16 | -22% |
| Austria | 49 | 38 | -11 | -22% |
| UK | 140 | 104 | -36 | -26% |
| Norway | 23 | 17 | -6 | -26% |
| Sweden | 44 | 31 | -13 | -30% |
| Turkey | 15 | 10 | -5 | -33% |
| Finland | 26 | 16 | -10 | -38% |
| Netherlands | 74 | 45 | -29 | -39% |
| Portugal | 25 | 15 | -10 | -40% |
| Switzerland | 44 | 25 | -19 | -43% |
| Luxembourg | 2 | 1 | -1 | -50% |

Table 1: Geographic locations of oncology trials initiated in 2004 and 2007.
Source: *TrialTrove* (accessed May 2008)

Number of Studies in Asia

(09.2005-10.2007)

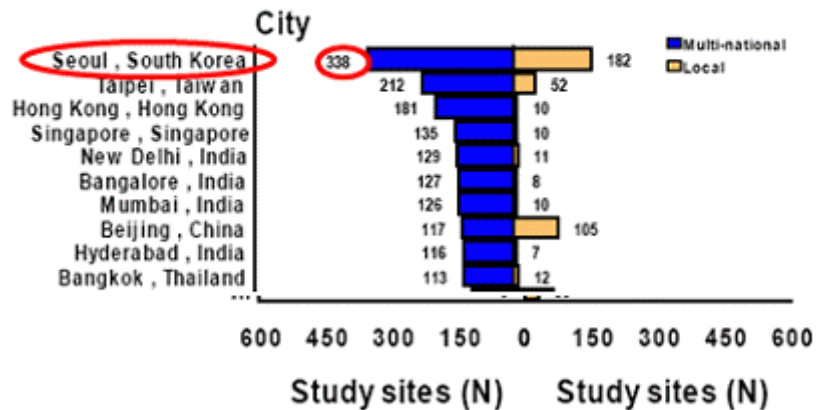
Number of protocols registered with ClinicalTrials.gov between Oct. 2005 and Sep. 2007



Source: *Clinical Trial Magnifier* Vol. 1:5 May 2008
www.ClinicalTrialMagnifier.com

Active Asian Cities in Clinical Trials

The top 10 most active Asian cities conducting industry sponsored clinical trials.



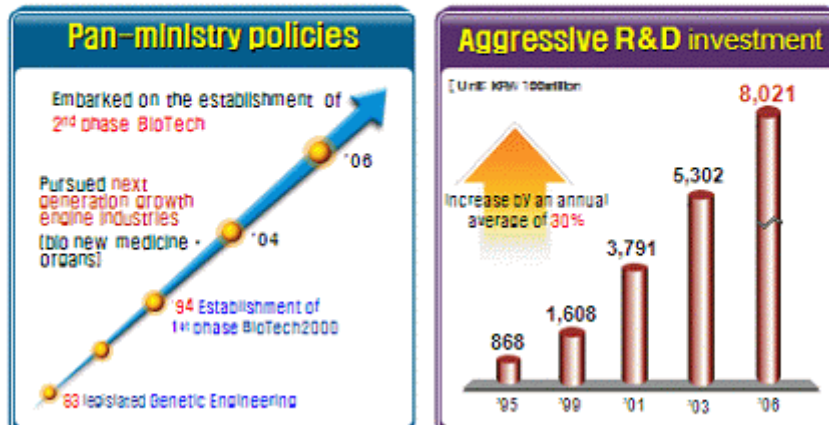
Source: Clinical Trial Magnifier Vol. 1:5 May 2008
www.ClinicalTrialMagnifier.com

Factors to increase MRCT in Korea

- 1. Strong government initiative**
 - Government's R&D strategy
 - Favorable regulatory environment
 - Changes in regulation in clinical trials
 - Parallel IND and IRB process
 - Reduced IND review period
 - KoNECT
- 2. Excellent sites and investigators**
- 3. Qualified and well operating IRBs**
- 4. Improving quality**
- 5. Availability of CROs**
- 6. Investment from sponsors**

1. Strong Government Initiative :Government's R&D Strategy

Continuous expansion of investment and creation of next-generation growth engines



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Government's R&D Strategy

National Technology Roadmap in Sept. 2002

• Clinical Trial Technology: capacity building

1. **Developing Formal/Systematic Educational Programs**
 - Clinical Investigators, Clinical Pharmacologist, Clinical Trial Pharmacist, CRA, CRC, IRB members, Regulatory personnel etc.
 2. **Establishing Center of Excellence for Clinical Trials**
 3. **Standardization of IRB Operation, and Quality Assurance/Accreditation mechanism**
 4. **Good Regulatory & Review Practices: based on sound regulatory sciences**
 5. **Improving Global Communications**
 6. **Improving Public Awareness**
- 

Government R&D Strategy

Presidential Committee on Healthcare Industry Innovation (醫療產業先進化委員會)

- Presidential Decree No. 156 (Aug. 2005.)
- chaired by prime minister

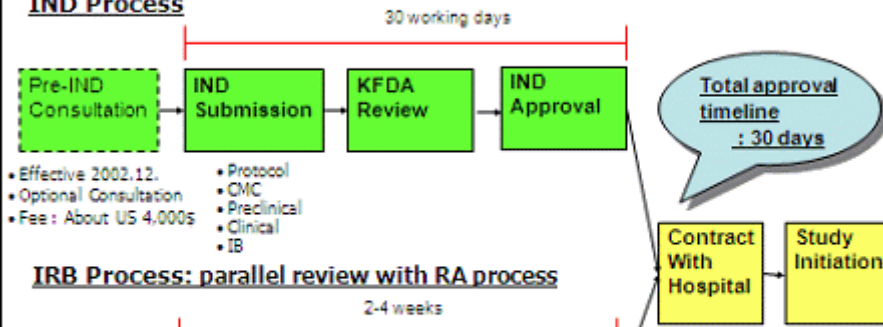


Favorable Regulatory Environment in Clinical Trial

| | |
|----------|---|
| Dec 1987 | KGCP established |
| Oct 1995 | KGCP Enforced & implemented |
| Jan 2000 | Revision of KGCP in accordance with ICH-GCP |
| 2001 | Introduction of Bridging Study |
| Dec 2002 | Separation of IND/NDA |

Favorable Regulatory Environment in Clinical Trial

IND Process



Favorable Regulatory Environment in Clinical Trial

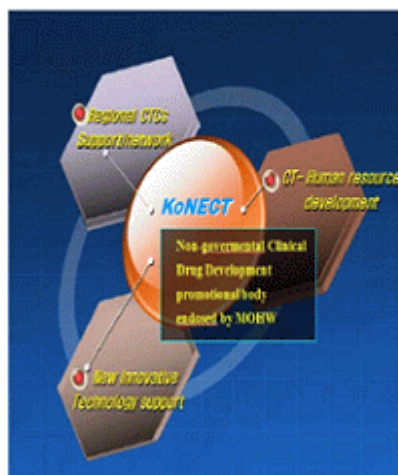
Reduced IND approval time



Korea National Enterprise for Clinical Trials (KoNECT)

2007. 12 – 6 years program

- **RCTC : 15 Regional Clinical trial centers**
 - 6 more CTC (2008, 2009)
- **Clinical Trials Professional Training Academy**
 - 12 Center of Excellence in Education & Training
 - Clinical Investigators, Clinical Pharmacologist ; (domestic/oversea)
 - CRA, CRC, CT Pharmacist
 - Pharmaceutical Medicine
 - Biostatistician, Pharmacovigilance, DB manager
- **New innovative technology development & Propagation**
 - 10 -15 Centers of Excellence in new technology
 - 6 major technologies related critical path.



2. Excellent sites and Investigators

Seoul National Uni. Hospital (SNUH)
 Yonsei Uni. Medical Center (YUMC)
 Samsung Medical Center (SMC)
 Asan Medical Center (AMC)

| | Licensed Beds | Outpatients /day | Doctors |
|------|---------------|------------------|--------------------|
| SNUH | 1763 | 5663 | 1126 (Faculty 336) |
| YUMC | 1841 | 5076 | 883 (Faculty 428) |
| SMC | 1348 | 5520 | 820 |
| AMC | 2181 | 6633 | 1180 (Faculty 305) |

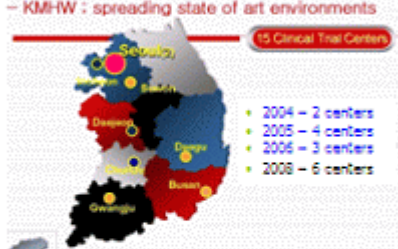





Clinical Trial Center at sites

Regional Clinical Trial Center Network Program
- KMHW : spreading state of art environments

15 Clinical Trial Centers

- 2004 - 2 centers
- 2005 - 4 centers
- 2006 - 3 centers
- 2008 - 6 centers

3. Qualified & Well-Operating IRBs

KAIRB (Korean Association of IRBs)

- ◆ Established in March 2002 to organize IRB education, enhance review capacities, and foster IRB networking.
- ◆ Published *Guidelines for Establishing and Operating IRBs* in Korean: February 2003
- ◆ Annual workshops for IRB members.

Some clinical trial centers achieved the accreditation by AAHRPP (Association for the Accreditation of Human Research Protection Program) / WHO FERCAP (Forum for Ethical Review Committee in Asia and the Western Pacific Region)



4. High quality of clinical trials

: Guideline for Designation of Institutions for Clinical Study

Purpose

To assure the quality of clinical study and site

Standard

- Appropriate facilities and equipments
- Resource pool to support clinical studies
- Activities of IRB
- Education program of GCP
- Structures and activities to manage clinical studies

Qualified Institutional Pool

Previous:



Number of accredited hospitals

| Class | Phase I | Phase II | Phase III |
|-----------------|-----------|-----------|------------|
| Hospital | 32 | 85 | 107 |
| Dental Hospital | 1 | 6 | 6 |
| Total | 33 | 91 | 113 |

Current: No classification depending on the phase

Qualified Institution are increased to **127 as of Oct. 2008**

Educational course for clinical trial Professions by KoNECT



5. Availability of CROs

Domestic CRO

C & R Research

LSK Global PS
LSK Global Pharma Services Co., Ltd.

DreamCIS
G-CSF

Medihelpline

IBioPharm (Preclinical)

ADMKorea

Global/Regional CRO

Q
QUINTILES

CMIC Apex

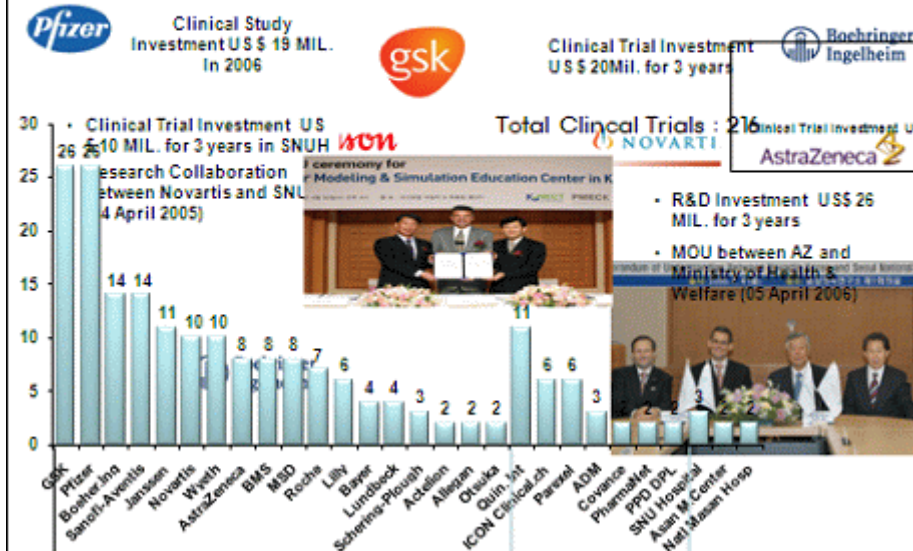
ICON Novortec

PPD Paraxel

COVANCE Choice
Pharma

pharmanet

6. Investment from sponsors



New progress

- ◆ CTN will be implemented
- ◆ Mutual recognition between IRBs
→ Central IRB
- ◆ Medical reviewers in KFDA
- ◆ NE Asian Tripartite Health Ministers Meetings

- Plenary V: Operational Aspects

Aspects on the Planning & Implementation the GCP & QA for MRCTs



Speaker:

Yuppadee Javroongrit (Thailand)

Assistant Director

Drug Control Division

Thailand Food and Drug Administration

Contents

- MRCTs - trend and approach
 - Global Clinical Trials
 - Clinical Trials in ASEAN/Thailand
- Key Factors
 - Relevant Technical Guidelines to MRCTs
 - Key Factors to the Country
- Operational Aspects towards MRCTs
 - Improvement/Amendment of the Regulation
 - Implementing the relevant Technical Guidelines
 - Understanding & Planning together - Stakeholders
 - Building & Strengthening Capacity - "Know-how" from the Original
- The Recommendation



Plenary V : Operational Aspects

Aspects

on the Planning & Implementation the GCP & QA for MRCTs

by

Yuppadee JAVROONGRIT, Ph.D.

Drug Control Division, FDA, THAILAND

The Multi-Regional Clinical Trials Seoul Workshop

Inaugural Workshop of the APEC Harmonization Center

Grand Hilton Hotel, Seoul, Korea

15-18 June 2009

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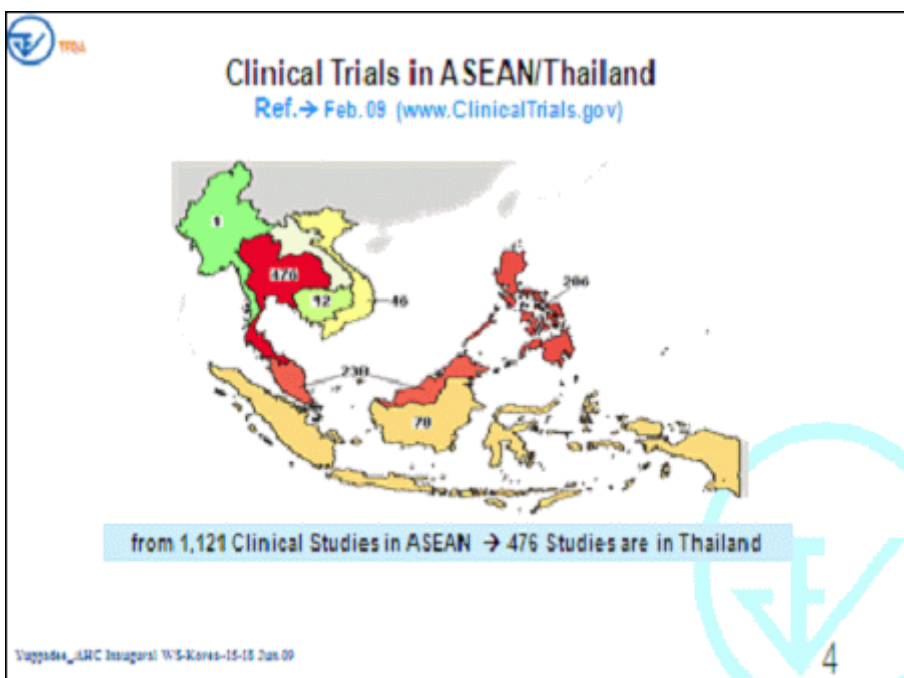
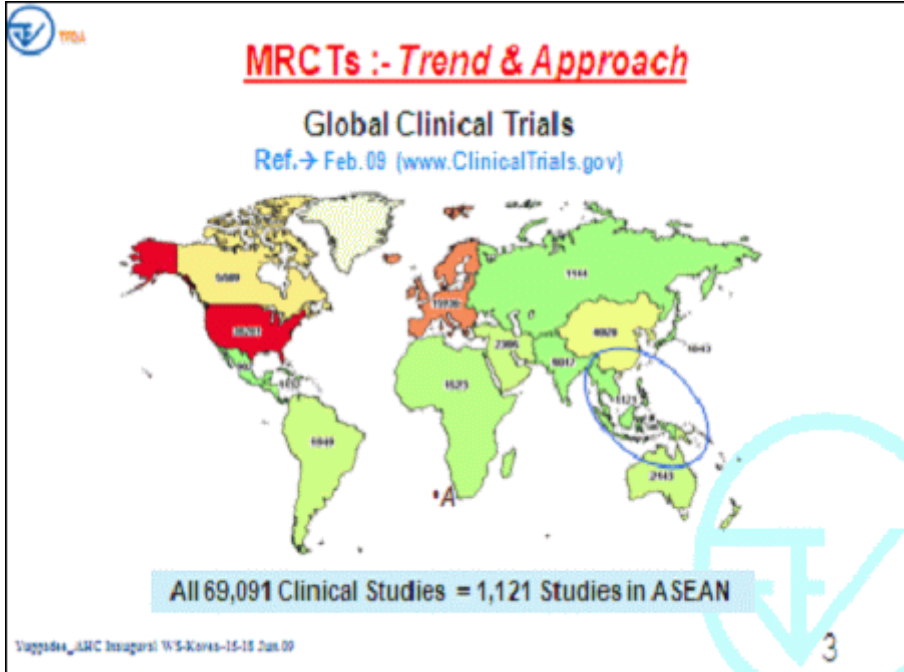


Topics

- MRCTs :- trend and approach
- Key Factors
- Operational Aspects towards MRCTs

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Key Factors - relevant Technical Guidelines to MRCTs

ASEAN Safety Guidelines (adopted ICH-S gls)

- S1A → Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals
- S1B → Testing for Carcinogenicity of Pharmaceuticals
- S1C → Dose Selection for Carcinogenicity Studies of Pharmaceuticals
- S1C(R) → Addendum to S1C: Addition of a Limit Dose and Related Notes
- S2A → Guidance on Specific Aspects of Regulatory Tests for Pharmaceuticals
- S2B → Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals
- S3A → Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies
- S3B → Pharmacokinetics: Guidance for Repeated Dose Time Distribution Studies
- S4 → Single Dose Toxicity Tests
- S4A → Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
- S5A → Detection of Toxicity to Reproduction for Medicinal Products
- S5B(M) → Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products
- S6 → Safety Studies for Biotechnological Products
- S7A → Safety Pharmacology Studies for Human Pharmaceuticals
- M3 → Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals



Key Factors - relevant Technical Guidelines to MRCTs

ASEAN Efficacy Guidelines (adopted ICH-E gls)

- E1 → The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
- E2A → Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- E2C → Clinical Safety Data Management : Periodic Safety Update Reports for Marketed Drug
- E3 → Structure and Content of Clinical Study Reports
- E4 → Dose-Response Information to Support Drug Registration
- E6 → Good Clinical Practice: Consolidated Guideline**
- E7 → Studies in Support of Special Populations : Geriatrics
- E8 → General Considerations for Clinical Trials
- E9 → Statistical Principles for Clinical Trials
- E10 → Choice of Control Group and Related Issues in Clinical Trials
- E11 → Clinical Investigation of Medicinal Products in the Pediatric Population

GCP → involve all Stakeholders
 → _could be the most collaborative Std. !!!



Key Factors - to the Country

| MRCTs | Timing / Stds. | P'ogenet | Coop. |
|---|---|---|---|
| <ul style="list-style-type: none"> - more Countries involve - sig. increase in Asia - speed-up IND studies - concerns :- - EI - Q of Research Team - Q of the Outcome - compliance to Stds. - competitive Timeline - imported Tax | <ul style="list-style-type: none"> • speed/short Timeline :- - IEC/IRB approval - Regulatory approval - Contract negotiation - total starting time • Standard :- - ICH-GCP - Competency of PI - Infrastructure - Regulatory | <ul style="list-style-type: none"> • increasing in the Trials • advantages :- - early detection/prediction on Safety/ADR | <ul style="list-style-type: none"> • ASEAN-PPWG • APEC-LSIF :- - global Cohort study - Biomarker study • Global - WHO - ICH • ICH • Country level :- - Japan & Korea & China - more..... |



Operational Aspects towards MRCTs

- Improvement/amendment of the *Regulation*
- Implementing the relevant *Technical Guidelines*
- Understanding & Planning together - *Stakeholders*
- Building & Strengthening Capacity – “*Know-how*”
from the Original





Improvement / Amendment of the Regulation

Thai Regulation on IND - Approach

Global Trials/Research

- **Global Trials:-**
 - Quality (Regulation, PI, Trial, ..)
- **Timing / Stds. :-**
 - speed/short Timeline
 - Inter. Stds. (GCP, GLP, GMP...)
- **P'cogenetics :-**
 - readiness
 - supportive Law/Reg.
- **Regional Coop:-**
 - actively involve

Competitiveness

- Approval Timeline
- Supportive Law/Regulation
- Consultation

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Strengthening Law/Regulation

Main Target

- to handle Clinical Trials/Researches of Thailand
- to facilitate & handle the Global Clinical Trials/Researches
- to help promote "Capacity & Competency" of Country for Clinical Trial in Competitive Environment

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Improvement / Amendment of the Regulation

Thai Regulation on IND – *the Amendment!*

Current

- need :-
 - Drug label
 - Drug leaflet
 - CFS (or EC Approval)
 - Clinical Trial Report
 - Clinical Trial Protocol
- Requirement :- voluntary
 - GCP
 - Report of "Unexpected-SADR"
- Scientific Review/Assessment
 - partial & initiative step
- Recognized ECs
 - by ThaiFDA
 - total of 10 ECs
- GCP Inspection :- N/A

Effective by Aug.09

- need :-
 - Drug label
 - Drug leaflet (for registered Drug)
 - Investigator Brochure
 - Patient Information Sheet (in Thai)
 - Clinical Trial Protocol
 - Info on Drug Quality & GMP
- Requirement :- mandatory
 - GCP & GLP
 - GMP
 - Report of "Unexpected-SADR"
- Scientific Review/Assessment
 - Systemic & Fully implement
- Recognized ECs
 - both Institutional and Central ECs
 - increasing in number
- GCP Inspection :- formal System
- IND → NDA

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Implementing the relevant Technical Guidelines

The Process / Action

- Law & Regulation
- Criteria
- Forms & SOPs
- Translation *English to Thai* Document
- Dissemination Information + Requirement
- Official Announcement
- Implementation System

**Translation → a difficult part
→ need the proper Interpretation !!**

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Understanding & Planning together - Stakeholders

Stakeholders

“ICH-GCP Clinical Drug Trials/Researches”

| | |
|---|--------------------------------------|
| Independent Ethics Committee (IEC).
Institutional Review Board (IRB) | Drug Regulatory Agency
(Thai FDA) |
| Investigators | Sponsors |



Understanding & Planning together - Stakeholders

The National Seminar

- 1997 -1999 :- *Preparatory phase*
- Since 2000 :- *Annual Seminar*
 - Title... "*Thailand Towards Center of Excellence in Clinical Trials-Annual Seminar*"
 - Composition... *GCP's Stakeholder*
 - Speaker... *National, and invited Outstanding International Experts*
 - Host... *rotation*
- Topic :-
 - Special Session
 - Normal Session

The 9th Annual Seminar (by Faculty of Medicine, Chulalongkorn University)
→ "Time to Act"
→ 20-21 Aug.09



The 7th Annual Seminar

by ThaiFDA (29-30 Aug.07)

- sub Title... "*Being Number One-Clinical Trial Hub of Asia/ASEAN*"
- Special Session :- The Global New Trend
 - The Global Drug Development
by *Mr.Hironobu SAITO* (Group Leader, Clinical Development Gr,
Asia Development Dpt, R&D Division,
DaiichiSankyo, Co.Ltd.)



The 8th Annual Seminar

by Faculty of Medicine, Chiang Mai University (14-15 Aug.08)

• sub Title...“*Healthy and powerful infrastructures for clinical researches in Thailand*”

• Special Lecture:- The Pharmacogenetics

- Rational use of pharmacogenetics in drug development and regulations”

by *Yoshiaki UYAMA, Ph.D.*

Review Director, Office of New Drug III
Pharmaceuticals & Medical Devices Agency,
Japan



Building & Strengthening Capacity “Know-how” from the Original

- ICH-Webinar
- the posted Training Materials on ICH-Website
- Seminar
- Consultation support from ICH Parties
- the intensive Training by ICH’s Trainers

Example of the most effective Training

→ APEC-LSIF Training Project in BKK, Thailand
“Capacity Building for DRAs on CT and GCP”



The Details

| | |
|---|---|
| 1. Development of the Projects | by <i>ThaiFDA</i> |
| 2. Submission for APEC-funding | → <i>APEC-LSIF & -CTI</i> |
| 3. Seeking support on the Trainers | → <i>ICH-GCG</i> |
| 4. Development of the Training Programme/Module | by- <i>Mr. Mike WARD (H.C.)</i>
- <i>Dr. David LEPAY (US FDA)</i>
- <i>relevant ICH Parties</i>
(<i>PMDA, US FDA, PhRMA, H.C.</i>) |
| 5. Logistic arrangement | by <i>ThaiFDA</i> |
| 6. Preparation for the Training | by <i>ThaiFDA</i> |
| 7. Conduct of the Trainings | by <i>Trainers & ThaiFDA</i> |
| 8. Post-Training Wrap-up | <i>Public Document, Rpt., Budget</i> |

The Project (1)

| Capacity Building for Drug Regulatory Agencies on Clinical Trial and Good Clinical Practice | | | | |
|---|--|---|---|---|
| Major Plan | Set 1
Review of Drug Development in Clinical Trial | | Set 2
GCP/Clinical Research Inspection | |
| | Preliminary WS
(17-21 Mar 08) | Advance WS
(02-06 Feb 09) | Basic WS
(27-30 May 08) | Advance WS
(02-06 Mar 09) |
| Trainers | -Dr. Gella LOURENCO (USA)
-Dr. Junio SATO (PHILA)
-Mr. Susan D'AMICO (PHILA*)
-Dr. Nataraj RAMADCR (PHILA*)
-Dr. Qaim NOORDI (USA)

*State -US - Health Canada
- PHILIA* - Novartis | -Dr. Norman VENTER (USA)
-Dr. William STEVENS (USA)
-Dr. Junio SATO (PHILA)
-Dr. Jodhithal CHOKEKUCHAL (PHILIA-Novartis, Thailand) | -Dr. David LEPAY (USA PHA)
-Dr. Jean TOTM-ALLEN (USA PHA) | -Dr. David LEPAY (USA PHA)
-Dr. Martin K. YAN (USA PHA)

Mentors
-Mr. Steven P. HARRIS (USA PHA)
-Mr. Qing X. HAN (USA PHA)
-Dr. Bob WILSON (PHILA)
-Mr. Steven P. HARRIS (USA PHA)
-Mr. Martin K. YAN (USA PHA) |
| Trainees | # 20 regulators
(AGS, -S, M, H, N, R, T, Y, Y)
(S, M, -S, C, A, S, A, S, T) | # 26 regulators
(AGS, -S, M, H, N, R, T, Y, R, T, Y)
(S, M, -S, C, A, S, A, S, T) | # 22 regulators
(AGS, -S, M, H, N, R, T, Y, Y)
(S, M, -S, C, A, S, A, S, T) | # 30 regulators
(AGS, -S, M, H, N, R, T, Y, T, Y, R, T, Y)
(S, M, -S, C, A, S, A, S, T) |
| Course | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Case Studies+Gr. Exercise | -Lectures
-Mock Inspection |

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The Training (1)

| Major Plan | Set 1: Review of Drug Development in Clinical Trial → Preliminary WS (17-21 Mar 08) | |
|------------|---|---|
| Day 1 | - Opening Ceremony (Senior Expert Thai/FDA-Mr. Hiral Sudharmastuti)
- Special Session - Overview of ICH & GCP (Dr. Norio)
- General Information (A. Higashimura)
Session 1: Status of CT Environment in Respective Countries
- Country report (Thailand)
- Status of CT+ Applications procedures:
- Canada (Dr. Lourenco)
- Japan (Dr. Sam)
- EU & USA (Mr. D'Amico)
- Large Pharma Perspective (Dr. Sokolov)
Session 2: Overview of Clinical Trial Oversight
- Origin of CT regulation, subject rights, GCP, ... (Dr. Lourenco)
- Roles and responsibilities of various players involved in conduct assessment of CTs (Dr. Lourenco)
- Good Regulatory Practice - Canadian & Japanese experience (Dr. Sam & Dr. Lourenco)
- Regulations / guidelines (ICH, WHO, etc) (Dr. Lourenco)
- Inspection (GCP, GMP) (Dr. Sam)
Session 3: Overview of Drug Development
- Clinical Development plan, phases, post-market assessment (Dr. Sam, Dr. Lourenco, and Dr. Sokolov) | Session 4: Clinical Trial Assessment: Overview (Dr. Lourenco)
Day 2
Session 5: Quality (GMP) considerations (Dr. Lourenco)
Session 6: Clinical Trial Assessment-Phase I (Dr. Lourenco-Lead)
(Dr. Sokolov-Industry perspective), (Dr. Sam & Mr. D'Amico-support)
Day 3
Session 7: Clinical Trial Assessment-BE Studies (Dr. Sam & Dr. Lourenco)
Session 8: Clinical Trial Assessment-Phase II (Dr. Sam-Lead)
(Dr. Lourenco & Mr. D'Amico-support)
Day 4
Session 9: Clinical Trial Assessment-Phase III (Mr. D'Amico-Lead)
(Dr. Lourenco & Dr. Sam-support)
Day 5
Session 10: Concepts of product life-cycle, DMURs and Safety Monitoring Board (Dr. Sam)
Session 11: Industry Perspective on Safety Monitoring Boards, and Product Life Cycle (Mr. D'Amico)
Session 12: Pharmacovigilance (Dr. Lourenco)
Session 13: Essential Elements of CT Assessment (Dr. Lourenco)
Session 14: Panel Discussion Q&A (Dr. Sam & Dr. Lourenco-Mr. D'Amico/4)
- Conclusion, Closing & Certification (ICH, Thailand, & Thai/FDA) |



TRCA

The Training (2)

| Major Plan | Set 1 - Review of Drug Development in Clinical Trial → Advanced WS (01-06 Feb.09) | | |
|--------------|---|---|--------------|
| Day 1 | <ul style="list-style-type: none"> - Opening Ceremony (DSC, Prof.FDA-Me.Tanphong) - Introduction of Faculty & WS Logistics (A.Miyevarathana) - Overview of the Advanced WS (Dr.Miye) - Country Report (Notes) - Follow-up from the Preliminary WS (Dr.Sam,Dr.Miye) <ul style="list-style-type: none"> - Regulatory Information Authority - San Francisco Sharing - examples for Review & requirements for Review - Refresher of preliminary course topics (Dr.Miye,Dr.Sorana,Dr.Sam) - What is required for setting up the business of a review operation? (Dr.Miye,Dr.CP,Dr.Sorana,Dr.CMC) | Day 4 | |
| Day 2 | <ul style="list-style-type: none"> - Chemistry and Manufacturing(Quality) Review (Dr.Sorana,Lead) <ul style="list-style-type: none"> - Examples and exercises | <ul style="list-style-type: none"> - Novel Design in Clinical Trials (Dr.Chalab/John-Lead) <ul style="list-style-type: none"> - Adaptive design - Personalized medicine - Ethics in Clinical Trials + Exercises (Dr.Miye-Lead) <ul style="list-style-type: none"> - Ethical Aspects for review - Role of Regulatory in the of R&D - Setting R&D standards - Postmarket vigilance: the concept of continuous safety through the lifecycle of a product + Exercises (Dr.Sam) <ul style="list-style-type: none"> - Risk management plan (Dr.Chalab/John) - Challenges (Dr.Miye) | Day 5 |
| Day 3 | <ul style="list-style-type: none"> - Data Selection: Review principles of data selection (Dr.Sam) <ul style="list-style-type: none"> - In the case phase 4 approval? - Interim and adaptive? - Critiquing Higher Risk Trial-Practical Approaches risk Exercise (Dr.Chalab/John & Dr.Miye) | <ul style="list-style-type: none"> - Clinical Trial Review Process (Dr.Miye/Dr.Chalab/John) <ul style="list-style-type: none"> - small group exercises - Personal exercise - Panel Discussions (Everyone) <ul style="list-style-type: none"> - Case - Challenges for implementation - Suggestions for future cooperation to APAC-LEAP - Closing & Certifies for Trainees + Prof.FDA | |

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The Training (3)

| Major Plan | Set 2 : GCP Clinical Research Inspections → Basic WS (27-30 May 08) | |
|--------------|--|---|
| Day 1 | <ul style="list-style-type: none"> -Opening Ceremony (MS, Th/FDA-Ms/Taylor) -Introduction of Faculty & WS Logistics (A. Hagan/Carthage) -Introduction of Participants & Country Reports/Policies -Review of GCP Goals, Principles, Roles, and Responsibility (The Process Approach to Clinical Research, International GCP Standards, Roles/Responsibilities for Inspectors, Sponsors, CRAs, and SDC, Regulator's Role in GCP, Q & A) -Informed Consent (Review of Required and Additional Elements of Consent, Informed Consent Process, Interactive Material Evaluating Informed Consent) -The Interface Between Regulatory Review and CT Inspection <ul style="list-style-type: none"> - Introduction to FDA's Clinical Research Review Process - Identifying Issues for Inspection (Case Examples) - Q & A | <ul style="list-style-type: none"> -Auditing Clinical Data -Q&A |
| Day 2 | <ul style="list-style-type: none"> -Review of Day 1 + Q&A -Anatomy of a GCP Inspection -Inspector's Preparation for a Clinical Investigator Inspection -Inspection Exercise / Case Study (Developing an Inspection Plan) -The Opening Interview -Mock Interview Exercise | <ul style="list-style-type: none"> Day 3 -Review of Day 2 + Q&A -Common GCP Deficiencies Encountered in Clinical Investigator Sites -Misconduct in Research (Fraud) -Documenting an Inspection -Assessing Sponsor and EC Compliance from a Clinical Investigator Inspection -Prepares for the Site Visit -Visit the Clinical Research Site Day 4 -Discussion of Clinical Site Visit and Accomplishment of Obj. -The Close-out Discussion -Summary of Clinical Investigator Inspecting -Inspecting Sponsors and CRO (- Case Study) (Dr. Turner) -Inspection of Ethics Committees (- Case Study) (Dr. Turner) -Enforcement Strategies to address Identified Serious Deficiencies -Wrap-up Q & A -Round Table Discussion (Identifying Specialized Topics and Defining Obj. and Approaches for the Advanced WS) -Closing Remarks, and Certification (US FDA + Th/FDA) |

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The Training (4)

| Major Plan | Set 2 : GCP Clinical Research Inspections → Advanced WS (01-06 Mar 09) | |
|--------------|---|---|
| Day 1 | <ul style="list-style-type: none"> -Opening Ceremony (MS, Th/FDA-Ms/Taylor) -Introduction of Faculty & WS Logistics (A. Hagan/Carthage) -Overview of the WS (Dr. Lopez) -Introduction of Participants & Country Reports/Policies (Organization, and Content) -Basic Concepts of BE that Underlie the Science of the Inspection (Dr. Fox) -Special Meeting (Nutrition & Nitroxy) | <ul style="list-style-type: none"> Day 3 & 4 -Mock Inspection (Mirror - Small Group) (6 Small groups, in 6 different Clinical Sites) Day 5 -Analytical/Analytical Facilities: components of BE Inspection (Dr. Fox) -Reports out of Group 1-4 -Wrap-up Q & A (Dr. Lopez) -Round Table Discussion <ul style="list-style-type: none"> - Evaluation - Gaps and Challenges for implementation - Suggestions for future cooperation to APFCC/EF -Closing Remarks, and Certification (US FDA, Mexico, Th/FDA) |
| Day 2 | <ul style="list-style-type: none"> -Clinical Components of BE Inspecting (Dr. Fox) -Review of the Basic GCP Inspection WS-Reporting (Dr. Lopez) -Small Group Meeting (Nutrition, Nitroxy - Small Groups) | |

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The Trainers & ThaiFDA Preliminary WS-Review of DD in CT



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The Trainers & Trainees Preliminary WS-Review of DD in CT



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The Trainers, Trainees, and ThaiFDA Basic WS- GCP/Clinical Research Inspection



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Benefit to the Operation (1)

• The Programme

- Lectures → gave "Great Information"
- Case Studies, Exercise & Mock Exercises → provided "Know-how"
- Ref.Link/Info. → support "further Understanding"

• Trainers

- Regulators

- provided Understanding to the issue, at the same ground
- also could share "Regulatory approach & interpretation"
- ICH's Regulator know the ICH Technical guideline very well

- Industry -R&D

- gave details on "Drug Development", in depth
- sharing and help complete the loop of understanding & Best practice

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Benefit to the Operation (2)

- **Optimization the Trainings' Outcome**
 - post the "Training Materials" *in the Website(s)*
 - exercising and implementing all Trainings' Knowledge/Experiences
 - follow-up & support "Consultation/Advice" further
for the successful & sustainable Implementation after the Trainings





The Recommendation

- **very useful Trainings programme**
 - essential Knowledge & know-how Experiences for DRAs
 - networking between ICH & Non-ICH, and among DRAs
 - one of the powerful tools of Harmonization
- **the Training Module :-**
 - well thought and well developed
 - could be benefit in Training, the DRAs
 - recommend as a Training Module, for other RHIs/DRAs
- **final recommendation**

- follow-up programme, of Trainers & Trainees, annually
- Continuation support from ICH-Regulators, for further Trainings



Thank you !!!

- Plenary VI: Regulatory Guidance/Perspectives/Issues

Regulatory Guidance/Perspectives/Issues



Speaker:

Herng-Der Chern (Chinese Taipei)

Director

Taiwan Center for Drug Evaluation

Contents

- Why ICH Guidance Important to Chinese Taipei - not an ICH member
- A Systematic Approach Led by Regulatory Authority
- Implementation vs. Adaptation vs. Good reference
- APEC Network under ISTWG, since 1999
- Theme and Topics
- FDA Spirit
- EMEA Format
- CDE expertise
- GCP implementation strategy
- Common Deficiencies in the Implementation of GCP
- Impacts of the implementation of GCP
- Bringing Study - ICH E5
- Critical Path Program-Increase the Interaction of New Drug Development and Regulatory Agencies
- Clinical trials of new drugs
- Challenge in Implementation of ICH Clinical Guidance
- PER Scheme 1979~2000
- Recommendations and Conclusions in 2008 APEC LSIF
- Suggestion to APEC LSIF

Implementation/Adaptation of ICH Clinical Guidelines into “Good Review Practice and Regulatory Partnership” in Chinese Taipei

June 16, 2009

Chern, Heng-Der, Executive Director

Center for Drug Evaluation

Chinese Taipei



Why ICH Guidance Important to Chinese Taipei – not an ICH member

- Best international practice for regulatory science – protect and promote public health
- Main stream of global drug development – good business for biopharmaceutical industry
- Good guidance to upgrade the regulatory infra-structure especially the clinical trial conduct

2/22

A Systematic Approach Led by Regulatory Authority

- Set up “ICH in Chinese Taipei” project, 1996
- Set up CDE – an experimental model of regulatory science in Asia, 1998
- APEC Network of Pharmaceutical Regulatory Science – since 2000
- Join international platforms: ICH GCG, DIA, APEC LSIF
- Propose “APEC PER Scheme” for regulatory partnership since 2006

3/22

Implementation vs. Adaptation vs. Good reference

- FDA Spirit
- EMEA Format
- PMDA/MHLW Experience in ICH E5

Comply with ICH guidance

- Consider – local challenge, feasibility, resource, risk-based approach, transition period in phase-in, existing guidance, impact to all stakeholders

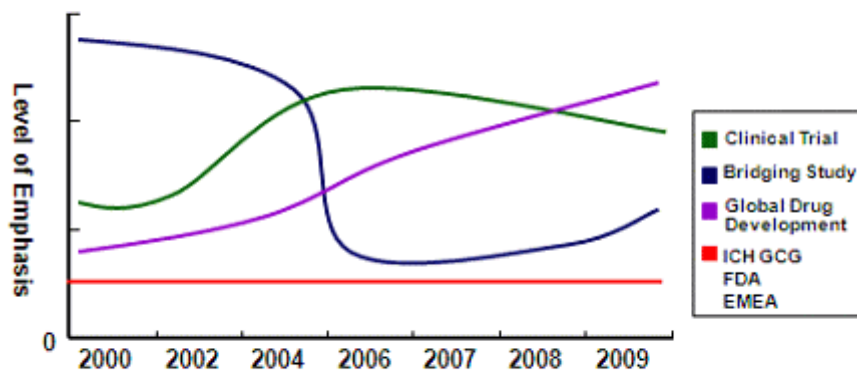
4/22

APEC Network under ISTWG, since 1999



5/22

Theme and Topics



6/22

FDA Spirit

- In house reviewer with Good Review Practice – project manager, clinical & statistic reviewers emphasis
- Placebo controlled study if possible emphasize clinical and statistic significance
- IND process, safe to proceed concept
- Free regulatory consultation, critical path project for in-depth consultation of index cases
- FDA points to consider as good reference

7/22

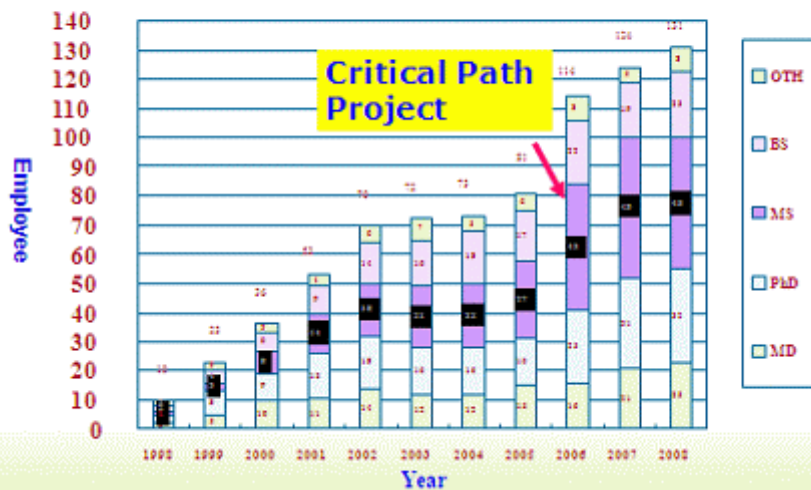
EMA Format

- Pre-approval evaluation for IND
- “Trust but verify if needed” for raw data submission or independent analysis
- EMA guidance as good reference



8/22

CDE expertise



9/22

GCP implementation strategy (I)

- Consistency between GCP and the spirit of ICH GCP
- Commissioned GCP inspection by medical center: the initial two years of remedial education during the transition period - Self audit form, examples and standard operation procedures
- GCP education workshop: many basic and advanced workshops
- Establishment of the Joint Institutional Review Board , and CDE review in accordance with GCP

10/22

GCP implementation strategy (II)

- Promote the SIDCER certification of the IRB, and the ACRP certification of the investigators
- Establishment of adverse events reporting system
- Examples of the Format of Informed Consent and the Principles of subjects enrollment in GCP
- Government awards 14 hospitals to set up clinical research centers, 4 Centers of Excellence for Clinical Trial and Research

11/22

Common Deficiencies in the Implementation of GCP

- Fail to understand the spirit of GCP guideline: incomplete record, not fully in compliance with the protocol
- Beyond the "safe, ethical" principle, excessive demands of scientific and rational study design, or detailed information on CMC
- Insufficient adverse event report, fail to understand the timeliness of report

12/22

Impacts of the implementation of GCP

- Introduction of clinical trials of unlisted new drugs globally
- Passed the FDA (three times) and EMEA (one time) GCP inspection
- To ensure the reasonable safety and ethics principles, eliminate the doubts of “taking the subjects as Guinea Pig”
- Verify the GCP training by GCP inspection
- Improve the implementation system of clinical trials

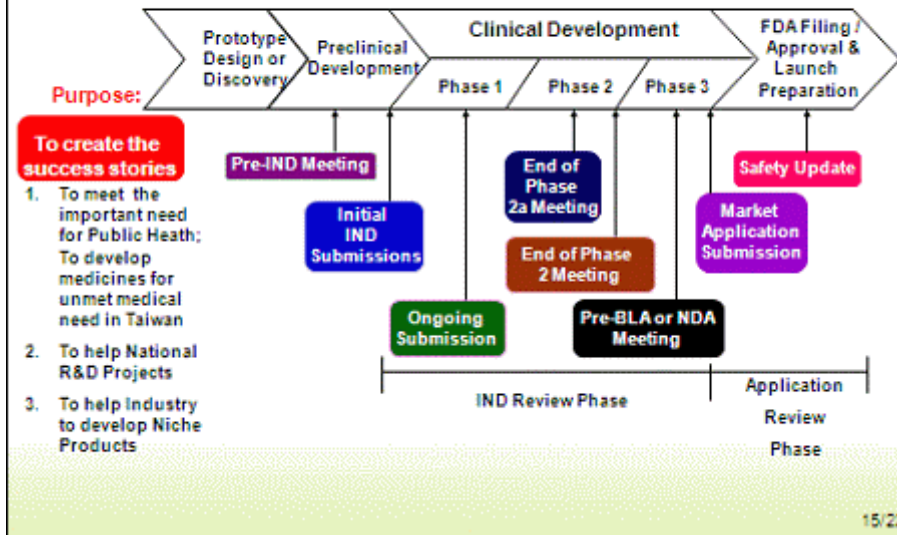
13/22

Bridging Study – ICH E5

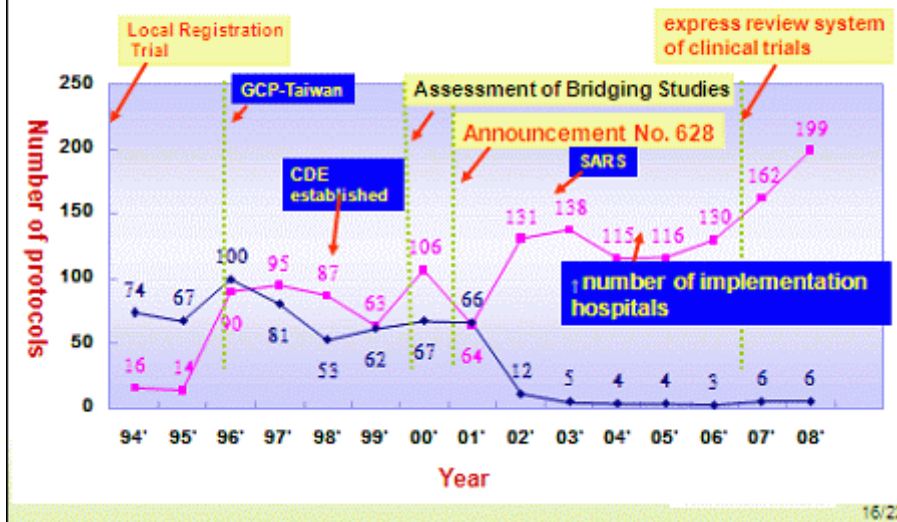
- Active player Japan, Korea, Chinese Taipei for implementation since ICH E5 announced
- Build in “ethnicity consideration” into multi-regional clinical trial or Pan-Asia study
- Two explanatory notes for ICH E5

14/22

Critical Path Program-Increase the Interaction of New Drug Development and Regulatory Agencies



Clinical trials of new drugs (1994~2008)



Challenge in Implementation of ICH Clinical Guidance

- Limited regulatory resource and capacity in emerging markets
- Different interpretation for details not specified, lack of overall concept & rationale of guidance, special local issues
- Segregated regional harmonization initiatives, lack of leadership and communication platform, heterogeneous regulatory environment

17/22

PER Scheme 1979~2000 - EFTA as secretariat



18/22

Recommendations and Conclusions in 2008 APEC LSIF (Life Science Innovations Forum)

Regulatory Harmonization session

- LSIF recommends that Ministers and Leaders endorse and support the establishment of the APEC Harmonization Centre (by Korea)
- LSIF supports the proposed feasibility study of the exchange between economies of evaluation reports (proposed by Chinese Taipei)
- LSIF agrees to established a Regulatory Steering Committee within the LSIF structure (proposed by Canada)

19/22

Suggestion to APEC LSIF

- Establish project of “APEC PER Scheme”
 - Secretariat: APEC Harmonization Center
 - Steering committee: APEC Regulatory Harmonization Steering Committee
 - Pilot Project: APEC Network of Pharmaceutical Regulatory Science – Regulatory Educational Workshop Sponsored by Chinese Taipei

20/22



Asia-Pacific
Economic Cooperation

**2009 The 8th Conference of APEC Network on
Pharmaceutical Regulatory Science**
Collaboration in New Drug Development and Drug Safety

- *Recent Reform of Drug Regulatory Agency*
- *Clinical Trials : Partnerships
Challenges and Solutions
GCP Inspection*
- *Drug Safety Beyond the Borders*
- *Role of APEC in Regional Harmonization*

2-4 Nov. 2009

Grand Hotel, Taipei
Department of Health
Chinese Taipei



21/22



- Plenary VI - Regulatory Guidance/Perspectives/Issues
Clinical Trial Regulatory Environment in China



Speaker:

Jianhua Ding (China)

Director, Division of American and Oceania
Affairs, Department of International Cooperation

State Food and Drug Administration

ICH GCG representative

Contents

- Three levels regulatory system
- Levels of authority
- SFDA Organizational Chart
- Affiliated Organizations to SFDA
- Clinical Trial Approval Procedure
- Application Dossiers
- Evaluation and Approval Timelines
- Special Procedure
- Patient Number Requirements
- CT Applicant Requirements
- Investigator Requirements
- Control of Samples
- Chinese GCP
- Characteristics of Chinese CT System
- International Clinical Trials Pre-conditions
- Utilization of International Multi-center Trial Result
- Rules for International Multi-center Trial
- Prospected Benefits from International CT
- Something we realized as Problematic
- Regulatory Improvement Needs
- New Moves Concerned
- Dealing with New Situation

Clinical trial Regulatory Environment in China

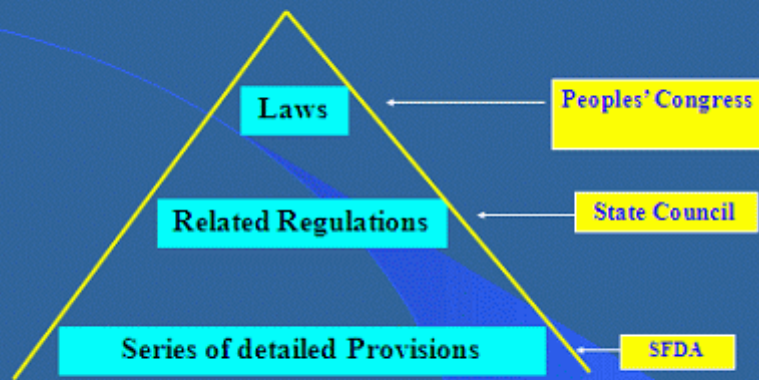
DING-JIANHUA

DEPARTMENT OF INTERNATIONAL AFFAIRS
STATE FOOD & DRUG ADMINISTRATION

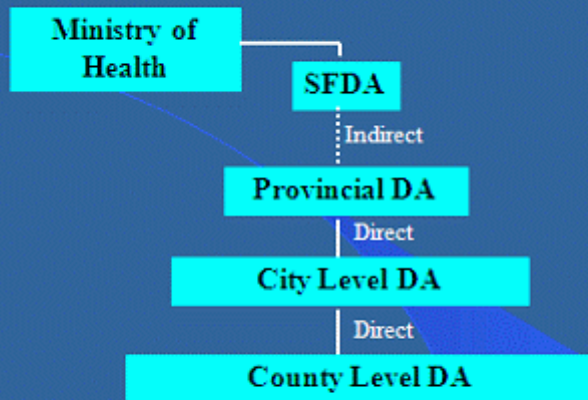
June 16, 2009, Seoul



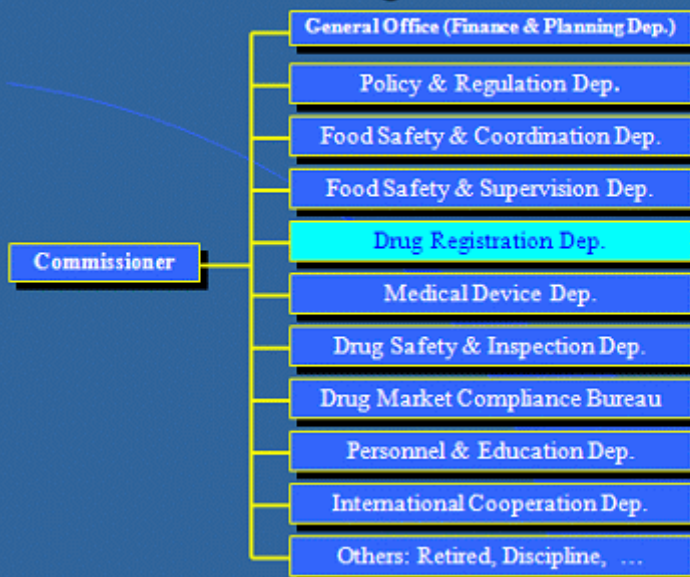
Three levels Regulatory system



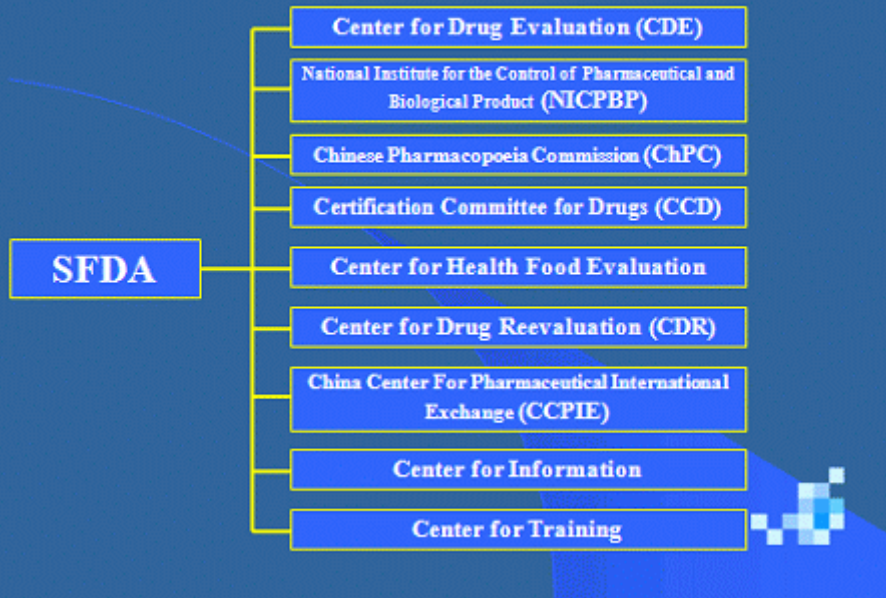
Levels of Authority



SFDA Organizational Chart



Affiliated Organizations to SFDA



Clinical Trial Approval Procedure



Application Dossiers

- Part I:** General data and Administrative Documents
- Part II:** Chemical, Pharmaceutical and Biological Data
- Part III:** Pharmacological and Toxicological data
- Part IV:** Clinical Data

Application Dossiers(1)

PART I

1. Name of the drug
2. Document for attestation
3. Aim and justification of the selected project
4. Summary and review of the study results
5. Sample of package inserts, drafting description and reference materials
6. Sample of package and label



Application Dossiers(2)

PART II

7. Review of the pharmaceutical study.
8. Manufacturing process and literatures for API; the formulation, manufacturing process and literatures for pharmaceutical preparation.
9. Identification data and literatures for chemical structure or components,
10. Quality study data and literatures
11. Draft specifications, justification, and reference standards or reference substances.
12. Testing report of the drug sample.
13. The origin and specifications of the excipients.
14. Stability data and literatures
15. Immediate packaging materials selection, and its specifications

Application Dossiers(3)

PART III

16. Review of the pharmacological and toxicological study data.
17. The main pharmacodynamics data and literatures
18. General pharmacology data and literatures
19. Acute toxicity data and literatures.
20. Long term toxicity data and literatures
21. Special toxicity data and literatures related to topical and systematic administration, such as hypersensitivity (topical, systematic and photosensitive toxicity), hemolysis and topical (blood vessel, skin, membrane muscle, etc) irritation, etc.
22. Interaction data and literatures of efficacy, toxicity and pharmacodynamics for multiple components.
23. Mutagenicity data and literatures.
24. Reproductive toxicity data and literatures
25. Carcinogenicity data and literatures
26. Drug dependence data and literatures
27. Animal pharmacokinetics data and literatures

Application Dossiers⁽⁴⁾

PART IV

28. Overview of related clinical study literatures.
29. Clinical study protocol and plan.
30. Clinical investigator Manual.
31. The copy of *Informed Consent* and ethics committee approval.
32. Clinical trial final Report.

Evaluation and Approval Timelines

1. Dossier Receiving: **5 days**
2. Provincial DA Primary Evaluation: **30 days (Local product)**
3. QC lab's tests: **60 days**; Bio-product: **90 days**
4. CDE technical Evaluation for CTA: **90 days**
(Special Procedure: **80 days**)
5. SFDA administrative approval: **30 days**
(Special Procedure : **20 days**)

Special Procedure

1. TCM derived from Herbal, animal, and mineral that have never been previously used as therapeutics
2. New chemical entity (NCE)
3. Anti-HIV/AIDS products (treatment, prevention, Diagnosis)
4. Products for malignant tumor
5. Products for rare diseases (orphan drugs)
6. Products for the diseases that efficacious treatment are not available yet

Patient Number Requirements

For NCE

1. Statistically meaningful
2. The minimum patient number requirements:
 - Phase I: 20-30 patients
 - Phase II: 100 patients
 - Phase III: 300 patients
 - Phase IV: 2000 patients

For first importation application:

1. PK study
2. 100 pairs of patients, controlled, randomized, study
3. At least 60 patients for each indication

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CT Applicant Requirements

- Chinese nationality
- Domestic Law person: pharmaceutical company, organization, institute, not individual
- For multi-center international trial, applicant is foreigners, but, an Chinese representative has to be authorized, as the agent. The agent should be a law person

Investigator Requirements

- Qualified hospitals are pre-selected and designated by SFDA and MOH, according to standardized procedure and requirements for personnel qualification, equipment, etc.
- Around 300 hospitals now, called “National CT Base Hospital”
- “National CT Base Hospital” are inspected by SFDA and MOH jointly



Control of Samples

- **Manufactured in GMP facilities**
- **Adequate scale-up**
- **Freely provided to subjects**
- **Sales not allowed**
- **“ For Clinical Trial Only” must be placed on the label**

Chinese GCP

- **Published in 1998, amended in 1999, latest revision Aug. 6, 2003**
- **Protecting subjects is the utmost purpose**
- **Helsinki Declaration as fundamental**
- **ICH, WHO guidelines as bases**

Characteristics of Chinese CT System

- Clinical Trials must be approved by SFDA prior to ethics committee approval
- Trials must be conducted by designated hospitals
- Designated hospitals are pre-selected by SFDA, as Clinical Bases
- Good Clinical Practice (GCP) works as guideline
- Large part trials for Generics

International Clinical Trial Pre-conditions

- At least three countries involved, with PI in abroad and same protocol.
- Drug already marketed abroad, or at least Phase II trial or Phase III trial has already commenced abroad
- No any trials for vaccines without marketing authorization abroad

Utilization of International Multi-center Trial Result

- For drug importation application, after the marketing approval by original countries or regions
- For domestic manufacturing application
- For ICH region marketing application



Rules for International Multi-Center Trial

- Phase I study again among Chinese population for some trials
- Report all adverse event of the whole trial, not only those found in China
- Inform SFDA of the ending of a trial, by preparing a Clinical Trial Report
- Only way to utilize the result is by submitting the whole set of data from the whole multi-center trials

Prospected Benefits from International CT

- Learn more international experiences
- Better GCP compliance by rigid monitoring, auditing and inspection
- More qualified investigator through the training and practice of international trials
- Less money required from government budget for GCP training, and more objectives can be achieved
- Possibly early access to new products, beneficial to public health

Something we realized as problematic

- **Huge CT approved and less CT Base Hospitals comparatively**
- **Investigators are less trained than required**
- **Lack of experiences in international trials**
- **Small and separated Ethics Committee by each hospitals**
- **Investigators more decidable or dominative than sponsors**
- **Lack of insurance policy for both investigators and subjects**
- **Relatively longer approval time than benchmark**

Regulatory Improvement needs

- Differentiation between IND and NDA
- Differentiation between technical requirements for IND and NDA, especially CMC
- Differentiation between approaches to technical evaluation for IND and NDA
- Reduction of large number of CT application for none-innovative product -waste of CT resources

New Moves Concerned

- China-Korea-Japan, tri-party on CT will bring new input to regional cooperation
- 2007 *Provisions for Drug Registration*, cut CT sample tests requirement, accept CDT dossier, approval time shortening
- Special Procedure provides pre-consultation with CDE
- RMB 800 billion (\$120 billion) government funds for health reform, some goes to CT for improvement.
- Government Initiative to encourage innovation by providing RMB 6.9 billion (\$1.0 billion)
- Big R&D center built in China

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Dealing with new situation

- Continuing regulatory improvement to support domestic need in innovation , attract more international multi-center CT
- Close connection with international community to utilize new achievement of ICH, APEC LSIF, and tri-party

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THANK YOU for your
attention.

Email: Dingjh@sfda.gov.cn



- Plenary VI: Regulatory Guidance/Perspectives/Issues

Regulatory Guidance/Issues - A Company Perspective



Speaker:

Min Irwin (China)

Medical Director of Medical Regulatory Affairs

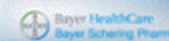
Bayer Schering Pharma, China

Contents

- Challenges
 - Challenges of Multi Regional Trials
 - A Win-Win Situation
- A Case Analysis
 - Make a first step: with Sorafenib in HCC
 - Background for AP/CN
 - Baseline Patient Characteristics: Asia-Pacific Study vs SHARP
 - Comparison of Efficacy Between the Asia-Pacific and SHARP Trials
 - First experience for BSP Asia-Pacific / China
- Best Practice
 - High quality data in AP/China
 - Patient enrolment and the high recruitment rate
 - Development Timing
- Experience Summary - for MNC

Regulatory Guidance/Issues - A Company Perspective

Min Irwin, MD, Ph.D
Medical Director of Medical and Regulatory Affairs
Bayer Schering Pharma, China



Topics

- Challenges
- A case analysis
- Best practice



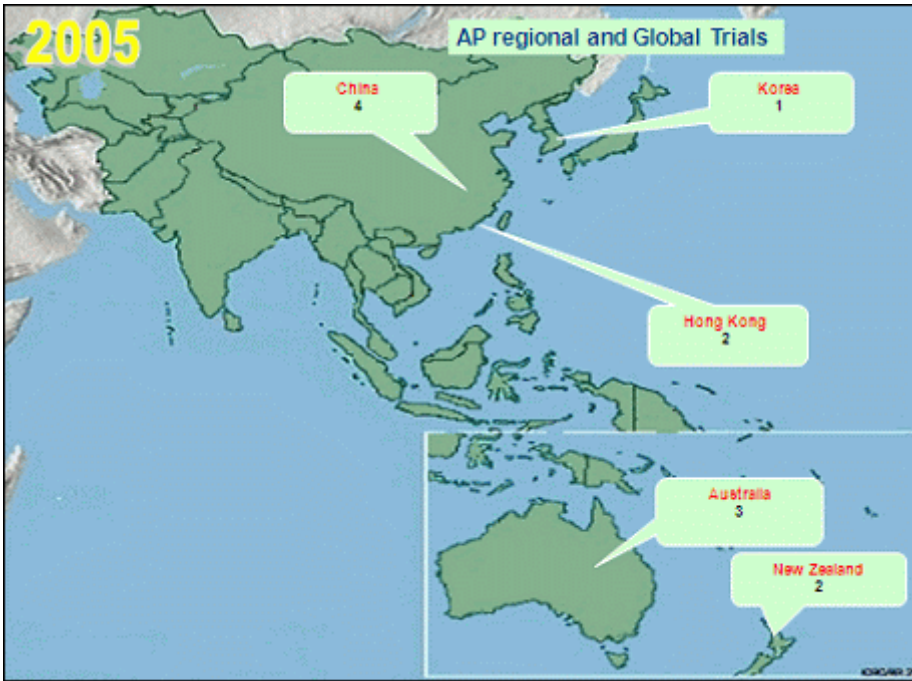
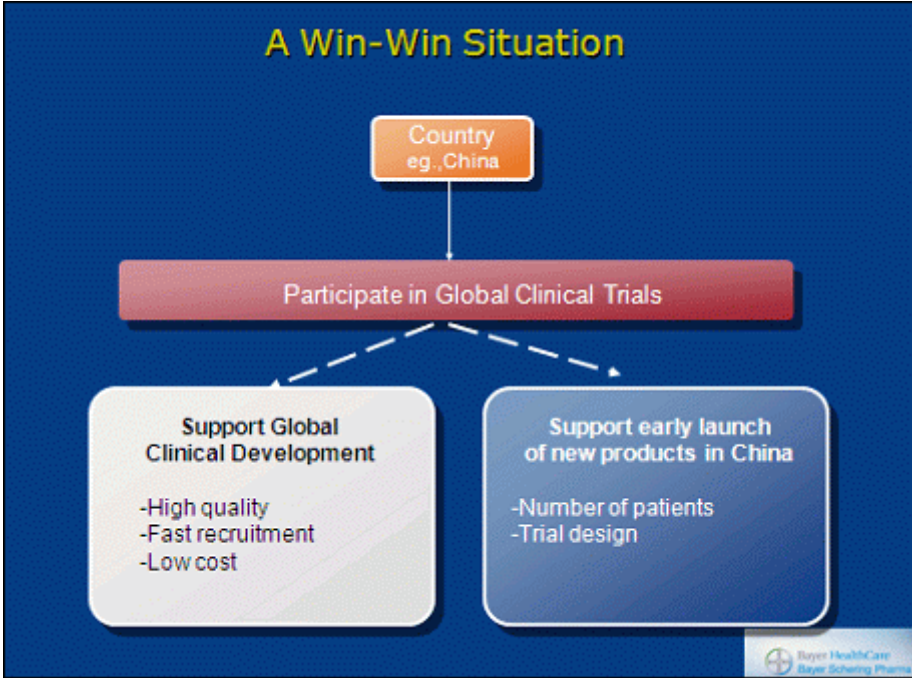
Challenges of Multi Regional Trials (1)

- Health Authority requirements
 - There is a lack of global harmonization
 - To obtain the same indication world wide we may need to study different endpoints, different comparators (dose, formulation, indication), different entry criteria
- Difference in standard of care
 - Medical practice patterns
 - Access to the health care system
 - Criteria for hospitalization and treatment



Challenges of Multi Regional Trials (2)

- Design considerations
 - Access to diagnostic tests
 - Access to measurement technology (MRI, OCT, PET)
 - Differences in standards (lab units, pulmonary function tests)
- Operational considerations
 - Site infrastructure (study co-coordinator, research pharmacist, research RN)
 - Electronic data capture (computers, band width, phones)
 - Drug storage capabilities
- Site qualifications and quality
 - Appropriate training
 - Quality of study conduct
 - Quality of data collection



Make a first step : with Sorafenib in HCC

- Sorafenib is the only systemic therapy approved by the FDA* and EMEA for the treatment of patients with HCC
- In the Phase III SHARP[†] trial (US, EU, ANZ), median survival and time to radiologic progression were 3 months longer for patients treated with sorafenib than for those who received placebo¹

* For unresectable HCC

[†]SHARP = Sorafenib HCC Assessment Randomized Protocol
1. Ulovet JM et al. 2008



Background for AP/CN

- Predominant hepatitis virus infection in Asia-Pacific region is HBV, not HCV^{1,2}
- Practice of surgical resection, transplantation, and other local therapies differs between Western and Asia-Pacific regions¹



• **Objective:** evaluate efficacy and safety of sorafenib in a population of patients from the Asia-Pacific region

1. De Villa and Lo. *Oncologist*. 2007;12:1321-1331.
2. Ulovet JM et al. *Lancet*. 2003;362:1907-1917.

Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.



Efficacy and safety of Sorafenib in a population of patients from the Asia-Pacific region

Eligibility

- Advanced HCC
- ECOG 0-2
- Child-Pugh A
- No prior systemic therapy

Stratification

- Macroscopic vascular invasion (portal vein) and/or extrahepatic spread
- ECOG PS
- Geographic region

R
A
N
D
O
M
I
Z
E
2:1

n=150

Sorafenib
400 mg bid

n=76

Placebo

SHARP
1:1

End points:

- Overall survival, time to symptomatic progression (FSH18-TSP), time to progression, response (RECIST), and safety
- No primary end point defined

Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.



Baseline Patient Characteristics: Asia-Pacific Study vs SHARP

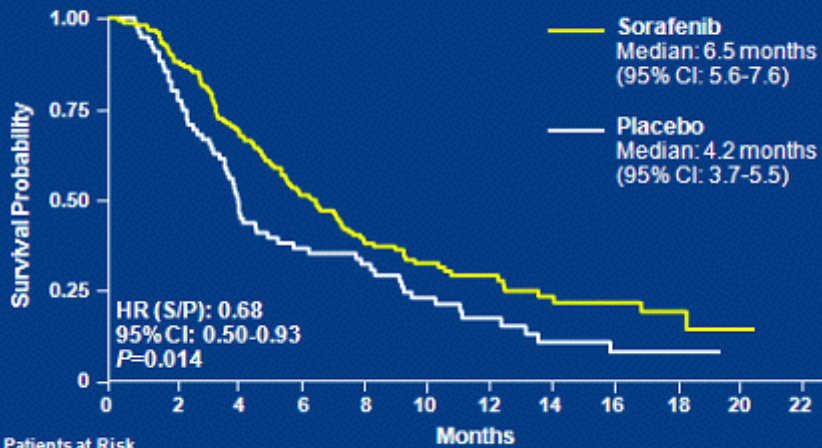
| | Asia-Pacific
(N=226) | SHARP ¹
(N=602) |
|-------------------------------------|-------------------------|-------------------------------|
| Median age (range), years | 51 (23-86) | 67 (21-89) |
| Sex (Male), % | 85 | 87 |
| ECOG PS (0/1/2), % | 26/69/5 | 54/38/8 |
| Macroscopic vascular invasion, % | 35 | 38 |
| Extrahepatic spread, % | 69 | 51 |
| BCLC Stage (B/C), % | 4/96 | 17/82 |
| Hepatitis virus status (HBV/HCV), % | 73/8 | 18/28 |
| No. of tumor sites, % | | |
| 1 | 11 | 44 |
| 2 | 35 | 31 |
| 3 | 20 | 12 |
| ≥4 | 35 | 13 |
| Sites of disease, % | | |
| Lung | 50 | 21 |
| Lymph nodes | 32 | 26 |

1. Uovis J. J. Clin Oncol. 2007;25(suppl):LBA1.

Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.



Overall Survival



Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.



Comparison of Efficacy Between the Asia-Pacific and SHARP Trials

| End point | Asia-Pacific ² | | SHARP ¹ | |
|-----------|---------------------------|---------|--------------------------|---------|
| | Hazard Ratio
(95% CI) | P-value | Hazard Ratio
(95% CI) | P-value |
| OS | 0.68
(0.50-0.93) | 0.014 | 0.69
(0.55-0.87) | <0.001 |
| TTSP | 0.90
(0.67-1.22) | 0.496 | 1.08
(0.88-1.31) | 0.768 |
| TTP | 0.57
(0.42-0.79) | <0.001 | 0.58
(0.45-0.74) | <0.001 |
| PFS | 0.62
(0.46-0.82) | <0.001 | 0.65
(0.52-0.79) | <0.001 |

- Patients on drug from SHARP trial experienced a 44% OS benefit
- Patients on drug from AP trial experienced a 47% OS benefit

1. Uvoet JM et al. 2008; In Press.

2. Adapted from Cheng A et al. Presented at ASCO Annual Meeting; May 30-June 3, 2008; Chicago, IL.



First experience for BSP Asia-Pacific / China

- Positive image of data provided by AP/CN
 - in terms of quality delivered
 - Fast recruitment and low screen failure rate (2 times less)
 - Complexity of protocols that can be run in the region
- Bayer China received SFDA approval for Sorafenib (Nexavar®) within 9 months of US approval



Real Life Issues

- Qualification of clinical sites and physicians
- The relationship between the subject and investigator becomes critical in the consent process
- Withdrew consent during treatment
 - subjects seek second and third opinions
 - Poor understanding of the consent process and clinical research
- Importance of independent data monitor board

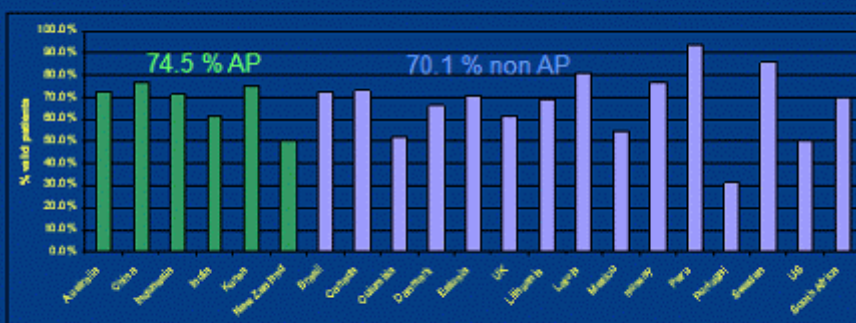


- Not only final results have to be considered to involve AP/China on global trials, we have to focus on:

- Quality
- Timelines and Recruitment rate
- Cost



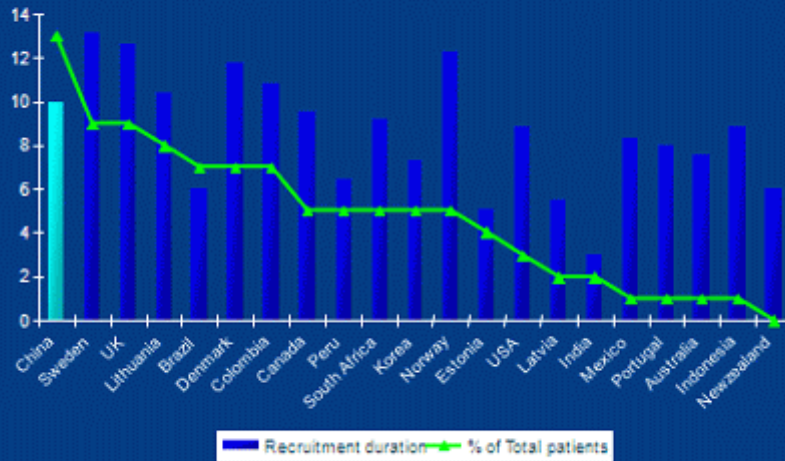
High quality data in AP/ China



BSP International Hemato-cardio Clinical trial (2006/2007)



#1 patient enrolment globally and the high recruitment rate saved 2 months to end the trial



BSP International Hematocardi Clinical trial (2006/2007)



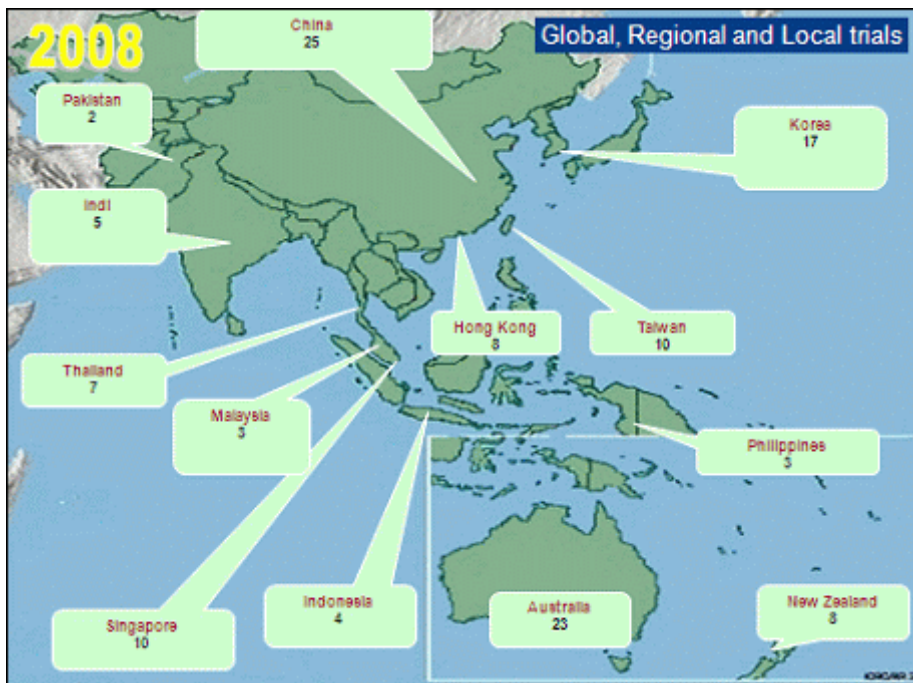
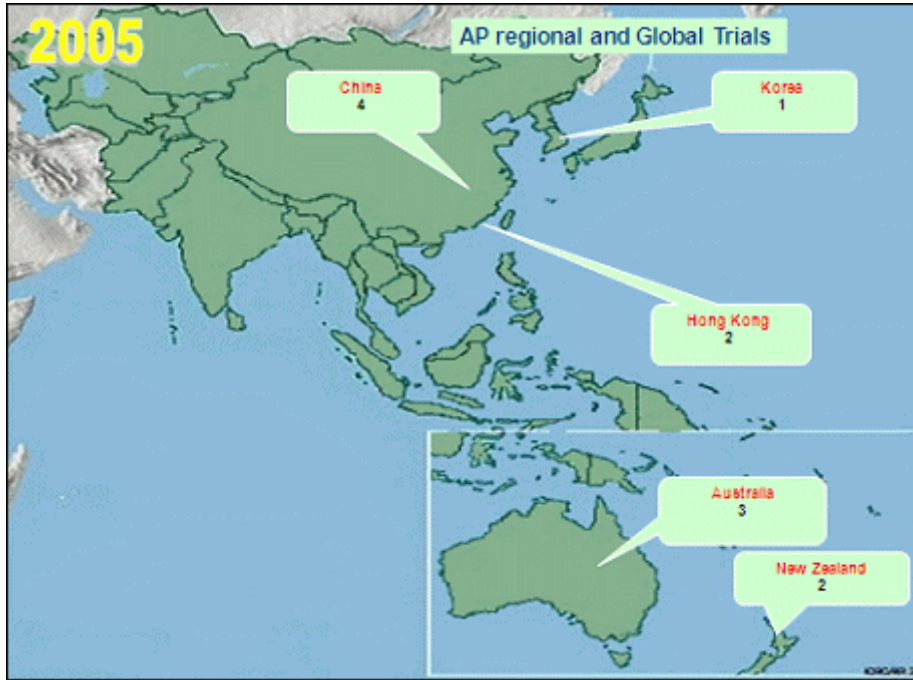
Development Timing in Global and China

Global



China





Experience Summary- for MNC

- Set realistic clinical development plan including AP needs
- Select smart Global regulatory strategy involving AP into early development to maximize the use of global studies for local registration
- Obtain the draft protocol from Global development for early preparation
- Proactively prepare investigator training to save time to start and insure high quality
- Continuously build up local internal study team
- Create a “win win win” situation : country, region and global



Thank you

- Plenary VI: Regulatory Guidance/Perspectives/Issues

(Additional Panelist 1) The View on the Implementation of ICH Clinical Guidelines



Presenter

Yuppadee Javroongrit (Thailand)

Assistant Director

Drug Control Division

Thailand Food and Drug Administration

Contents

- Agreement/Mandatory
 - ASEAN Safety Guidelines (adopted ICH-S gls)
 - ASEAN Efficacy Guidelines (adopted ICH-E gls)
- Implementing the adopted Technical Guidelines
 - The Process/Action
- Regulatory Perspective
 - Implementation of ICH Clinical Guidelines



Plenary VI : Regulatory Guidance/ Perspectives/ Issues

“Additional Panelist”

The View on the Implementation of ICH Clinical Guidelines

by

Yuppadee JAVROONGRIT, Ph.D.

Drug Control Division, FDA, THAILAND

The Multi-Regional Clinical Trials Seoul Workshop

Inaugural Workshop of the APEC Harmonization Center

Grand Hilton Hotel, Seoul, Korea

15-18 June 2009

Yuppadee_AHC Inaugural WS-Korea-15-18 Jun 09

1



Topics

- agreement / mandatory
- implementing the adopted Technical Guidelines
- Regulatory Perspective

Yuppadee_AHC Inaugural WS-Korea-15-18 Jun 09

2



ASEAN Efficacy Guidelines (adopted ICH-E gls)

- E1 → The Extent of Population Exposure to Assess Clinical Safety for Drug: Intended for Long-Term Treatment of Non-Life-Threatening Conditions
- E2A → Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- E2C → Clinical Safety Data Management : Periodic Safety Update Report for Marketed Drug
- E3 → Structure and Content of Clinical Study Reports
- E4 → Dose-Response Information to Support Drug Registration
- E6 → Good Clinical Practice: Consolidated Guideline**
- E7 → Studies in Support of Special Populations : Geriatrics
- E8 → General Considerations for Clinical Trials
- E9 → Statistical Principles for Clinical Trials
- E10 → Choice of Control Group and Related Issues in Clinical Trials
- E11 → Clinical Investigation of Medicinal Products in the Pediatric Population

Vagstad4_4RC Inaugural WS-Korea-15-18 Jun 09

5



Implementing the adopted *Technical Guidelines*

The Process / Action

- Law & Regulation
- Criteria
- Forms & SOPs
- Translation *English to Thai* Document
- Dissemination Information + Requirement
- Official Announcement
- Implementation System

**Translation → a difficult part
→ need the proper Interpretation !!**

Vagstad4_4RC Inaugural WS-Korea-15-18 Jun 09

6



Regulatory Perspective

“Implementation of ICH Clinical Guidelines”

- working together with Stakeholders
 - *internally*
 - *regionally*
- proper and adequate “Training & Consultation”
 - *from ICH’s Regulator & Inventor*
 - *essential and needed !*
- available of “Q&A” session in ICH Website
- regular “Platform” for discussion could support !
- Regulator Forum should enlarge and reach-out more !!!

Vagpdee_UMC Inaugural WS-Korea-15-18 Jun 09

7



Vagpdee_UMC Inaugural WS-Korea-15-18 Jun 09

8

- Plenary VI: Regulatory Guidance/Perspectives/Issues

(Additional Panelist 2) Regulatory Guidance/Perspective/Issues



Panelist:


Marco Antonio Llanas Blanco (Mexico)

Sanitary Authorization Commission


COFEPRIS

Contents

- Committee of New Molecules
- Functions
- Evaluated Proceedings
- Type of Proceeding
- Evaluation Process for Clinical Trials
- Minimal Requirements
- Approval Time
- Definition of New Molecules
- Necessary Changes to Increase the Investigation
- Purpose



COMISIÓN FEDERAL PARA LA PROTECCIÓN
CONTRA RIESGOS SANITARIOS




Federal Commission for the Protection against Sanitary Risks (COFEPRIS)


“Regulatory Guidance/Perspectives/Issues”

Marco Antonio Llanas, MD.

June, 2009.



Vivir Mejor



SALUD




COMISIÓN FEDERAL PARA LA PROTECCIÓN
CONTRA RIESGOS SANITARIOS



Committee of New Molecules:

- Permanent members:
 - Advice of General Salubrity.
 - Commission of Analytical Control and Extension of Cover.
 - Commission of Evidence and Handling of Risks.
 - General Coordination of the National Institutes of Health.
 - Mexican Institute of the Industrial Property.



Vivir Mejor



SALUD



COMISIÓN FEDERAL PARA LA PROTECCIÓN
CONTRA RIESGOS SANITARIOS



Committee of New Molecules:

- Federal Commissioner of the Federal Commission for the Protection against Sanitary Risks. **President.**
- Commissioner of Sanitary Authorization. **Technical Secretary.**
- Executive Director of Product Authorization and Establishments. **Auxiliary Secretary.**
- Director of the National Center of Pharmacovigilance. **Auxiliary Secretary.**
- Representatives of the Academic Associations



Vivir Mejor

SALUD 

3




COMISIÓN FEDERAL PARA LA PROTECCIÓN
CONTRA RIESGOS SANITARIOS




Committee of New Molecules:

- Non Permanent members:
 - Academies, Universities, Associations, Advice and Schools of diverse disciplines.
 - Directors of:
 - IMSS (Mexican Institute of Social Insurance)
 - ISSSTE (Institute of Social Security and Services of Workers of the State)
 - DIF (National System for Integral Development of Family)
 - SEDENA (Secretariat of the National Defense)
 - GDF (Government of the Federal District)
 - Directors of Hospitals of Sector Health.



Vivir Mejor

SALUD 

4

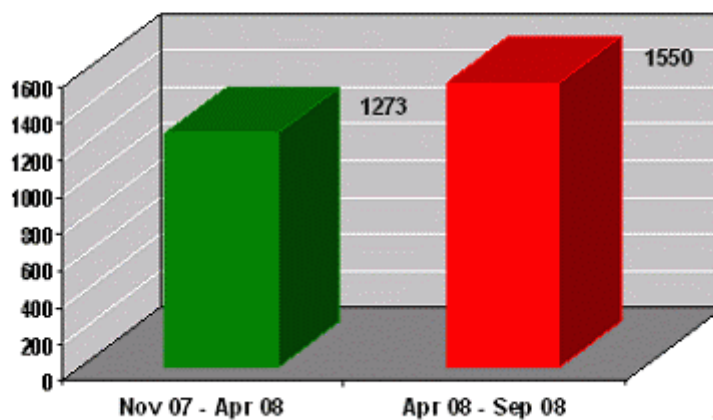


Functions:

- Evaluate the expedition, prorogation or revocation of the clinical trials authorization.
- Evaluate the Sanitary Registry Authorization of new drugs, devices, procedures and experimental activities for use in human.



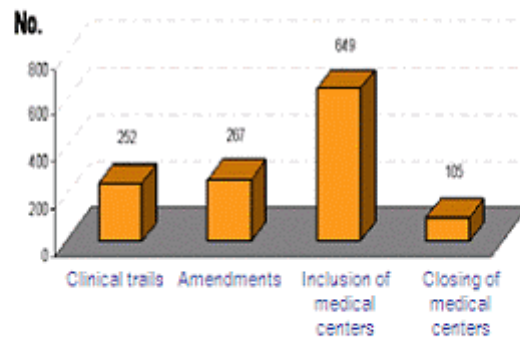
Evaluated proceedings:



Secretaría de Salud/COFEPRIS/CMN, 2008



Type of proceeding :



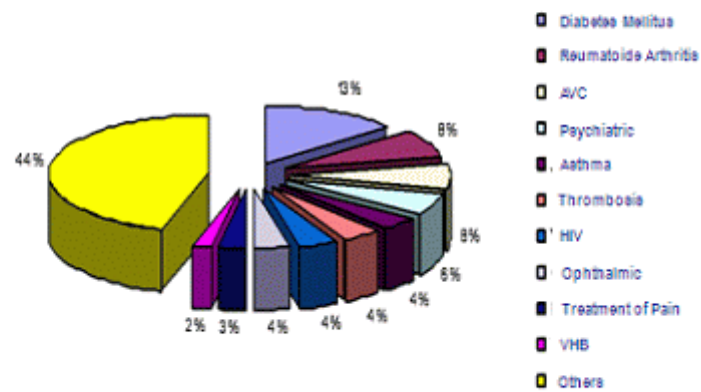
1273 proceedings (november, 2007 – April, 2008)

Secretaría de Salud COFEPRIS/CMN, 2008

7



Type of proceeding:



Secretaría de Salud COFEPRIS/CMN, 2008

8



Evaluation process for clinical trials:

- Fulfillment of the established in the Regulation of the General Law of Health in matter of Investigation for the Health
- Authorization request COFEPRIS-04-010-A/
COFEPRIS-04-010-B
- Corresponding payment



Minimal requirements:

- Article 222 of the General Law of Health
 - Security and effectiveness
- Article 167 of the Regulation of Consumptions for Health
 - Identity and purity
 - Stability
 - Therapeutic effectiveness and security
 - Therapeutic indication and Projects of label
 - Patent (Intellectual Property)
 - Identification of Origin and Certificate of GPM
 - Certificate of free sale of the origin country



COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

www.cofepris.gob.mx

COFEPRIS :: Solicitudes - Windows Internet Explorer

COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

www.cofepris.gob.mx | INICIO | MAPA DE SITIO | DIRECCIÓN | CONTACTO | IDIOMAS | SALUD

Domingo 14 de junio de 2009

TU ESTÁS AQUÍ: Inicio | Trámites y servicios | **Formatos** | **Solicitudes**

Solicitud

- Formato (Tamaño: 645 KB)
- Guía de llenado (Tamaño: 117 KB)
- Instructivo de llenado (Tamaño: 122 KB)
- Lista de documentos anexos (Tamaño: 414 KB)

TRÁMITES Y SERVICIOS

- Formatos
- Avales
- Formato incorporado con establecimientos médicos
- Cross Trámites
- Solicitudes
- Trámites PLAFEST
- Trámites incorporados con Servicios de Salud

Vivir Mejor

SALUD

COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

Approval time:

- Clinical trials:
 - From 20 to 90 working days
 - Depends the proceeding, phase of study and type of drug or device
 - COFEPRIS can request supplement data only once during the review phase
 - Sponsor can respond in 10 or 20 working days, depending the requirements (administrative or technicians)

Vivir Mejor

SALUD

12



Approval time:

- New Molecules (Sanitary Registry):
 - 180 working days
 - Depends the type of drug
 - COFEPRIS can request supplement data only once during the review phase
 - Sponsor can respond in 20 or 45 working days, depending the requirements (administrative or technicians)



Definition of New Molecules :

- Drug or Medicine.
 - It does not have registry at world-wide level
 - With registry at world-wide level but not in Mexico
 - Drug combination, that does not exist in the national market
 - Existing drug in the market that it tries to commercialize itself with another therapeutic indication

Decree in the Official Newspaper of the Federation , January 02, 2008.





Necessary changes to increase the investigation:

- Continuous update
- Exchange of information with the rest of the world
- Coordinate work meetings
- Propose new pharmacovigilance mechanisms
- Modification and standardization of the regulation laws
- Definition of guidelines for the evaluation of biotechnological



Purpose :

Guarantee the security and clinical effectiveness through fulfillment of phases III and IV in Mexico



Annexes

I. Messages - Opening Remarks / Welcoming Address

- Congratulatory Message by President of Republic of Korea

Excellencies, distinguished guests, ladies and gentlemen,

I would like to extend my warm welcome to all of you.

I am greatly delighted that APEC Harmonization Center is established here in Seoul, Republic of Korea for the first time in the world. I would like to express my sincere gratitude to all of you, whose consideration and help enable the foundation of the Center in Seoul.

Today's gathering is very meaningful to me as I was in the APEC Summit Meeting in Lima, Peru where the establishment of the Center in Seoul was endorsed by APEC leaders and ministers last November.

Distinguished participants,

The future of newly growing areas such as life science, pharmaceutical, and medical device industries looks very bright amid the current global economic crisis.

I believe that the APEC harmonization Center which is open today will greatly contribute to the development of these newly emerging fields as well as mutual collaboration and co-existence by achieving regulatory harmonization and the elimination of trade barriers among member economies.

I also expect that the workshop will give new momentum to life science and medical device industries, serving as an opportunity to promise healthy future for the humanity.

The Korean government pledges our utmost commitment to collaboration with APEC member economies and successful operation of the Center.

I would like to extend my welcome to all of you who came to this beautiful city of Seoul and hope the best for all of you. Thank you for your attention.

Myung-bak Lee

President of Republic of Korea

- Opening Remarks by Commissioner of KFDA (Korea)

Honorable Director General Victor Alejandro Dongo Zegarra of DIGEMID (Dirección General de Medicamentos, Insumos y Drogas), Deputy Secretary General Werawan Tangkeo of TFDA (Food and Drug Administration Thailand), Chairperson Mike Ward of APEC LSIF RHSC (Regulatory Harmonization Steering Committee), Co-chairperson Kohei Wada of ICH GCG (International Conference on Harmonization, Global Cooperation Group), and distinguished delegations and guests from around the world!

Honorable Chairperson Byun Ung-jun of the National Assembly's Health, Welfare and Family Affairs Committee, Vice Minister Yoo Young-Hak of the Ministry for Health, Welfare and Family Affairs, distinguished participants, and ladies and gentlemen!

I wholeheartedly welcome all of you. It is truly an honor to present an opening speech on behalf of the Korea Food and Drug Administration of the Republic of Korea. I am delighted that Inaugural Workshop of the APEC Harmonization Center is held in Seoul with this enjoyable, beautiful greenery.

Humankind has been fighting numerous diseases from a long time ago. Drugs are one of the most important means of saving the humanity from diseases, and a wide array of drug products are being developed even at this time. Following the development and synthesis of chemical compounds for pharmaceutical applications, gene therapy products, cell therapy products and other therapies using high-end technology came along.

But still, we are suffering from many incurable diseases, and, even worse, we have recently witnessed newly emerging threats including Avian Influenza and a new strain of Influenza A (H1N1) that have never been seen before. Against this backdrop, we should continue to exert coordinated efforts worldwide to combat these diseases, share outcomes from drug development process, and harmonize our protocols and regulatory procedures.

I am confident that APEC harmonization center will play a key role not only in promoting a strategic and consistent approach to regulatory harmonization within the APEC region in line with international standards, but also in training and capacity building of its regulatory authorities within the context of a regional strategy considering the needs and capacities of member economies. The Center is also expected to serve as a forum for industry and academia as well as regulatory authorities.

The theme of the first workshop is multi-regional clinical trials. Recognizing that Asia-Pacific region has been rapidly gaining importance as a place of global drug development, the workshop aims to harmonize the compliance requirements among member economies and to remove unnecessary regulatory procedures on clinical trials in the region.

I hope that this workshop will stimulate interactive discussions and bring new ideas, insights, and approaches to develop advanced regulatory harmonization within the APEC region on the existing building blocks of international organizations such as ICH.

I also expect that the AHC will provide a new framework for networking within member economies, especially for collaboration and harmonization among regulatory authorities, industry and academia. KFDA pledges cooperation and commitment to resolve pending issues common interest of APEC members.

I would like to conclude my speech with my sincere appreciation to the LSIF program planning group and Korean staff for organizing this workshop. I wish all participants the best of luck and health. Thank you for your attention. It is my privilege to declare the workshop open.

Yeo Pyo Yun
Commissioner of KFDA

- Welcoming Address by Chair of Health, Welfare and Family Affairs Committee (Korea)

Excellencies, Honorable guests from Korea and abroad,

Ladies and gentlemen!

On behalf of Health Welfare and Family Affairs Committee of National Assembly of Republic of Korea, I would like to extend warm welcome to all participants from APEC member economies to Inaugural Workshop of the APEC Harmonization Center on Multi-Regional Clinical Trials.

Healthcare and life sciences have been recognized as one of significant fields for the socio-economic development and their proper development is critical to guarantee economic competency. The development of healthcare and life science industry can be ensured by the proper policy and regulatory system and requires not only active cooperation among government, industry, and academia but also world-wide exchange of information and regulatory harmonization. The need for the united efforts among nations can be exemplified by the fact that the faster development of surveillance system against a newly emerging epidemics such as influenza A subtype H1N1 and the rapid delivery of efficient medicine to patients cannot be done by any single country but by the cooperation of nations.

This is why I greatly welcome the endeavors of all of you to make this workshop possible in order to actively resolve these global pending issues, especially the efforts of healthcare regulatory authorities from APEC member economies, LSIF APEC Harmonization Center and LSIF Regulatory Harmonization Steering Committee.

Distinguished participants,

In keeping pace with the global flow, Korea Health, Welfare, and Family Affairs Committee in National Assembly has put much efforts to establish the framework of policy and regulations starting from January 2008, which can support R&D to build capacity for new drug development and infrastructure for clinical trials by expanding the clinical trials centers and improving the health industry management system according to international standards. Consequently, I cannot hide my feelings of joy and gratitude for having this opportunity to educate and discuss the issue of Multi-Regional Clinical Trials at the first workshop.

Today, I hope that through this workshop the unconstructive regulations be successfully lifted and that ethically- and scientifically-justified clinical trials be conducted according to the international standard. I also expect that this workshop offer an essential foundation for the practical and systematic development of clinical trials, as a variety of issues regarding healthcare and drug development will be discussed and resolved.

Finally, I sincerely hope that the worthy initiative from this workshop provide a beacon to guide us toward sound advancement of healthcare system which benefits us all and it leads us to the economic development of all APEC member economies and the improvement of "quality of life" of our people.

Thank you.

Ung Jun Byun

Chair of Health, Welfare, and Family Affairs Committee

The National Assembly of Republic of Korea

- Congratulatory Remarks by Vice Minister of Ministry for Health, Welfare, and Family Affairs

Honorable Director General Victor Alejandro Dongo Zegarra of DIGEMID (Dirección General de Medicamentos, Insumos y Drogas), Deputy Secretary General Werawan Tangkeo of TFDA (Food and Drug Administration Thailand), Chairperson Mike Ward of APEC LSIF RHSC (Regulatory Harmonization Steering Committee), Co-chairperson Kohei Wada of ICH GCG (International Conference on Harmonization, Global Cooperation Group),

Honorable Chairperson Byun Ung-jun of the National Assembly's Health, Welfare and Family Affairs Committee, Commissioner Yeo Pyo Yun of Korea Food and Drug Administration, President Bup-Wan Kim of the Korea Health Industry Development Institute,

Distinguished government officials from APEC member economies, and participants from industry and academic professionals from Korea and abroad,

Ladies and gentlemen!

I would like to extend my welcome gratitude to all of you.

Today, I would like to offer my sincere congratulations for Inaugural Workshop of the AHC.

The APEC Harmonization Center aims to provide advanced training program on regulatory harmonization in order to achieve international synchronization of regulatory management system on medicinal products and medical devices.

I believe that the cooperation of APEC member economies for our mutual goal will present the utmost model to achieve the universal value of the healthy life of the humankind by global collaboration.

Korean government is a supporter and upholder of member economies' efforts to achieve this goal.

In this regard, Korea committed to have APEC harmonization center established in Seoul and willing to support its first workshop with pleasure. We pledge our continuous commitment to the Center.

The Ministry of Health, Welfare, and Family Affairs of Republic of Korea has put our continuous efforts to support the operation of the AHC and the improvement of healthcare policy of KFDA.

In parallel, we has also thrown our persistent efforts into establishing provisions against newly emerging pandemic influenza virus or chronic disease and geriatrics derived from environmental change and aging society and supporting the development of excellent medicines and establishment of management system.

We are actively collaborating with other nations to establish the framework for advanced healthcare system.

Dear participants,

The place where this workshop is held, "Hong-Eun Dong" was a pathway of long-history for foreign delegations to enter Korea. Its name holds the meaning of "the grand bestowment of a good-will".

In the place with such a meaningful name, we have gathered to secure the better quality of life for our people, and even further, to guarantee the concerted economic development of member economies.

I encourage your active participation to the Workshop over the coming four days to establish practical network among regulatory authorities and industry professionals. I wish that you make this workshop as a stepping stone to achieve our long-lasting hope for the betterment of human health.

I would like to conclude my speech with my warm welcome to all participants to the Inaugural Seoul Workshop of the AHC. I wish that this Seoul workshop with luxuriant foliage would be a memorable one to all of you.

Thank you very much.

Young Hak Yoo

Vice Minister of Ministry for Health, Welfare, and Family Affairs

- Welcoming Address by President of the Korea Health Industry Development Institute (Korea)

Excellencies,

Chair of Health, Welfare and Family Affairs Committee, Byun Ung Jeon,

Commissioner of KFDA, Yun Yeo Pyo Director General of DIGEMID, Victor Dongo,

Co-chair of ICH GCG, Kohei Wada,

and Chair of RHSC, Mike Ward

Distinguished Participants,

Ladies and Gentlemen,

I would like to welcome you all to Korea and express my appreciation to everyone who will be participating in the APEC Harmonization Center's Multi-Regional Clinical Trials Workshop for the next three days.

I am proud to acknowledge that we have a wide international representation from various APEC economies, and this workshop will most certainly help serve as a platform to discuss and educate the issues of regulatory harmonization broadly and Multi-Regional Clinical Trials specifically for participants of the APEC region.

We are in a new era where global pressures have intensified. In many respects the circulation of brain power around the world is just as critical as the circulation of goods and services. Therefore, we must be much more engaged on a global scale and we will contribute all our effort into making the AHC a center worthy of regulatory harmonization education provision.

For my part, I will commit myself in grasping the opportunity provided by the AHC to do the best I can to promote regulatory harmonization in the APEC region by providing resources and education for the cooperation between not only scientists and specialists but also policymakers, business leaders, and academic leaders from all over the world.

KHIDI has always welcomed developing relations with international organizations for increased cooperation and facility in the field of public health. Last year in August, I had presented during the Senior Officials Meeting in Lima, Peru regarding the establishment and progress of the AHC, and that presentation was met with much fervor and support.

As one of the main advocators for the establishment of this center, words cannot express how proud and pleased I am to stand here today, in the fruits of such efforts. As the AHC continues to flourish and provide regulators and industry members with vital resources, I promise that KHIDI will also be there to support and guide all the efforts of the AHC.

In closing, I would like to give a reminder that the path before us will by no means be a brisk walk through the park. However, I am inspired and delighted to gain courage in the fact that within the framework of APEC is such a great endeavor to bring together renowned scholars, officials, and industry authorities who will help us move forward in developing a deeper understanding of our commitment to regulatory harmonization.

I encourage everyone to be active with the goal of prospering humankind in mind and I wish you all a wonderful time here in Seoul. Thank you.

Bup Wan Kim

President of Korea Health Industry Development Institute

III. Articles of the workshop

- Press Release

APEC Harmonization Center For Life Sciences To Hold Inaugural Ceremony And Workshop

Seoul, 9 May 2009

The APEC Harmonization Center (AHC), established under the authority of the APEC Life Sciences Innovation Forum (LSIF), will be hosting its inauguration ceremony and a workshop on multi-regional clinical trials on the 15-18 of June at the Seoul Grand Hilton Hotel. This is the first of three workshops that will be hosted by the AHC in 2009.

The inauguration ceremony, to be held at 11:00 am on June 15th, will mark the establishment of the AHC as a platform to address and solve priority concerns of APEC member economies on regulatory harmonization in the life sciences sector. The center is based in Seoul and sponsored by Korea Food and Drug Administration (KFDA) and operated by the Korea Health Industry Development Institute (KHIDI) as the Secretariat.

Equally important as the launching event of the AHC is the workshop to follow, taking place June 15-17. The workshop will include many insightful presentations and discussion sessions on multi-regional clinical trials and will raise awareness and understanding on the topic, particularly among developing economies that may not be familiar with some of the issues. In this context, the workshop will also explore the broader benefits and challenges of regulatory harmonization in the APEC region and will serve as an educational forum for regulators and policy makers, thus equipping key stakeholders to develop effective harmonization strategies. In addition, the first meeting of the LSIF Regulatory Harmonization Steering Committee will take place June 17-18 and will further raise awareness and understanding on the key issues, as well as develop next steps in response to APEC's goal of effective facilitation and liberalization of trade and investment among APEC economies.

The AHC in collaboration with the APEC LSIF and International Conference on Harmonization, KFDA and KHIDI are making the final preparations for these events. APEC economy government officials, drug regulatory authorities, as well as members of public and private sectors have been invited to participate.

For more information please contact: ahckorea@khidi.or.kr

Source: KHIDI

Website: <http://www.khidi.or.kr>

- Article

Seoul to host inaugural workshop of the AHC on June 15

Singapore, June 11, 2009: The Korea Health Industry Development Institute (KHIDI) is organizing a four day workshop on Multi-Regional Clinical Trials starting from June 15 in Seoul, Korea in association with the Korea Food and Drug Administration (KFDA). The workshop is the inaugural workshop of the APEC Harmonization Center (AHC).

The objectives of this workshop are to provide information to government policy makers, regulators, academics, and other public and private sector stakeholders on the harmonization of standards and regulations in life science products.

Speakers will be sharing information on different topics such as the Values and Challenges of Multi-Regional Clinical Trials, Intra-Regional Efforts to Streamline the Conduct of Clinical Trials, The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group, ICH Overview, Multi-Regional Clinical Trial Design Issues that Clinical Researchers should understand in order to Succeed, Operational Aspects, Regulatory Guidance/ Perspectives / Issues.

Both APEC (Asia Pacific Economic Cooperation) broadly and Life Sciences Innovation Forum (LSIF) have recognized the benefits of regulatory harmonization within APEC, including in the context of APEC's trade facilitation and regional economic integration agendas. The workshop will raise awareness and discuss the challenges and opportunities of conducting multi-regional clinical trials (MRCTs) in a manner appropriate for the complexities of the regulatory decision making process, and commence the first meeting of the LSIF Regulatory Steering Committee.

Source: BioSpectrum Bureau

III. Major Scenes of the workshop

- Inaugural Ceremony

| | |
|---|--|
|  |  |
| <p>Opening Remarks
<i>(Yeo-Pyo Yun)</i></p> | <p>Welcoming Address
<i>(Ung Jun Byun)</i></p> |
|  |  |
| <p>Congratulatory Address
<i>(Young Hak Yoo)</i></p> | <p>Congratulatory Address
<i>(Kohei Wada)</i></p> |

- Inaugural Ceremony



Bup Wan Kim



Mike Ward



VIPs



Sand Animation



Group Photo

- Welcome and Introduction



Seung Hee Kim



Kyung Won Jang



Mike Ward



Audience



Audience



Audience

- Plenary I (The Value and Challenges of Multi-Regional Clinical Trials)



Session Chair
(Mark Paxton)









Speaker
(Toshi Kobayashi)









| Speaker
<i>(James Hung)</i> | Panel Discussion |
|---|--|
|  |  |
| Audience | |

- Plenary II (Intra-Regional Effects to Streamline the Conduct of Clinical Trials: The Tripartite Initiative and the ASEAN Pharmaceutical Product Working Group)

| | |
|---|--|
|  |  |
| <p>Session Chair
<i>(Justina A. Molzon)</i></p> | <p>Speaker
<i>(Haruo Akagawa)</i></p> |
|  |  |
| <p>Speaker
<i>(Kyung Won Seo)</i></p> | <p>Speaker
<i>(Jianhua Ding)</i></p> |
|  |  |
| <p>Speaker
<i>(Yuppadee Javroongrit)</i></p> | <p>Panel Discussion</p> |







- Plenary III (ICH Overview)

| | |
|---|--|
|  |  |
| <p>Session Chair
<i>(Toshi Kobayashi)</i></p> | <p>Speaker
<i>(Yoshiaki Uyama)</i></p> |
|  |  |
| <p>Speaker
<i>(Martha A. Brumfield)</i></p> | <p>Panel Discussion</p> |
|  |  |
| <p>Questions from the audience</p> | <p>Audience</p> |

- Opening Night Reception





- Plenary IV (Multi-Regional Clinical Trial Design Issues that Clinical Researchers Should Understand in Order to Succeed)

| | |
|---|--|
|  |  |
| <p>Session Chair
<i>(Ling Su)</i></p> | <p>Speaker
<i>(William Wang)</i></p> |
|  |  |
| <p>Speaker
<i>(James Hung)</i></p> | <p>Speaker
<i>(Allan Donner)</i></p> |
|  |  |
| <p>Panel Discussion</p> | <p>Panel Discussion</p> |

- Plenary V (Operational Aspects)

| | |
|---|--|
|  |  |
| <p>Session Chair
<i>(William Wang)</i></p> | <p>Speaker
<i>(Ling Su)</i></p> |
|  |  |
| <p>Speaker
<i>(Yil Seob Lee)</i></p> | <p>Speaker
<i>(Yuppadee Javroongrit)</i></p> |
|  |  |
| <p>Questions from the audience</p> | <p>Audience</p> |

- Plenary VI (Regulatory Guidance/Perspective/Issues)

| | |
|---|--|
|  |  |
| <p>Session Chair
<i>(Martha A. Brumfield)</i></p> | <p>Speaker
<i>(Herng-Der Chern)</i></p> |
|  |  |
| <p>Speaker
<i>(Jian-hua Ding)</i></p> | <p>Speaker
<i>(Min Irwin)</i></p> |
|  |  |
| <p>Panel Discussion</p> | <p>Audience</p> |

- Breakout Session 1 (Regional Specific Issues)



Moderators



Audience

- Breakout Session 2 (Site Management, Data Management and GCP) & Group Photo



Moderators



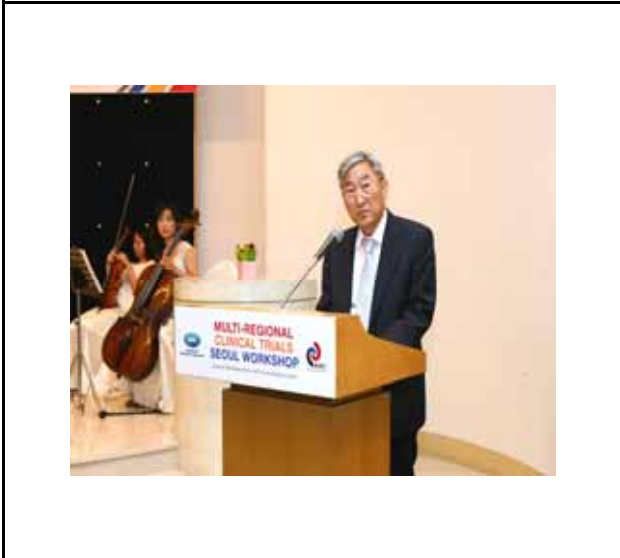
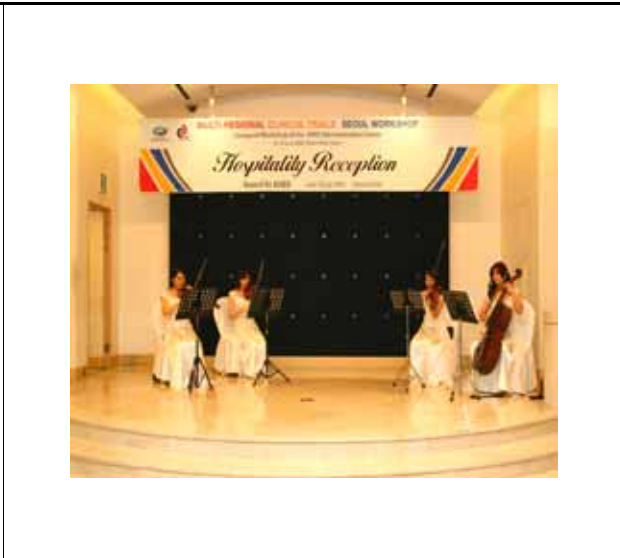
Audience

Discussion



Group Photo

- Hospitality Reception



- Breakout Session 3 (Multi-Regional Clinical Trials Design Issues that Clinical Researchers Should Understand in Order to Succeed) & Breakout Session 4 (Specific Therapeutic Areas)



Moderators



Audience

- Plenary-Feedback



- Summary /Next Steps/ Adjournment & Group Photo



Summary / Next Steps / Adjournment



Summary / Next Steps / Adjournment



Group Photo

- RHSC (Regulatory Harmonization Steering Committee) Meeting



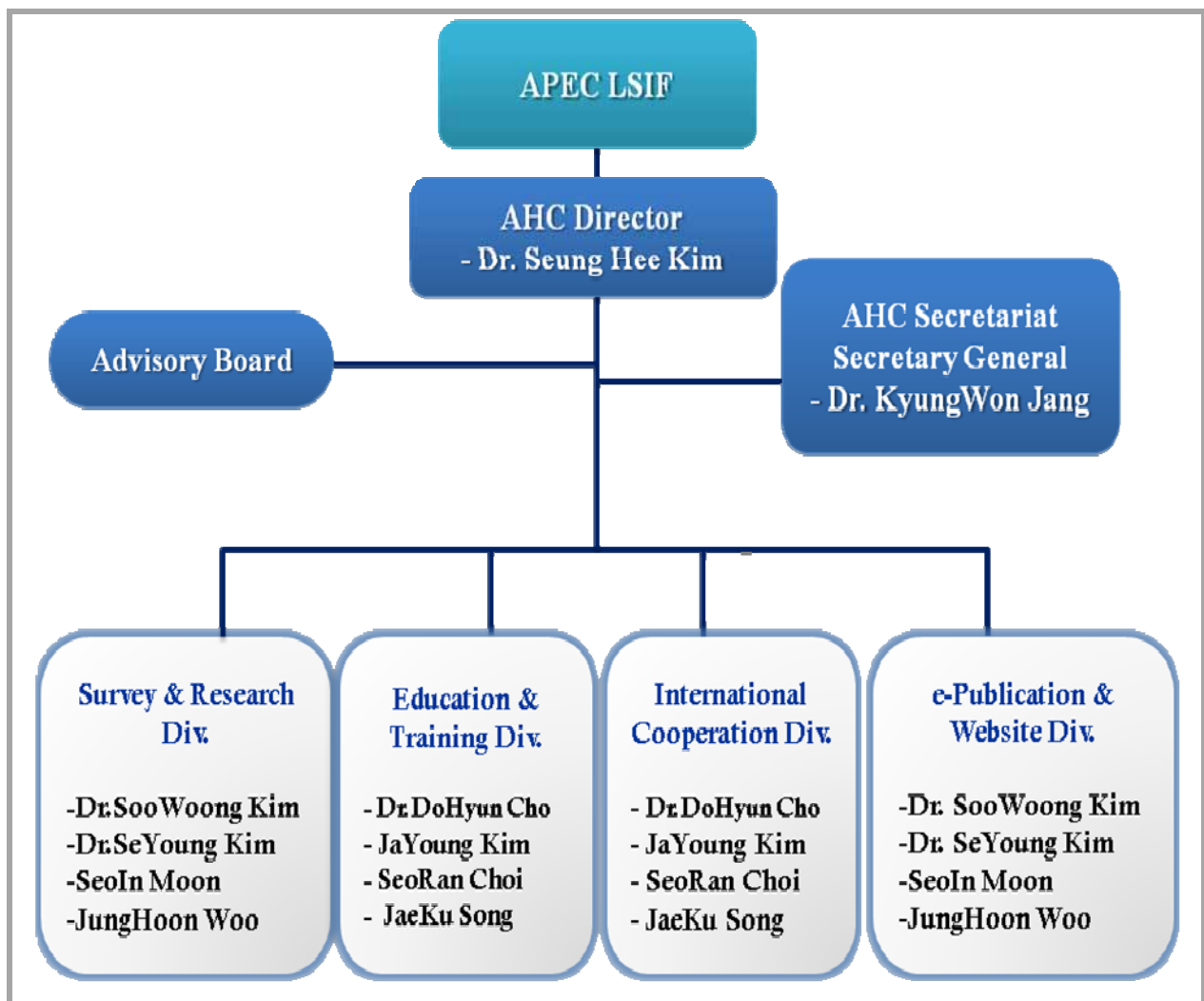
- GMP Pharmaceutical Ware Visit / Clinical Site Visit



IV. APEC Harmonization Secretariat (KHIDI)

AHC Secretariat is provided by KHIDI (Korea Health Industry Development Institute). KHIDI is a non-profit government affiliated organization, working in cooperation with the government, industry, and academia in policy making, promoting industry, and supporting R&D. The secretariat is in charge of operating the AHC, directed by APEC LSIF and APEC LSIF RHSC, and with support of the AHC Advisory Board.

Organization Structure






Staffing & Contacts

Secretary General

| | | |
|-------------------|---|--|
| Dr. KyungWon Jang |  | jangkw@khidi.or.kr
+82-2-2194-7385 <ul style="list-style-type: none"> • Oversee operations and management of the Secretariat |
|-------------------|---|--|




Program Coordinator

| | | |
|------------------|---|--|
| Dr. SooWoong Kim |  | poohaa00@khidi.or.kr
+82-2-2194-7457 <ul style="list-style-type: none"> • Team leader <ul style="list-style-type: none"> - Division of Survey & Research - Division of Education & Training - Division of International Cooperation - Division of e-publication & Website |
| Dr. SeYoung Kim |  | seykim@khidi.or.kr
+82-2-2194-7210 <ul style="list-style-type: none"> • Coordinate Activities on: <ul style="list-style-type: none"> - Division of Survey & Research - Division of e-publication & Website |
| JaYoung Kim |  | jayoungkim@khidi.or.kr
+82-2-2194-7435 <ul style="list-style-type: none"> • Coordinate Activities on: <ul style="list-style-type: none"> - Division of Education & Training - Division of International Cooperation |

Program Support

| | | |
|-----------------------------|--|--|
| <p>SeoRan (Rachel) Choi</p> |  | <p>srchoi@khidi.or.kr
+82-2-2194-7323</p> <ul style="list-style-type: none"> • Support Functions on: <ul style="list-style-type: none"> - Division of Education & Training - Division of International Cooperation • AHC Communications, Administrative Affairs |
| <p>SeoIn (Simon) Moon</p> |  | <p>seoin@khidi.or.kr
+82-2-2194-7323</p> <ul style="list-style-type: none"> • Support Functions on: <ul style="list-style-type: none"> - Division of Survey & Research - Division of e-publication & Website • AHC Communications, Administrative Affairs |
| <p>JaeKu (Jack) Song</p> |  | <p>theweaks@khidi.or.kr
+82-2-2194-7234</p> <ul style="list-style-type: none"> • Support Functions on: <ul style="list-style-type: none"> - Division of Survey & Research - Division of Education & Training - Division of International Cooperation - Division of e-publication & Website |

Special Support

| | | |
|-----------------------------|---|---|
| <p>Dr. DoHyun Cho</p> |  | <p>suicho@khidi.or.kr
+1-212-826-0900</p> <ul style="list-style-type: none"> • KHIDI NY Office Director • Regional Communications & Cooperation focal point <ul style="list-style-type: none"> - North and South American Region |
| <p>Minhye Park</p> |  | <ul style="list-style-type: none"> • KHIDI NY Office • Regional Communications & Cooperation focal point <ul style="list-style-type: none"> - North and South American Region |
| <p>Jung Hoon (John) Woo</p> |  | <p>johnwoo@khidi.or.kr
+65-6884-7926</p> <ul style="list-style-type: none"> • KHIDI ASEAN Office (Singapore) Director • Regional Communications & Cooperation focal point <ul style="list-style-type: none"> - ASEAN, APEC Secretariat |



Members:

Front Row (Left to Right): Seoln (Simon) Moon, SeoRan (Rachel) Choi, Dr. Kyung Won Jang, JaeKu (Jack) Song, Dr. GangYong Park

Second Row (Left to Right): Dr. SeYoung Kim, Dr. SooWoong Kim, HwaSeok (Brian) Suh, JaYoung Kim

Location and Contact Details

**APEC Harmonization Center
Secretariat**

Korea Health Industry Development
Institute (2 Fl.)

57-1 Noryangjin-Dong, Dongjak-Gu,
Seoul 156-800, Republic of Korea

Tel) +82-2-2194-7323

Fax) +82-2-822-8811

E-mail) ahckorea@khidi.or.kr

Website) www.apec-ahc.org

