신약개발을 위한 임상시험 국제 워크샵

- 국제협력 및 기술동향 -

Clinical Development of New Drug

- Global Cooperation and Technical Update -

March 31(Wed), 2004

Auditorium
Clinical Research Institute
Seoul National University Hospital

Korea Health Industry Development Institute

Clinical Trial Center, Seoul National University Hospital

Korea Pharmaceutical Manufacturers Association

Korean Research-based Pharmaceutical Industry Association

Scottish Development International

Korean Society for Clinical Pharmacology and Therapeutics

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Opening Address

Ladies and Gentlemen, On behalf of the Organizing Committee of the symposium entitled "Clinical Development of New Drug; Global Cooperation and Technical Update," I would like to express my sincere gratitude to all participants here to join and discuss current issues of global new drug development, especially focused on Asian perspectives.

.

Since late 90's I think ICH-Harmonization process has quite influenced on Drug development and registration strategy in Korea. We adopted Good Clinical Practices Regulation quite early in Korea, and subsequently many of collaborative efforts among regulatory body, academy and industry contributed to high quality clinical trials which we see these days. Regulatory changes in new drug approval adopting ICH E5 guideline and permission of clinical investigation of foreign drugs under developmental phase in Korea were also timely evolution toward globalization of Korean drug regulations.

However, in spite of our previous dramatic changes in highly debated issues in new drug regulation, details of recent progress in efficiency of new drug development and global contribution of Korea seem to be not satisfactory compared with the progress in other non-ICH countries including APEC region.

Those might be due to our lack of understanding or interest in rapidly changing global environment or lack of channel to share international information.

At this moment, I would like to express special thanks to Korea Health Industry Development Institute promoting this valuable symposium to provide updated information on current global drug development strategy. Today we will hear many excellent presentations and current global perspectives in new drug development. I hope that this symposium will serve as a good opportunity for us to think of our future

perspectives in new drug development and global contribution of Korea as a whole.

March 31, 2004

Sang-Goo Shin, MD,PhD

Director

Clinical Trial Center/SNUH

Congratulatory Remark I

Dear colleagues and distinguished guests:

It is my great honor and pleasure to be here with you; and I extend a warm welcome to all participants from abroad. Particularly, I would like to convey my sincere appreciation to Dr. Kyeong-Ho Lee, President of Korea Health Industry Development Institute (KHIDI), Dr. Sang-Goo Shin, the Director of Clinical Research Institute, SNUH (Seoul National University Hospital) and the organizers of this wonderful workshop on the Clinical Development of New Drugs in Korea.

As we all know, international cooperation in the clinical study is the key factor in the promotion of the new drug development and clinical trials. Through the exchange of knowledge and friendship, a workshop such as this one would bring the international cooperation to a higher level. In this respect, I would like to congratulate for already a successful workshop.

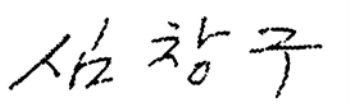
A successful development of a new drug requires orchestrated efforts from the academia, industry and regulatory agency. As a commissioner of the Korea Food and Drug Administration, I believe that the role of the administration in the clinical development of new drugs is to implement the internationally harmonized guidelines in a timely manner and to maintain the consistency in the decision process. As an example, new guidelines for IND and GCP that conform to those of the ICH have been previously introduced by the administration. Through the reorganization of the administration and the recruitment, we are trying to expand the personnel of the branches that deal with the decision process. We hope that, by maintaining the expertise of our staff, the consistency is retained in the review process. We will continue to do so to further assist the industry and the academia. However, our efforts will not be fruitful without the reactions from the industry and academia. Efforts from the industry and academia such as the establishment

of infrastructure for clinical studies are cruicial in the realization of the successful development of new drugs. In that sense, this workshop may represent a meaningful starting point and I have high hope for the active role of the KHIDI and SNUH in the clinical development.

Again, I would like to congratulate you on the organization of the workshop on Global Cooperation for Clinical Development. I sincerely hope that you will find this workshop to be a place for the exchange of science and friendship.

Thank you very much.

March 31, 2004



Chang-Koo Shim, PhD

Commissioner

Korea Food and Drug Administration

Congratulatory Remark

Dear distinguished colleagues and guests:

I am extremely honored to address at today's International Workshop on Clinical Development of New Drugs.

First of all, I would like to express my appreciation to the organizing committee for their superb job in preparing for this workshop. It was also a pleasure to meet many distinguished delegations from the field of clinical drug development. I would like to thank them all for their valuable contributions.

As you all know, we are experiencing a rapid transition in paradigm shifts of socio-economic values from industrial society to information society and subsequently to bio-society. Increased global concerns and greater demands for the improvement of quality of life by provision of healthy human life is a key feature of this new bio-society.

This transition to bio-society has started with the rapid technological development in genetic engineering, which made human beings able to manipulate living organisms. Such new technology has become the basis for the development of new drugs, which created significant benefits to human health as well as huge business opportunities in the pharmaceutical industry.

Clinical trial is a key step in the development of new drugs by enabling us to scrutinize the quality and safety of new drug candidates before putting them into medical practice. However, we have to face the reality that there are differences and gaps in technological capacities and regulatory programs between the leading countries and ours in clinical development of new drugs.

Therefore, we are here to exchange information on the latest clinical development of new drugs. In this regard, today's workshop will be extremely valuable for the pharmaceutical industry, researchers in academia, and medical doctors and nurses in hospital to learn more about the current knowledge and approaches for clinical development of new drugs.

Finally, I wish that all participants have an enjoyable and useful time at this symposium.

Thank you for your kind attention.

March 31, 2004

Kyeong-Ho Lee, PhD

President

Korea Health Industry Development

Scientific Program

12:30-13:30	**Registration**
13:30-13:35	**Welcome Address** **Sang-Goo Shin, President, Clinical Trial Center, SNUH**
13:35-13:45	**Congratulatory Remarks** **Chang-Koo Shim, Commissioner, KFDA** **Kyeong-Ho Lee, President, KHIDI**
Session I	**Clinical Drug Development : Global Perspectives** **Chairman : Kyung-Hwan Kim, Yonsei University**
13:50-14:30	***Changing Strategy to Meet the New Demand for Global Drug Development*** **John Hall, Quintiles**
14:30-15:10	***ICH - Past, Present and Future*** **Cynthia Wang, Merck Research Laboratory**
15:10-15:50	***Global Vision for Drug Development – an Asian Perspective*** **Edmund Tsuei, Pharma Development Operation, Asia Roche**
15:50-16:00	**Coffee Break**
Session II	**Clinical Drug Development ; Special Considerations** **Chairman : Hoon-Kyo Kim, Catholic University**
16:00-16:40	***Pharmacogenomics : Impact/Application in future New Drug Development*** **In-Jin Jang, College of Medicine, Seoul National University**
16:40-17:20	***The Impact of Bridging studies in Asia*** **Carly Anderson, CMR International Ltd.**
17:20-18:00	***Good Review Practice is the First, but not the Least, Step for the KFDA*** **Howard Lee, CDDS, Georgetown University**

18:00-	**Closing Remark** **Yong-Kwon Yeom, KHIDI**

Session I

Clinical Drug Development : Global Perspectives

- ***Changing Strategy to Meet the New Demand for Global Drug Development***
  John Hall, Quintiles

- ***ICH - Past, Present and Future***
  Cynthia Wang, Merck Research Laboratory

- ***Global Vision for Drug Development – an Asian Perspective***
  Edmund Tsuei, Pharma Development Operation, Asia Roche

Session 1

Changing Strategy to Meet the New Demand for Global Drug Development

JOHN M HALL, PhD

Senior Vice President, Strategic Development, Quintiles Ltd., Scotland

ABSTRACT

The presentation outlines the challenges faced by the pharmaceutical industry as it copes with the loss of major products through patent expiry. New technologies are being introduced which will change the way in which new leads are generated and which will result in an increase in product candidates entering early development and will also change the way patients may be diagnosed and treated. Those involved in the clinical development process will need to adapt and develop new strategies to cope with these demands. The use of Electronic Data Capture leading eventually to E-clinical processes are discussed together with new approaches to clinical trial design which have the potential to reduce development time and costs while improving patient safety.

Changing Strategy to Meet the Growing Demand for Drug Development

John M Hall PhD
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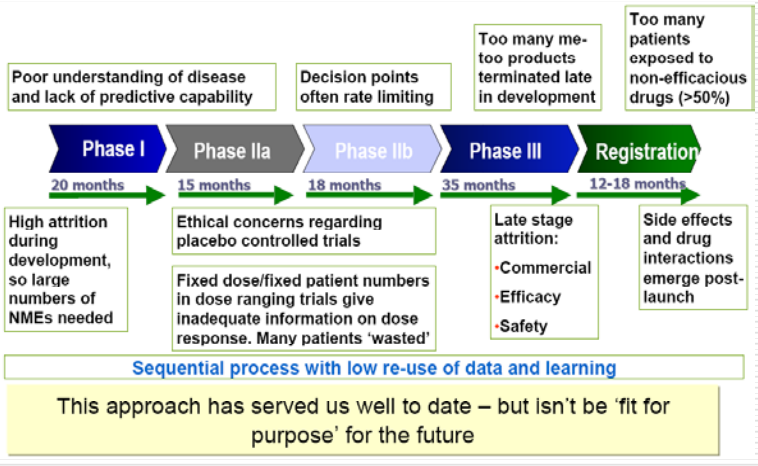
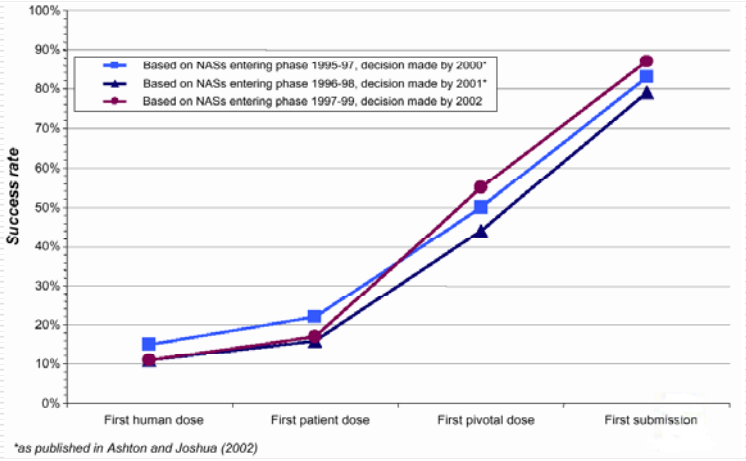
The Traditional Development Process is Inefficient

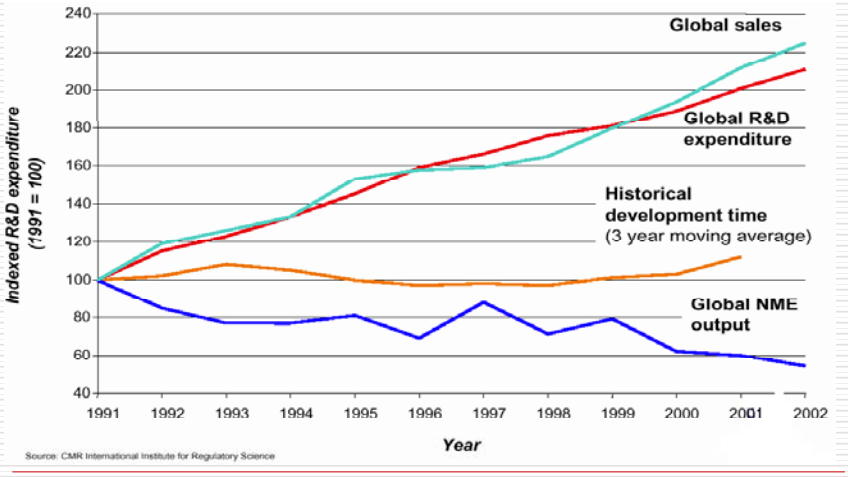


Source: S. Arlington IBM Consult

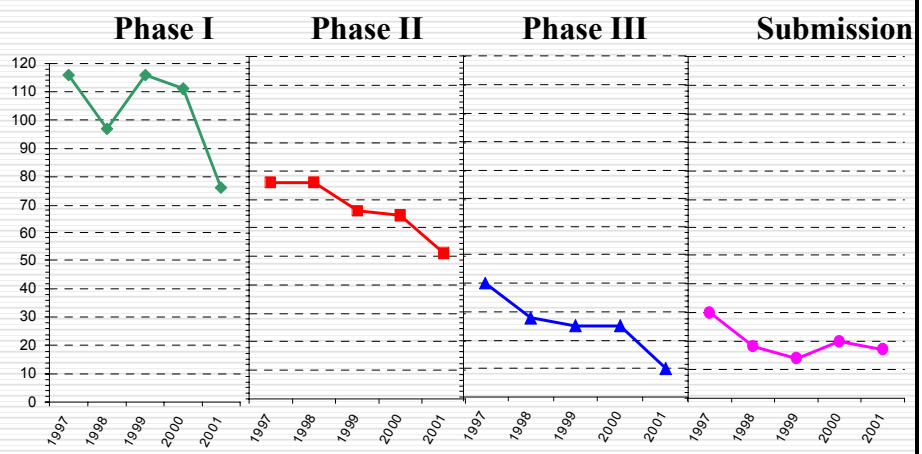
Risk by Development Stage



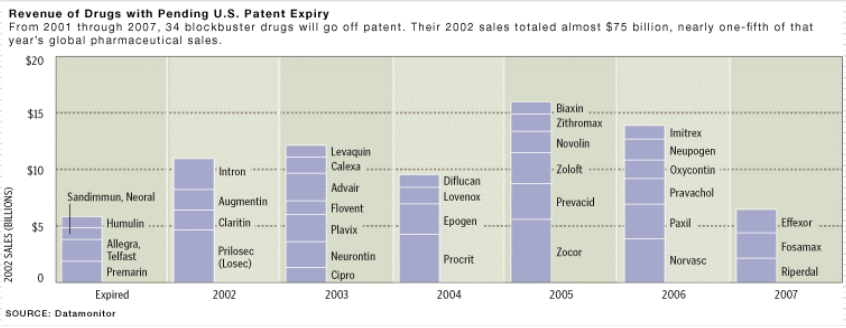
Industry Trends



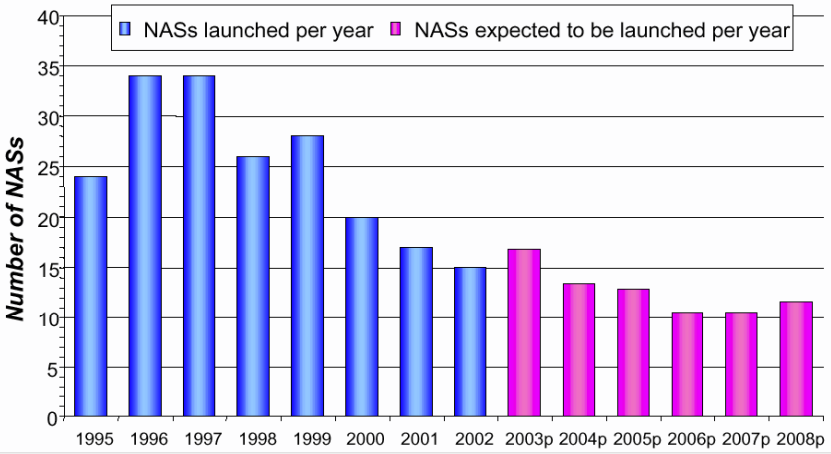
Number of New Active Substances Entering Each Phase of Development by Year(1997-2001)



Revenue of Drugs with Pending U.S. Patent Expiry



Industry Productivity



Emphasis on Discovery

R&D Investment by development phase (2001)

Clinical (Phases II & III)	**30.3**
Discovery	**25.1**
Non-clinical	**17.2**
Other	**10.0**
Phase I	**6.4**
Regulatory	**5.8**
Post Marketing	**5.2**

In the past five years Discovery spend has outgrown the overall growth rate of R&D expenditure

Emergence of New Discovery Tools

GENOMIC TECHNOLOGIES	SCREENING TECHNOLOGIES
• Antisense Technique • Comparative Genomics • Differential Display • DNA Microarrays • EST And Genomic Sequence Database Analysis • Expression Cloning • Expression Profiling • Functional Expression • Functional Genomics • Gene Arrays • Gene Chip • Gene Knockouts • *In Situ* Hybridisation • KO Animal Models / Cell Systems • Literature Screen • Model Systems • Nucleotide Seq & Syn • Overexpression Models • Positional Cloning • Protein Production (*E. Coli*, Mammalian Vaculovirus) • QPCR • Reporter Assays • Taqman • Transcript Profiling • Transgenesis • Yeast 2 Hybrid • Transgenic Models	• LTS, MTS, HTS, UHTS • Bioscout • cDNA Library Database • Cell-Based Assay • ELISA • Fluorescence, FP-(Fluresence Polarization), FQ-(Fluoresence Quenching), FRET-(Fluoresence Residence Energy Transfer) • Gene Family Screening • Homology Analysis • Cell Based, Biochemical, Usual Detection Methods (Bioluminescence, Fluorescence, OD), LTS • ICEN • *In Silico* Protein-Protein Interaction Prediction • Ligand Displacement Enzyme Inhibition • Luminescence • Miniaturisation • Radioactive • Random Knockouts Ligand Displacement • Reporter Assays, • Robotics & Automation W/ Multiple Assay Formats • SAR By NMR And Crystal Lead (X-Ray) • Sequence Search • Spa • Standard Binding Studies, Target Binding • Transactivation Assays

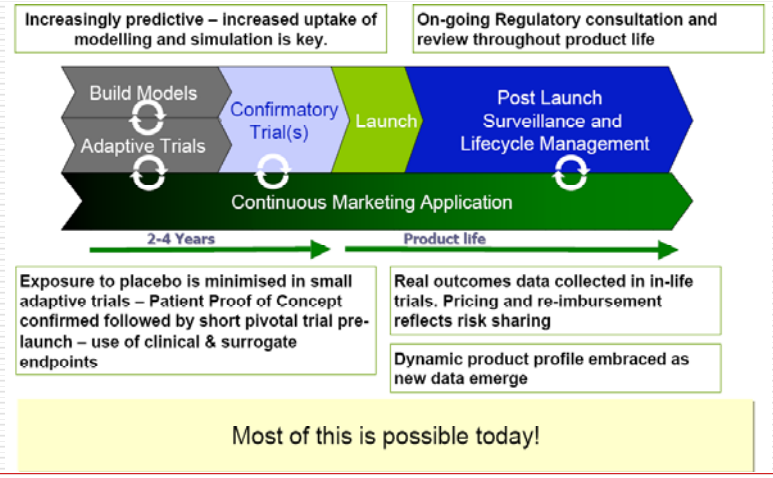
CMR International

Source:CMR International Discovery Performance Metrics Programme

What are the Consequences of These Trends for Clinical Development?

- Rapidly growing demand for new products means:
  - Need to re-think and dramatically improve clinical development (time and cost improvements)
  - Focus on rapid and effective proof of concept trials
  - Redesign of the trial process to take full advantage of available and emerging technologies
  - Redesign of clinical trial design to take advantage of novel statistical approaches
  - Re-evaluation of the traditional double blind placebo or comparator population approach to clinical development to take account of the emergence of individualised (genomic-proteomic based) medicine

A Future Strategy for Development?



Source: S. Arlington IBM Consulting

What are the Advantages of Electronic Data Capture (EDC) ?

- Access to Information:
  - One source for information, many users, many locations
  - Controls and security easy to implement
  - Communication of Information - Site, Sponsor, CRO
  - Simple presentation of information (charts, graphs etc)
- Merging and Integration:
  - Electronic documents
  - Electronic images (cardiograms, scans)
  - Raw eCRF data, meta data, derived data, lab data... ...Provided we have standards!

EDC Process gains

- Faster availability of clean study data provides an opportunity for more proactive trial management
- Investigator login provides opportunities to speed the recruitment process, and improved site trial management
- Technology provides opportunities for improved communication between monitor, site and sponsor/CRO
- Proactive data analysis could lead to early termination of study for potentially good (enough data) and bad (drug safety) reasons but both save time and money!

EDC Implementation Makes Possible an "E-Clinical" Vision

A fully integrated, web-enabled process that:

- Harmonizes and integrates the activities of various functional areas into one overall process
- Enables efficient and effective management of clinical trials in "real-time" – Adaptive Trial Design
- Facilitates collection, processing and, where necessary, reporting of data (including safety) in "real-time"
- Incorporates electronic data capture (EDC)
- Forces the development of standards to maximize integration capabilities

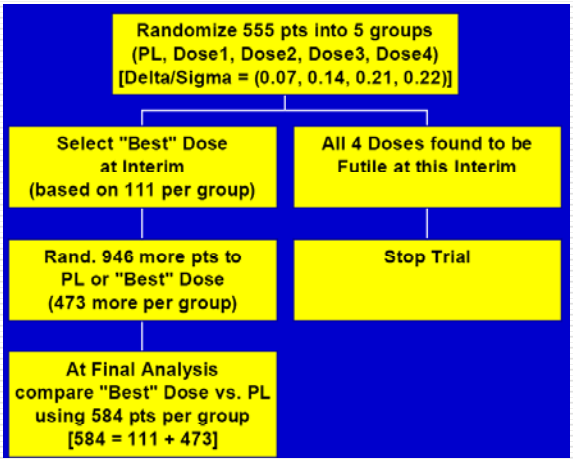
Where are Adaptive Designs Useful?

- Single Study Submissions (SSS)
  - Large multi-centre study with same Phase II & III endpoints
  - New stage of closely related disease
  - New patient population
  - New combination therapy
  - Orphan indication
- Where typically Phase II, Phase III#1 and Phase III #2 would be carried out in sequence
- In place of a typical multi-armed Phase III trial

Adaptive Phase II/III Design

- Combine dose selection and confirmatory stages
- Start with 2-5 doses & placebo
- Select "best" dose at interim and continue with "best" dose & placebo
- Stop development early if all doses are determined at interim to be ineffective
- Not suitable where major safety concerns are likely to apply

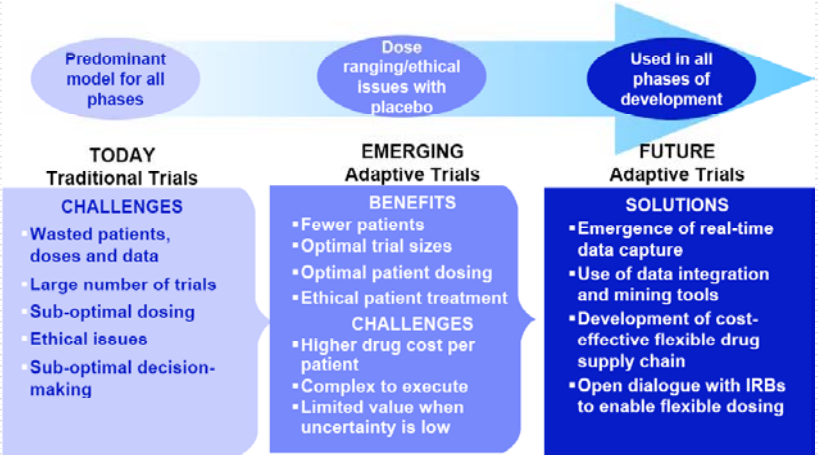
Flowchart for a Typical Adaptive Phase II/III Design



Benefits of Adaptive Designs Combined with E-Clinical Technology

- Improved patient safety
- Improved (speed/accuracy) adverse event reporting
- Fewer patients needed but increased power
- Reduced development costs (~30%)
- Reduced development times

A Future Strategy for Clinical Development



Source: S. Arlington IBM Consult

The Goal?

	Current Model	Future Model Targets
Time from Target Identification to Launch	12-14 Years	~3-5 Years
Pre-launch Cost of Development	~$800 million*	<$200 million
Success Rate from Entry into Man	5-10%	50% or better

Source: S. Arlington IBM Consult

Session 1

ICH – Past, Present and Future

CYNTHIA WANG, MD

Executive Director, Regulatory Affairs International at Merck and Co. Inc.

ABSTRACT

ICH- the International Conference on Harmonization started in the late 1980's. At that time, there was recognition that there were needs for dialog between agency and industry on the real and perceived differences in the requirements for products registration in the 3 regions. The objective was to identify areas for modification and harmonization which could lead to more economical use of human, animal and material resources without compromising safety.

Under the umbrella of the ICH steering committee which included regulators and industry representatives, an initial scope of work was identified which covered areas of quality, safety and efficacy. Over the ensuing years, the expert working groups have developed harmonized guidelines through a 5 step procedure leading to final incorporation into local guidelines and requirements. ICH conferences held in rotation in each of the 3 regions have tracked the progress in each of the areas. To date, there have been 6 conferences and over 50 guidelines have been harmonized. The scope has also been expanded to include multidisciplinary topics such as the Common Technical document [CTD].

With the globalization of clinical trials, the E6 Good Clinical practice [GCP] guideline and the E5 guideline on acceptability of foreign data have been of particular interest in this region. A number of countries have actually formally adopted these guidelines into their local requirements or informally put them into practice. The challenge will be to ensure consistent and harmonized implementation.

In addition to representatives of the 3 regions, there are also observers to the ICH from Canada, the Nordic countries as well as the World Health Organization [WHO]. In 1999, the Global Cooperation Group [GCG] was established under the ICH steering Committee. Its primary focus was to disseminate information on the ICH process. Over the years, its role has evolved into the development of activities with other harmonization activities. These include the Asia-Pacific Economic Cooperation [APEC], Association of South East Asian Nations [ASEAN] as well as groups in the Middle East, Africa and Latin America. GCG will be establishing the bridge between ICH and other non-ICH harmonization initiatives. A new mandate for the GCG was approved by the ICH steering committee last November. As the representative of the ICH steering committee, the GCG will be inviting representatives from these initiatives to be a member of the GCG. Through these efforts, the vision of global harmonization could become a reality.

International Conference on Harmonization – ICH

Past, Present and Future

Cynthia Wang M.D.

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ICH Overview

- Establishment of ICH
- ICH – the structure and the process
- The future of ICH
- The Global Cooperation Group

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ICH : Key Milestones

- 1989 : WHO ICDRA meeting – specific plans
- 1990 : Birth of ICH at EFPIA meeting
- 1991 : First ICH Conference in Brussels, then rotating through each of the 3 regions
- 1999 : GCG established by ICH SC
- 2003 : ICH 6 - the new GCG mandate

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Drug Development, Pre-ICH

- Significant disharmony in regulatory requirements
  - Duplicate testing (Q, S, E)
  - Net loss of time and resources
  - Delayed patient access to innovation drugs
- The Issue
  - Best practice not defined across regional regulations
  - Redundant local requirements
- The Solution
  - Harmonization, based on good science and best practice

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International Conference on Harmonization (ICH)

Aims

- Harmonizing technical requirements for pharmaceutical products
- Prevent unnecessary duplication of effort
- Ensuring that medicines are developed as efficiently and cost-effectively as possible

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ICH Terms of Reference

- Provide a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry on differences in technical requirements for product registration in the EU, USA and Japan
- Identify areas where modifications in technical requirements or greater mutual acceptance could lead to more economical use of human, animal and material resources, without compromising safety
- Make recommendations on practical ways to achieve greater harmonization

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International Conference on Harmonization (ICH)

Participants

- Regulatory Authorities
  - European Commission
  - Japan - Ministry of Health
  - USA - FDA
- Trade Associations
  - European Federation of Pharmaceutical Industry Association
  - Japanese Pharmaceutical Manufacturers Association
  - Pharmaceutical Research and Manufacturers of America
  - International Federation of Pharmaceutical Manufacturers Association
- Observers
  - Canada, Nordic Countries, WHO

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ICH Organization

- ICH Steering Committee
- Expert Working Groups
  - Quality
  - Safety
  - Efficacy
  - Multidisciplinary
- ICH Coordinators
- ICH Secretariat
- ICH Contact Network

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ICH Steering Committee

- 14 Members
  - Two from each of the six parties to ICH
  - Two from IFPMA
- 3 Observers
  - WHO
  - EFTA
  - Canada
- Functions
  - Oversees the progress of harmonization initiatives
  - Oversees the preparation of the Conferences

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ICH – The Process

Step 1
- Preliminary discussion of topic by EWG
- Preliminary draft
- Consensus draft to Steering Committee

Step 2
- Consensus draft to regulatory agencies for formal consultation - (6 months)

Step 3
- Comments collected
- Regulatory rapporteur amends draft
- Sign off by EWG

Step 4
- Steering committee endorses final draft

Step 5
- Recommendations incorporated into domestic regulations

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ICH - Present

- 6 International conferences
- Over 50 ICH guidelines have been finalized
- Common dictionary - MEDRA
- Common format
  - ICH E 3 Clinical study report
  - Common technical document CTD - Implemented July 2003
- ICH Vision
  - Maximize the success of ICH through effective and consistent guideline implementation
  - Outreach to other regions

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ICH Outside the 3 Regions

- Enthusiastic attendance at ICH conferences
- Adoption of ICH guidelines
  - E2 : Clinical Safety data management
  - E5 : Ethnic factors in the acceptability of foreign data
  - E6 GCP: Good Clinical Practice
- CTD concept
- Concept of Harmonization

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Evolution of the ICH Vision

- Maximize the success of ICH through effective and consistent guideline implementation
- Monitor new needs for harmonization
  - Update to include new Science/technologies
  - To avoid divergent regulations
- Outreach to other regions
  - Establishment of the Global Cooperation Group (GCG) in 1999

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Evolution of GCG Activities

- Initial focus was on sharing information on ICH and its guidelines
  - Series of brochures
  - Presentations at conferences
- In recent years, the focus has evolved
  - Provide opportunity for ICH to understand the needs of other regions
  - Active collaboration with non-ICH regional harmonization efforts

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Evolution of GCG Activities

- Criteria for partnership organizations established
  - Asia-Pacific Economic Cooperation (APEC)
  - Association of Southeast Asian Nations (ASEAN)
  - PAHO Pan American Network of Drug Regulatory Harmonization (PANDRH)
  - Southern Africa Development Community (SADC)
  - Gulf Cooperation Council (GCC)
- Three joint meetings in 2003—in coordination with ICH SC
- ICH 6
  - 'Partnerships in Harmonization' symposium :~700 attendees
  - A new mandate for the GCG

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GCG Mandate (1)

- GCG will represent of ICH SC outside ICH regions
- 'Permanent Representatives from other harmonization initiatives
- Criteria for Partnership with ICH
  - Defined group of countries harmonizing drug regulation
  - Science-based; clear scientific harmonization objectives
  - Currently active and meeting regularly
  - Mechanism to disseminate information on activities with ICH GCG

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GCG Mandate (2)

- Transparency
  - Meeting summaries on public ICH website
  - GCG mailbox will receive questions for GCG
- Process
  - Meetings will identify topics and process issues associated with harmonization for discussion and collaboration
  - SC will be consulted for approval on all activities before undertaken

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The New GCG

- Expanded membership and expanded work program
- GCG including new permanent representatives will continue to meet 2-3 times per year
- Work program will be developed
  - Harmonization topics and process issues
  - Discussion, collaboration
  - Potential for joint program of activities

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Session 1

Global Vision for Drug Development – An Asian Perspective

EDMUND TSUEI, PhD

Head, Pharma Development Operation, Asia, Roche Products Pty Ltd.

ABSTRACT

The global drug development climate is changing. Productivity has decreased over the past decade with increasing development cost and decreasing number of new medicinal products launched. Contributing to the increased development costs includes the increasing number of patients in drug development program. Approximately 42% of drug development cost is in clinical development. The slowing of growth of the global pharmaceutical market together with declined period of exclusivity for innovation further add economic pressure to improve efficiency of drug development. The fast-growing biotechnology sector has contributed to the change in the drug development landscape. Over the past decade, the percentage of biopharmaceuticals under development has almost doubled and they enjoy a higher success rate.

The pressure on faster and less expensive drug development without sacrificing quality has led to increasing participation of countries outside the traditional countries in Western Europe and North America. The number of foreign inspections by the US FDA has increased more than ten fold from 1991 to 2000.

The benefits of participating in global drug development will be discussed. Quality is an area where there cannot be any compromise. To achieve high quality, investigators must be supported by infrastructure – research coordinators, laboratories, pharmacies, hospital records, ethics committees, etc. Ethics in clinical trials are very topical at the moment and have received a lot of media attention. US FDA has been auditing institutional review boards since 1977 and quality of ethics review is considered to be an integral part of the overall study quality. For Korea and Asia to be competitive in global drug development, resources must be invested to develop infrastructure to ensure high quality as well as strict adherence to ICH GCP. Countries need to find efficient ways of utilizing scarce resources to achieve quality.

To maximize the shrinking period of exclusivity, clinical trials must be conducted in a time-efficient manner. Whilst patient availability gives the Asian region an advantage in terms of patient recruitment, investment in resources at regulatory agencies and ethics committee will shorten evaluation time and make the region an even more attractive place to conduct quality clinical trials. The US FDA users pay model has achieved significant reduction in evaluation of new drug applications.

Clinical drug development is a global business and competition is fierce. The investigators, institutions, regulatory agencies and the pharmaceutical industry will need to form a partnership and work together to achieve quality of the highest standard as well as time- and cost-efficient conduct of studies.

Session II

Clinical Drug Development : Special Considerations

- ***Pharmacogenomics : Impact/Application in future New Drug Development***
  In-Jin Jang, Seoul National University

- ***The Impact of Bridging studies in Asia***
  Carly Anderson, CMR International Ltd.

- ***Good Review Practice is the First, but not the Least, Step for the KFDA***
  Howard Lee, Georgetown University

Session 2

Pharmacogenomics: Impact/Application in Future New Drug Development

IN-JIN JANG, MD, PhD

Associate Professor, Dept. Pharmacology, Seoul National University
Clinical Pharmacology Unit, Seoul National University Hospital

ABSTRACT

The fact that that all diseases are in part genetic is the beginning of the recognition that genetic information can contribute to solving critical problems that face the new drug development, the rising cost and the attrition of candidates in the pipeline. Genetic information can help in the discovery process through helping to prioritize useful approaches; it can be used to support decision-making in early development and it can be used to better understand drug response. Pharmacogenomics has a huge potential as an innovative technology for drug discovery and development. It will deliver a new generation of medicines.

The application of toxicogenomics disciplines ranges from hypothesis testing of toxicity to safety evaluation. However, validation of the results for use in registration and marketing is limited and can only be evaluated on a case by case basis at the present time. As the science progress, the regulatory implications of toxicogenomic data will be transparent and lead to relevant guidance documents. In early clinical development, the use of pharmacogenetics improves decision making through: (1) increased understanding of PK

variability. (2) Increasing therapeutic windows by identifying required dose adjustments for predicted "outliers." (3) Reducing trial sizes by identifying robust responders in proof of concept trials. (4) Improved decision making by the use of pharmacogenetics to reduce placebo response rates, etc. Issues related to the use, development and implementation of predictive biomarkers must be addressed in late stage drug development: (1) Predictive value, sensitivity and specificity of markers. (2) Biological significance and validity of markers. (3) Parallel development of diagnostic with pharmaceutical compound. (4) And recruitment related issue of subject selection vs. all comers. Application of pharmacogenetics in post marketing will raise the issues such as (1) Logistics and feasibility of post-marketing pharmacogenomic application. (2) Dynamic label management. (3) Pharmacogenetic impact on post marketing surveillance. (4) Post-launch test integration, etc. Application of individual's genetic information to drug development has ethical, legal and societal Issues, too. Ethical guidelines and legal regulations including data protection may frame pharmacogenetic research.

There are many other issues raised in the "1st FDA-PWG-PhRMA-DruSafe Workshop: Pharmascogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making" regarding reference population, validation of technological platforms, sample collection timings, size/power, ethnic diversity, biomarkers, trial design such as inclusion/exclusion (stratification), exploratory data versus supportive or clinical decision making data, etc. Some of these issues are addressed in draft guidance "Guidance for Industry Pharmacogenomic Data Submissions." In the draft guidance, there are criteria for voluntary submissions of research data as a Voluntary Genomic Data Submission (VGDS) and also submission of genomic data that may be required under current regulations.

Despite many currently unresolved issues, pharmacogenomics and pharmacogenetics will be considered in all phases of drug development through greater clarity on the application of genetic biomarkers, optimization of

risk/benefit ratio by continued dialogue between academia, industry and regulatory scientists, etc.

Pharmacogenopmics: Impact/Application in Future New Drug Development

In- Jin Jang, MD, PhD

Department of Pharmacology, Clinical Pharmacology Unit & Clinical Trial Center

Seoul National University College of Medicine & Hospital

Definitions

Pharmacogenetic test: An assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics) including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors and other proteins

Pharmacogenomic test: An assay intended to study interindividual variations in whole- genome or candidate gene single- nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response

Definitions

Biological marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Valid biomarker: A biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results

Definitions

Valid biomarker:

- Known valid biomarker: A biomarker that is measured in an analytical test system with well- established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results
- Probable valid biomarker: A biomarker that is measured in an analytical test system with well- established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. A probable valid biomarker may not have reached the status of a known valid marker because, for example,
  - The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.
  - The data elucidating its significance, although highly suggestive, may not be conclusive

Markers of Genetic Variation

Polymorphism: *A genetic variation that is observed at a*

SNP	A single base change in DNA which can lead to altered gene expression or altered activity of the expressed protein
Insertion/deletion polymorphism	The insertion or deletion of a repeating segment of DNA, which can affect gene expression and/or activity
Haplotype	The sum of all the SNPs in a given gene or region of a chromosome. Since a haplotype reflects the net effect of all the individual SNPs, consideration of haplotypes is more likely to result in statistically significant associations with phenotype than are individual SNPs
LOH[1]	During tumor formation, regions of chromosomes may be lost. These patterns alter protein expression levels in the tumor and can be indicative of drug response
Gene amplification[1]	The synthesis of extra functional copies of genes, which can lead to altered levels of protein expression
Methylation patterns[1]	The methylation state of a promoter affects the level of gene expression, which in turn may affect drug response

Human polymorphic cytochrome P450 enzymes

Enzyme	Major Variant Alleles	Mutation	Consequence	Allele Frequency	
				Caucasians	Orientals
CYP2A6	*CYP2A6*2*	L160H	Inactive enzyme	1–3	0
	*CYP2A6*3*	2A6/2A7 conversions	Not known	0	0
	*CYP2A6*4*	Gene deletion	No enzyme	1	15
	*CYP2A6*5*	G479L	Defect enzyme	0	1
CYP2C9	*CYP2C9*2*	R144C	Reduced affinity for P450 reductase	8–13	0
	*CYP2C9*3*	I359L	Altered substrate specificity	7–9	2–3
CYP2C19	*CYP2C19*2*	Aberrant splice site	Inactive enzyme	13	23–32
	*CYP2C19*3*	Premature stop codon	Inactive enzyme	0	6–10
CYP2D6	*CYP2D6*2xn*	Gene duplication/multiduplication	Increased enzyme activity	1–5	0–2
	*CYP2D6*4*	Defective splicing	Inactive enzyme	12–21	1
	*CYP2D6*5*	Gene deletion	No enzyme	4–6	6
	*CYP2D6*10*	P34S, S486T	Unstable enzyme	1–2	50
	*CYP2D6*17*	T107I, R296C, S486T	Reduced affinity for substrates	0	N.D.
CYP2E1	*CYP2E1*2*	R76H	Less enzyme expressed	0	1
	*CYP2E1*3*	V389I	No effects	<1	0
	*CYP2E1*4*	V179I	No effects	<1	N.D.
CYP3A4	*CYP3A4*2*	S222P	Higher K_m for Substrates	3	0
	*CYP3A4*3*	M445T	Unknown	0	<1

*N.D., not determined. This allele has a very high frequency among Black Africans and African Americans.

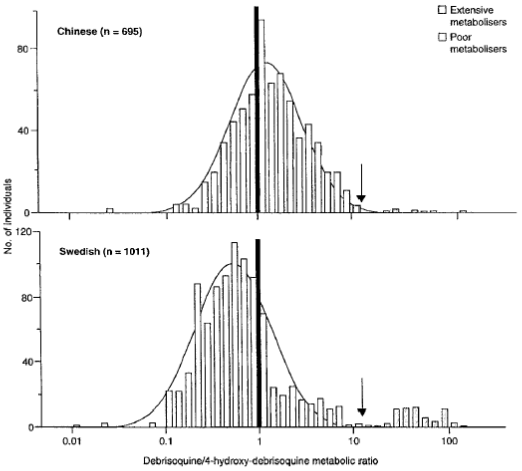
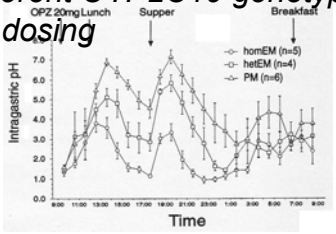


FIG. 10. *Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio in Chinese and Swedish Caucasian healthy individuals.*

The arrows indicate a metabolic ratio of 12.6, the antimode between extensive metabolizers and poor metabolizers as established in Caucasian populations. A thick line is drawn at a metabolic ratio of 1.0. Most Chinese extensive metabolizers have a ratio >1, while most Swedish extensive metabolizers have a ratio <1 (from Bertilsson et al., 1992).

Clinical significance of DME polymorphism

Median data on 24-hour intragastric pH profiles in the different CYP2C19 genotype after omeprazole 20 mg dosing



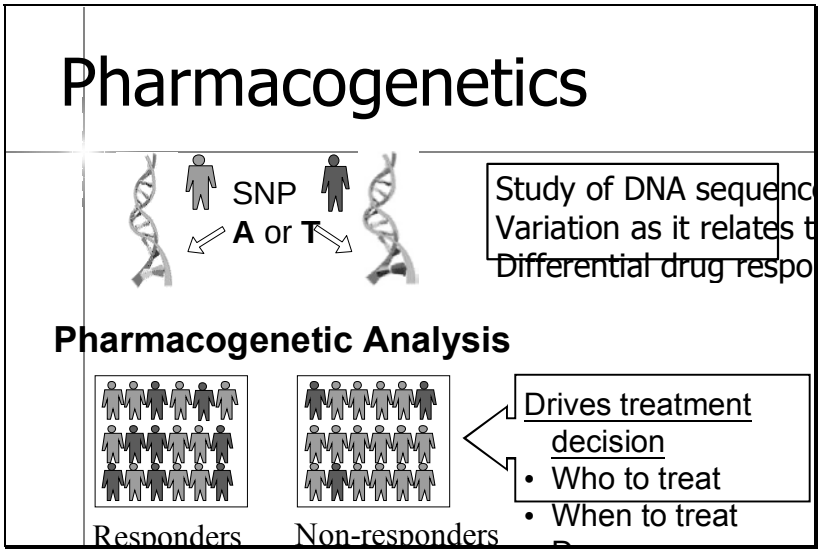
Clin Pharmacol Ther 1999;65:552-561.

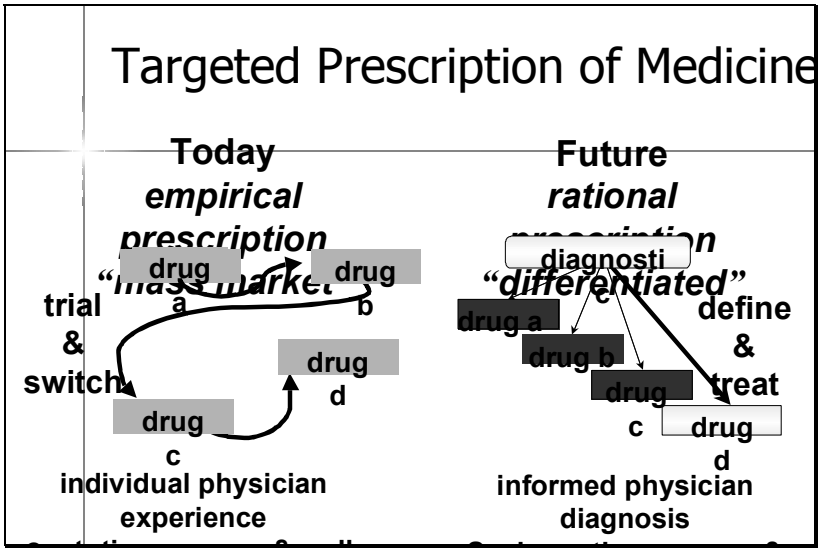
PK difference between CYP2C19 genotype

PD difference

Genotype is required to rationalize the dosing

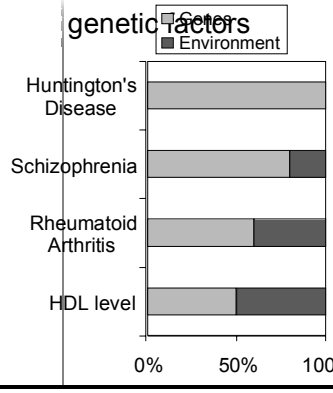
PK: pharmacokinetics, PD: pharmacodynamics


Pharmacogenetics
SNP
A or T
Study of DNA sequenc
Variation as it relates t
Differential drug respo
Pharmacogenetic Analysis
Drives treatment decision
• Who to treat
• When to treat
Responders
Non-responders


Targeted Prescription of Medicine
Today
empirical prescription
"mass market"
drug a
drug b
drug c
drug d
trial & switch
individual physician experience
Future
rational prescription
"differentiated"
diagnosti
drug a
drug b
drug c
drug d
define & treat
informed physician diagnosis

We Are Studying Genetic Diseases…

Heritability: The proportion of the disease that is due to genetic factors



Hereditability in PK

CL_{ren} ; intra-indiv var (within indiv)
inter-indiv var (between indiv)

$Var_{(between)} = Var_{(environ)} + Var_{(gen)} + Var_{(measurement)}$

$Var_{(within)} = Var_{(environ)} + Var_{(measurement)}$

$Var_{(gen)} = Var_{(between)} - Var_{(within)}$

Fraction of Var d/t genetic factor =
$[Var_{(between)} - Var_{(within)}] / Var_{(between)}$

Ex) ethanol(ADH) 0.57
dextromethorphan (CYP2D6) 0.97
Metformin (450 ml/min) 0.91

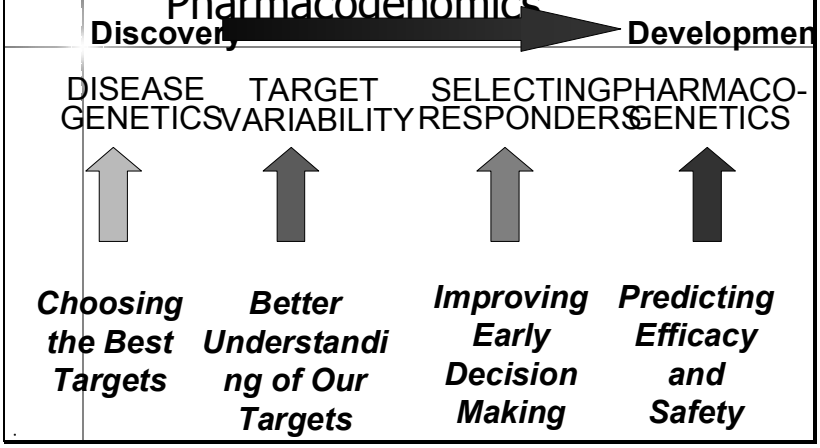
Current Drug Development

- Limited targets
- Costly
- Inefficient
- Significant ADR
- Poor response rate

Pharmacogenomics can help drug development

- Creating opportunities to increase the value of the drugs we develop using genetics
  - Obtain greater understanding of disease
    - Predict disease severity, onset, progression
    - Identify genetic subtypes of disease
    - Aid in discovery of new drug targets
  - Distinguish subgroups of patients who respond differently to drug treatment
  - Aid interpretation of clinical study results

Applying Pharmacogenomics



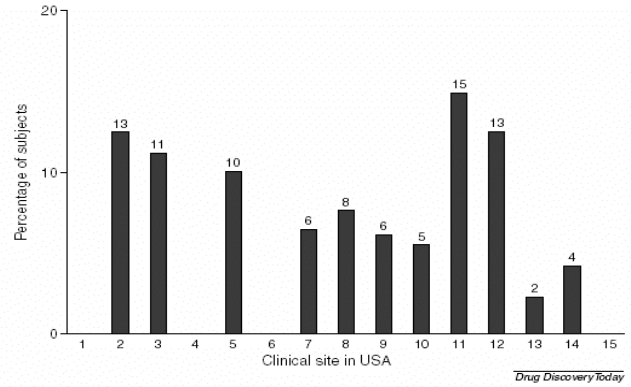


Figure 1. The incidence of CYP2D6 poor metabolizers (PMs) across 15 clinical trial sites in the USA. The population is primarily Caucasian. The average percentage of PMs across all sites was 6%; the range was 0%–15%.

Cancer: a Model for PG Approaches

Genetics of Cancer → **Phenotype of Cancer**

- Accumulation of molecular events
  - LOH
  - Oncogene activation
  - Tumor suppressor inactivation
- Stages of phenotype
  - dysplasia/premaligant
  - differentiation
  - invasive
  - metastases

Accumulation of molecular events

Tumor Phenotype

Need for In Vitro Diagnostics

- The expectation for a *genomic* medicine is one that is marketed with an IVD test
- IVD's may become an essential component of drug labelling…..expectation for testing prior to prescription
  - 6-mercaptopurine
    - thiopurine S-methyltransferase deficiency: 1 in 300
- Practical and economic issues for regulators as well as healthcare delivery infrastructures

Testing and Quality

- SNP Assay Validation; standardized sample & technology
- Reference Population; case by case
- Gene expression arrays; reliability concern (precision, accuracy, interlaboratory reproducibility)

Ethical issues

Ethical Guidelines for Analytical Research on the Human Genome/Genes (March 29, 2001)

The present Guidelines do not apply to the registration-oriented clinical studies and post-marketing surveillance of drugs to be conducted under the Pharmaceutical Affairs Law.

<Ethical guidelines by three ministries>

However,

- ***In actual PG applied clinical trials, it is considered that this ethical guideline should be followed.***
- ***Many different interpretations of this ethical***

Informed Consent

- Utilizes a separate consent for donation of a blood sample which will be anonymized prior to analysis.
- Participation is optional.
- Consent to "use a small sample of my blood to study the chemicals which make up all of my genes and contain my genetic information."
- Purpose for collecting sample is defined.
- Clearly states that information identifying the subject will not be included with the blood sample.
- NO INFORMATION WILL BE MADE AVAILABLE TO SUBJECT OR ANY OTHER PARTICIPANT OR MY PHYSICIANS.

Categories for Genetic Research Samples and Data*

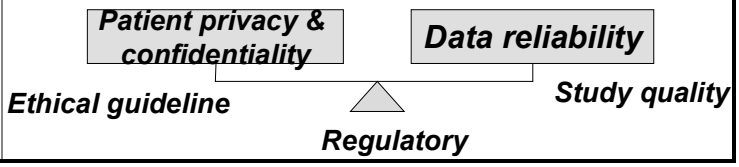
- **Identified Samples/Data** are those labeled with personal identifiers such as Name or Social Security Number. Use of a clinical trial subject number does not make the sample/data identified.
- **Coded Samples/Data** are those labeled with a clinical trial subject number that can be traced or linked back to the subject only by the investigator. Samples do not carry any personal identifiers.
- **De-Identified Samples/Data** are double coded and labeled with the unique second number. The link between the clinical study subject number and the unique second number is maintained, but unknown to investigators and patients. Samples do not carry any personal identifiers.
- **Anonymized Samples/Data** are double coded and labeled with the unique second number. The link between the clinical study subject number and the unique second number is deleted. Samples do not carry any personal identifiers.
- **Anonymous Samples/Data** are those that do not have any personal identifiers and identification of the subject is unknown. Anonymous samples may have population information (e.g., the samples may come from patients with diabetes, but no additional individual clinical data).

*From the Pharmacogenetics Working Group Working Paper 1

How to manage information security

- ***Genomic data for registration should be auditable to confirm data reliability.***
- ***How should we collect and handle personal genomic samples and data with high security?***

Harmonized procedures of sample collection, storage, analysis are necessary.



Ethnicity and genetic variation drug response

- Individual drug response vs ethnicity
  - For DMEs the key difference is a genetic one
  - Similarly for other genes
- Clinical trials can take account of key genetic variation
  - Where correlation between genetic variation and drug response is close this can give greater understanding of ethnic differences

Need for Education

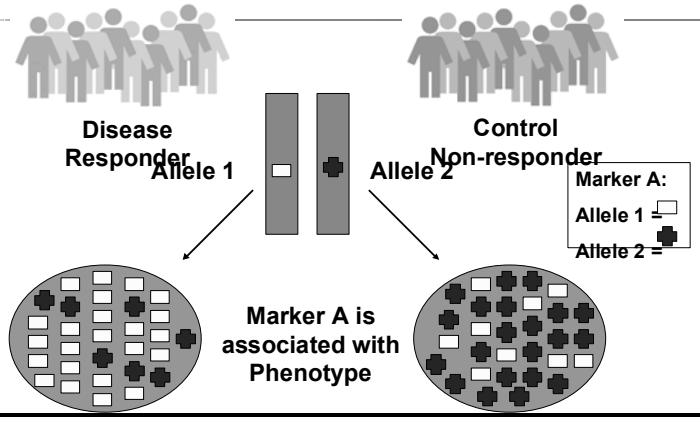
- *Industry*
- *Regulatory*
- *Investigator, Clinical Research Coordinator*
- *IRB members*
- ……
- *Physicians*

Frequent opportunities for exchange of information &

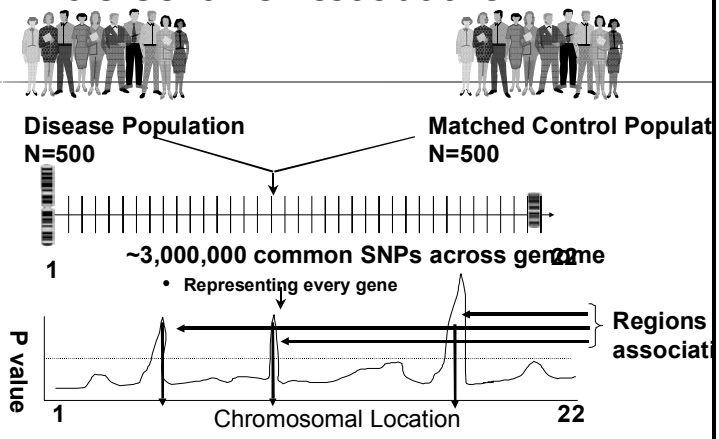
Candidate Gene vs. Whole Genome

- **Candidate Gene Approach**
  - Hypothesis dependent
  - Drug target or genes in the target pathway
  - Drug metabolizing enzyme genes
  - Genes that play a role in the disease
  - Limited by our understanding of disease
- **Whole Genome SNP Map**
  - Hypothesis-independent
  - New statistical methods needed to mine data

Human Genetic Association Study



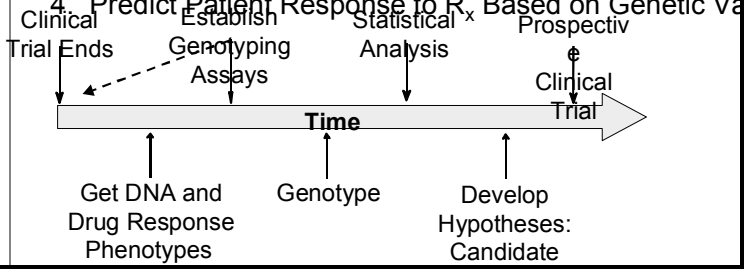
Whole Genome Associations



Informatics to ID gene(s) mapped to associated

Strategy in Pharmacogenomic Research

1. Collect Patient DNA from Clinical Trials
2. Identify Genetic Variation
3. Correlate Genetic Variation with Clinical Response
4. Predict Patient Response to R_x Based on Genetic Va



Pharmacogenomics related to drug response

Gene	Drug	Functional Consequence
Metabolism		
CYP2C9	Warfarin	Slow metabolism, increased risk of bleeding
CYP2C19	Omeprazole	Rapid metabolism, decreased efficacy
TMPT	Azathioprine	Toxicity and efficacy in leukemia
Target gene		
ADBR2	Salbutamol	Efficacy in asthma
5HT2A	Clozapine	Long term outcome in tx of schizophrenia
Stromelysin-1	Pravastatin	Risk of coronary artery restenosis
a-adducin	Thiazides	Efficacy in treatment of essential hypertension
"Unrelated" toxicity		
KCNE2	Clarythromycin	Risk of developing long QT syndrome

Generating Hypotheses: DMEs or Drug Transporter Mechanisms

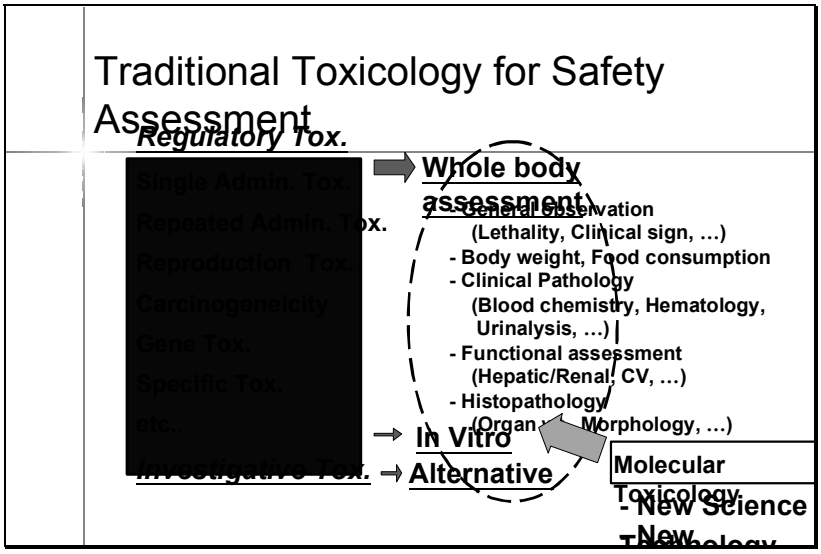
- Are there genetic differences in key drug metabolism pathways?
- Do transporter protein genotypes influence bioavailability?
- Are levels of active metabolites influenced by genetic variation?
- Do allele frequencies vary among ethnic groups?

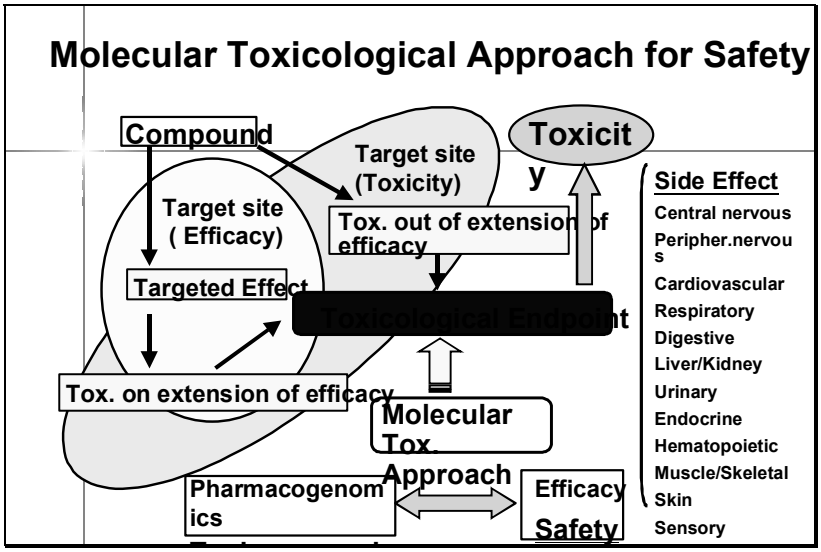
Generating Hypotheses: Disease Genes

- Are there known genetically-defined patient subpopulations with more uniform disease characteristics?
- Are there known genetic markers for populations at-risk for the disease?
- Are there known genetic predictors of clinical outcomes?
- Are there known genetic differences among ethnic groups?

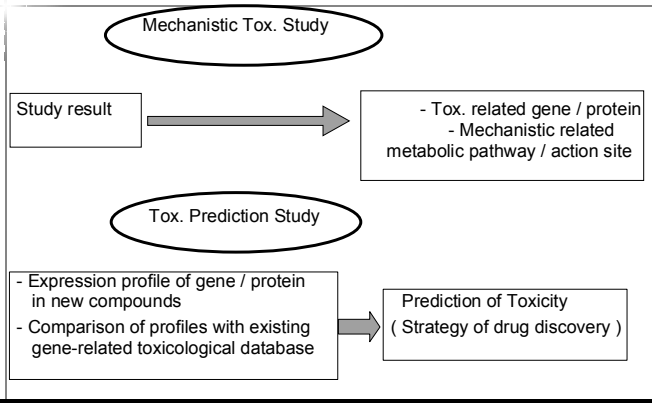
Generating Hypotheses: Drug Target or Related Pathways

- Which genotypes used in Discovery's screens/assays? Are they found in the disease population?
- What are the functional consequences of different genotypes?
- Does drug binding/activity differ among variants?
- Any genetic differences in related pathways influencing drug activity (e.g., ligand turnover; upstream/ downstream signaling)?
- Do any inherited diseases result from mutations in drug's target?
- Do allele frequencies vary among ethnic groups?


Traditional Toxicology for Safety Assessment
Regulatory Tox.
Single Admin. Tox.
Repeated Admin. Tox.
Reproduction Tox.
Carcinogeneicity
Gene Tox.
Specific Tox.
etc.
Investigative Tox.
Whole body assessment
- General observation (Lethality, Clinical sign, …)
- Body weight, Food consumption
- Clinical Pathology (Blood chemistry, Hematology, Urinalysis, …)
- Functional assessment (Hepatic/Renal, CV, …)
- Histopathology (Organ, … Morphology, …)
In Vitro
Alternative
Molecular Toxicology
- New Science
- New


Molecular Toxicological Approach for Safety
Compound
Target site (Toxicity)
Target site (Efficacy)
Tox. out of extension of efficacy
Targeted Effect
Toxicological Endpoint
Tox. on extension of efficacy
Molecular Tox. Approach
Pharmacogenomics
Efficacy
Safety
Toxicity
Side Effect
Central nervous
Peripher.nervous
Cardiovascular
Respiratory
Digestive
Liver/Kidney
Urinary
Endocrine
Hematopoietic
Muscle/Skeletal
Skin
Sensory

Significance of Toxicogemonics / Toxicoproteomics Approach --- Mechanistic investigation & prediction of toxicity



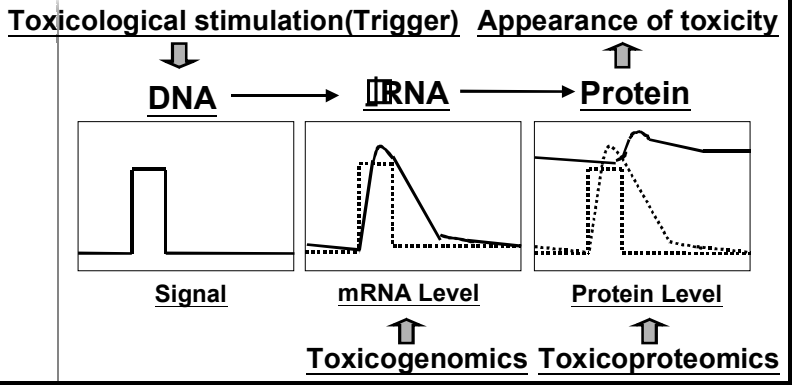
Genes on the toxicology gene chip

Functional group	Type of genes
Stress response	Oncogenes
	Acute phase response
	Signal transduction
Cell proliferation	Transcription factors
	Cell cycle regulation
	Growth factors and receptor
	Tumor suppressors
Apoptosis	Caspases
	Apoptic regulators
DNA damage	DNA repair
	DNA morphology
Inflammation	Cytokines
	Vasoregulators, etc.
Oxidative stress	Glutathione metabolism
	Oxidase
	Protein thioles
Drug metabolism	Cytochrome P450s
	Glutathione transferase

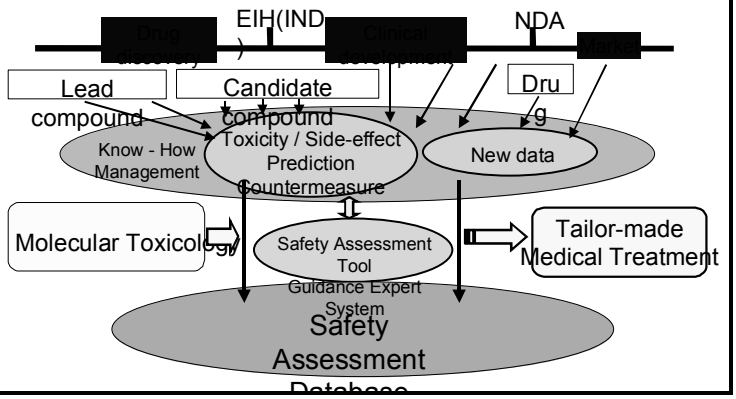
Toxicogenomics? Toxicoproteomics? Meta

DNA	:	Genome (Genomics)	→ Gene-polymorphism (SNPs etc)
RNA	:	Transcriptome (Transcriptomics)	→ Gene expression profile (mRNA)
Protein	:	Proteome (Proteomics)	→ Protein synthesis profile (Molecular function)
Biochemicals (Metabolites)	:	Metabolome (Metabolomics)	→ Metabolite-pattern profile (Urine, etc)

ming of gene expression and protein synth
--- Toxicological assessment point ? ---



Safety Database for Tailor-made Medical Treatment



The 2002 Workshop on Pharmacogenetics/Pharmacogenomics in Drug Development and Regulatory Decision-Making
--- Sponsored jointly the FDA, DruSafe PhRMA and PWG ---
May 16 - 17, 2002 at the University of Maryland, Shady Grove Conference Center

Toxicogenomics in Drug Development
: Where are we today & where are we g

Industry and regulatory agencies viewed this meeting as an o
to discuss how such data should be included/evaluated in IND
applications.

Where are we now ?
Where would we like to be ?

Preclinical Pharmacology, Safety and Toxicogenomics

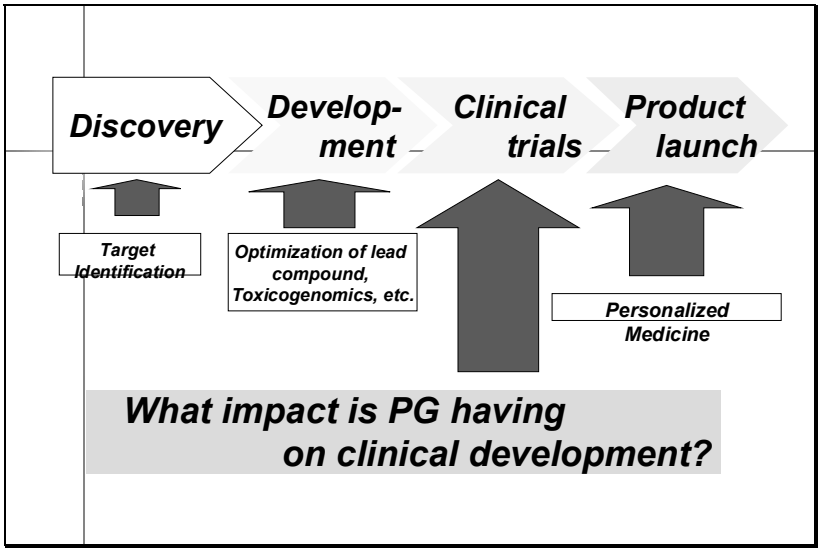
- Toxicogenomics to Predict Human Toxicity; major potential use is Ho. generation
  - many different effect of toxin aside from changes in gene expression (membrane integrity)
  - may miss critical gene expression changes in minor cell population
  - lack of functional knowledge → need multidisciplinary approach (cellular, tissue level, protein expression)
- Routine Use for Making Safety Decision; sample should not be collected in routine GLP toxicity → not necessarily correlate with changes in protein expression
- Value to Industry and Regulatory; generate Ho. & provide possible explanation
- Guide Study Design or Species Selection for Long- Term Toxicology Studies; dog & monkey genomes are not well characterized
- Reference DB for Potential Human Toxicity Prediction; rat & human, gene expression, histopathology, hematology & clinical chemistry data with know toxin/drug at multiple dose and time → prioritize drugs by predicting and avoiding likely human toxicity

As a conclusion,

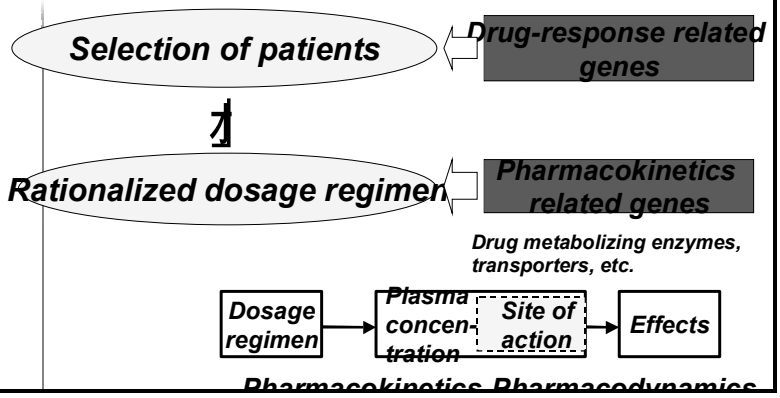
The application of toxicogenomics discip
ranges from hypothesis testing of toxicit
safety evaluation.
However, validation of the results for use
registration and marketing is limited and
only be evaluated on a case by case basi
present time.
As we progress, the regulatory implicatio
toxicogenomic data will be transparent a

Box 1. Issues raised by pharmacogenic studies.

- Pharmacogenic study design
- Data management
- Regulatory submission rules
- Informed consent participation
- Protection of confidential information
- Standardization of clinical end points
- Tissue banking procedures
- Appropriate use of pharmacogenic data obtained from retrospective analysis
- Data mining and sharing from valuable and limited clinical material



For personalized medicine

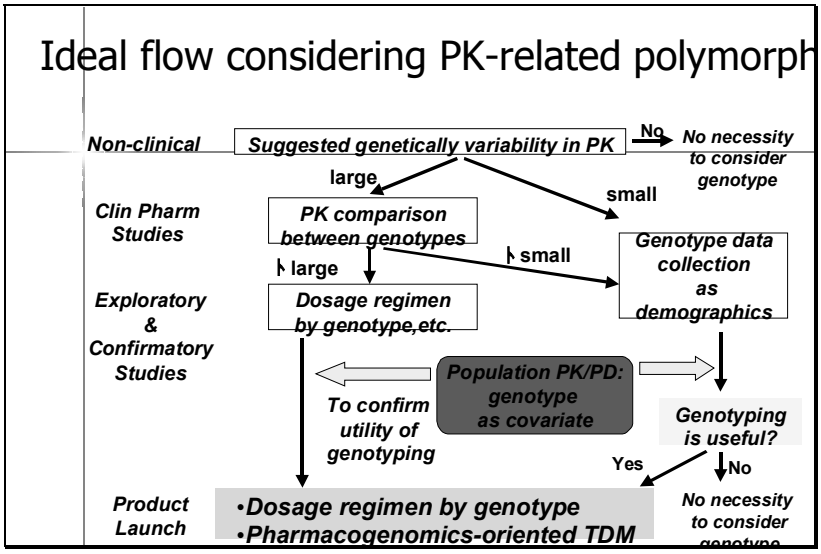


Points of concern in clinical development considering DME polymorphism

- *Genotype could not fully predict patient's metabolic capacity because many other factors influence pharmacokinetics.*
- *Pharmacokinetic comparison between genotypes is not sufficient in small number of healthy volunteers*
- *What evidence supports the efficacy of a lower dose in patients with poor metabolic capacity?*

Important to evaluate the exposure-response relationship with genetic demographics

Ideal flow considering PK-related polymorph



Early Clinical Development (Phase I/II);

- 80% of Pharmacogenomic tests in >70 IND/NDAs are CYP DNA (drug metabolism) related
- Rational Use;
  - use mRNA expression profile for inclusion/exclusion vs validate association by replication first.
  - Exclude subject with potential risk for AE/nonresponse vs included as in the real- world (close monitoring).
  - Blood collection in all studies vs in narrowly defined (type of study or phase)

Early Clinical Development (Phase I/II);

When to be used for Inclusion/ Exclusion (Stratification) or to be Explored Post Hoc?;

- Not for FIH studies, except for well- established variants (ex CYP2D6, 2C19, 2C9).
- Unique opportunity for relationship among genetic variants and AEs or gene expression profile (if tissue is available).
- Correlate with preclinical data (DME, transpoters, targets, pharmacological pathways).
- Include all genotype in PoC studies (dose may adjusted according to genotypes).
- Genotypes treated as other covariates but more confirmation before used for stratification (covariate in the post hoc analysis)

Early Clinical Development (Phase I/II);

When to be used for Inclusion/ Exclusion (Stratification) or to be Explored Post Hoc?;

- Factors considered in the context of stratification (inclusion/ exclusion)
  - Therapeutic area; *more willing to stratify in oncology vs depression*
  - Safety or efficacy; *for safety than efficacy*
  - Magnitude of effect; *narrow therapeutic index than wide one*
  - Stage of knowledge of the variant or expression profile;
    - CYP2D6 → not exclude PM if therapeutic benefit expected,
    - May not enough information to exclude target gene variant in Phase II
  - Allele frequency of the variant;
    - common allele frequency (> 15%) stratify,
    - if < 10% consider 2 separate studies.
    - Some safety, dose- ranging studies in minor subgroup can be done postmarketing.
  - Dose response; *evaluate in both group without rationale*
  - Other factors; *biological validity, extent of replication, number of genes or SNPs, optimal timing/tissue handling for RNA expression, etc*.

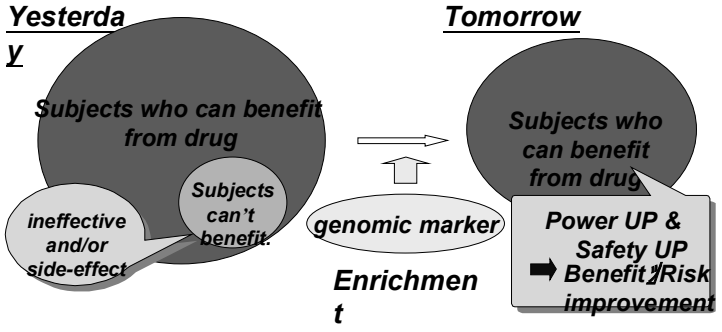
Early Clinical Development (Phase I/II);

- When/How Sample Collected for Genotyping/mRNA expression profile/SNP profile?
  - Scientific rationale; polymorphic DME, drug interaction study involving polymorphic DME, variant affecting safety (long QT gene), DME enzyme not fully understood before,
- How Predictable AE or Non-response Affect Risk/Benefit Assessment and Labeling?
  - Factors considered before genotype for dosing;
    - safety, seriousness of AE
    - consequences of non-response
    - incidence of clinical outcome
    - variability in the clearance
    - how well an AE can be managed
    - education of physicians

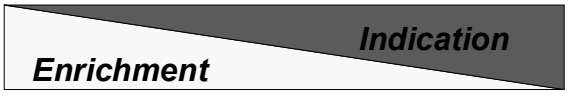
For Patient Selection

- ***In case of identifying the drug-response genomic marker in clinical development***
- ***In case of genetically targeted population has been clearly determined***

Impact of drug-response genomic markers



Enrichment & Indication



- **Possibility to prove efficacy & safety**
- **Narrow indication**

- **Possibility to prove efficacy & safety**
- **Broad indication**

- *Proof of concept vs. practical effectiveness?*
- *Safety should be evaluated in all population, not limited to enriched subject?*

How could we keep balance between enrichment & indication?

Issues for genomic marker discovery

Association ≠ Causality!!!

Retrospective analysis starting from drug-response phenotype

Necessary

- *Multiplicity/Sensitivity*
- *Confounding*

Prospective confirmatory trial with fully informative population

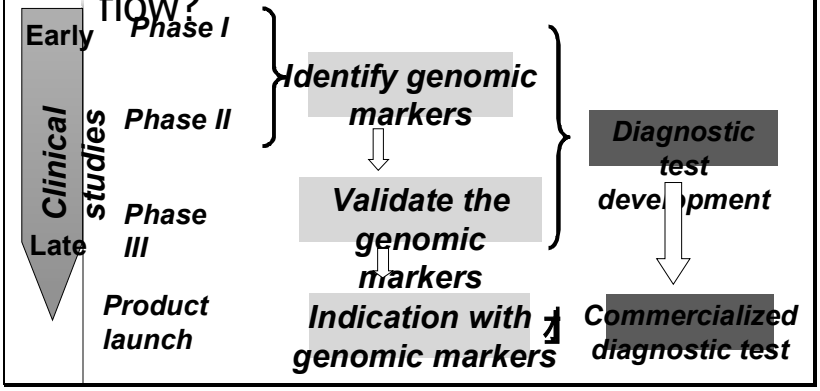
Late Clinical Development (Phase III);

- Background;
  - Role in late phase are further exploration of genetically defined population or the confirmation of pharmacogenetic data to support labeling and approval of otherwise unregisterable drug.
  - Questions without definitive answers now are; retrospective study for registration?, what extent need to be replicated? post hoc study for registration? Acceptable data? Ethnic diversity?
- How Influence Safety & Efficacy data before Registration?
  - robustness of results,
  - identifiable patients?
  - Will be used only in this enriched population in practice?
  - Diagnostic test must be available

Late Clinical Development (Phase III);

- Data from Samples from Previously Completed Clinical Study;
  - retrospectively collected sample but prospectively tested → already unblended; only for Ho. Generation vs has own design and protocol, blined analysis; acceptable for registration
  - Statistical power of genetic analysis
  - Study population of original study; not randomized for genetic test
  - Careful collection and storage of sample
  - With adequate informed consent
  - Nature of tests to be used
- Need an independent prospective trial with genotype in the basic design
- Use of anonymized Samples or Data? → data should be linked to patient identity for registrational use otherwise for Ho generatio0n.
- What charateristics for Association Data? Case- by- case. Replication not always possible, Statistical challenge. False negative or false positive
- Implication of Ethnic Diversity

What changes will PG bring in clinical development flow?



What products are genomic marker especially valuable for?

Products with

- *marginal efficacy*
- *narrow therapeutic window*

Products for

- *disease with irreversible progression*
- *disease which needs long term to evaluate the drug-response*

What products are easy to find genomic marker?

With objective & quantitative end point for phenotype determination

ex) diabetes, hyperlipemia, etc.

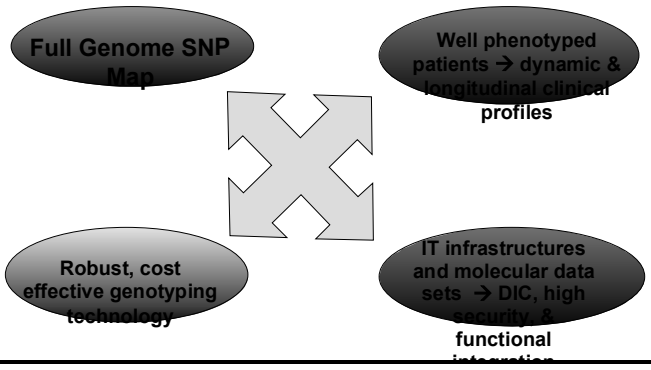
But, easy to monitor without genomic marker?

- *Highly needed for CNS drug*
- *Cancer would be difficult to predict response by analysis of blood specimen.*

Adverse Drug Reactions: A Growing Problem

- Drug-related mortality and morbidity estimated to cost U.S. health care system $177Bn in 2000
  - Represents over 10% of total U.S. health care spending
  - Nearly double the 1995 estimate
  - Approximately equal to the costs of medicines
    - Ernst and Grizzle, J. Am Pharm Assoc 2001; 41:192-9
- During the past 25 years, 1 in 5 medicines were found to have serious side effects that were not recognized at the time of marketing
  - Lasser et. Al. JAMA 287(17):2215-2220.
- The rate of drug withdrawals has not changed over time

Key Requirements for Functional & Clinical Genomics



Abbott-Genset Zileuton Genetics Project
(a phenotype-to-genotype approach)

- Zileuton; @ 4% of subjects → elevated AST/ALT
- Selected 37 candidate genes
  - Zileuton metabolism and mechanism
  - Hepatic homeostasis
- 200 markers (4 - 6 SNPs/candidate genes)
- 69 case & 104 control genotyped;
- A case control association study
- Identified 2 genes; (+) in 30% of target population

Abacavir of GSK

- A potent HIV-1 nucleoside reverse transcriptase inhibitor
- High incidence of severe hypersensitivity (on average 5%) → 2-4 death per 10,000 treated patients
- Two studies; HLA-B polymorphism (*HLA B5701)*
  - Prospective study of 200 patients
    - 18 case; 14 (+) marker, 4 carrier in 167 tolerant patients
    - 78% sensitivity, 98% specificity (100% by haplotype with 2 more markers)
  - Retrospective case/control study
    - 85 cases/115 control
    - Sensitivity 46%, specificity 96% (55% & 99% with Caucasian only)
- Ethnic difference; 9 African descent cases → no carriers
- Reduce incidence from 9% to 2.5% by genotyping in Australian group

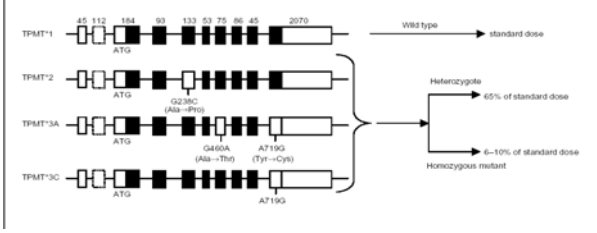
Is the association of HLA B-57 found in minority samples?

(CNA30032 Subjects: Summary of Allelic Test Results, GSK Data on File)

Ethnicity / Gender	Cases / Controls	Allele 57 Freq. Cases / Controls	Allelic Association p
All Ethnicities	165 / 139	17% / 2%	2.51×10^{-11}
Whites	82 / 74	23% / 1%	7.27×10^{-10}
White Males	56 / 52	23% / 1%	1.34×10^{-7}
White Females	26 / 22	23% / 2%	2.69×10^{-3}
Blacks	36 / 29	8% / 5%	0.07
Black Males	21 / 19	10% / 8%	1.00
Black Females	15 / 10	7% / 0%	0.51
Hispanics	43 / 27	11% / 0%	1.27×10^{-2}
Hispanic Males	32 / 21	9% / 0%	0.08
Hispanic Females	11 / 6	14% / 0%	0.54

TPMT Polymorphisms Direct Dosing for Thiopurine Drugs

Figure 3. Putative schema for use of TPMT pharmacogenetics.

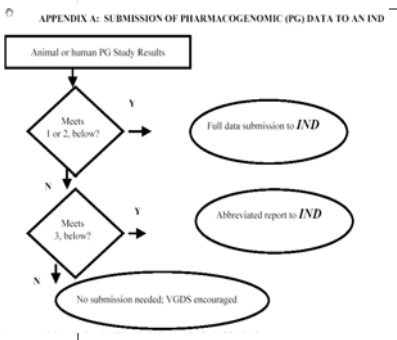


The diagram illustrates the use of TPMT pharmacogenetics to optimize 6-MP therapy for childhood ALL, as a model to demonstrate the prospective use of genotype to guide treatment. This approach requires prospective validation before it can be recommended for broad application in the optimization of thiopurine therapy. McLeod and Siva, Pharmacogenomics 3(1):89-98, 2002.

FDA Guidance: PGx Data Submissions

- Draft guidance published Nov 3, 2003
- What types of data required/not required to be submitted
- What types of data appropriate for/not appropriate for regulatory decision-making
- Procedures for voluntary genomic data submissions (IND, NDA, BLA)
- FDA to establish Interdisciplinary PGx Review Group (IPGRG)
- Open forum discussion between industry and FDA

Regulatory Perspectives; FDA Draft Guidance



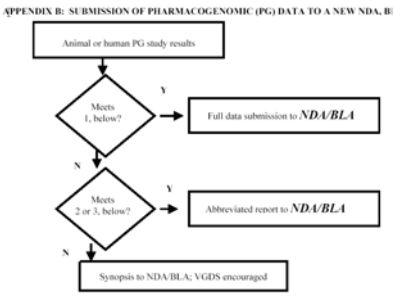
Pharmacogenomic data must be submitted to the IND under § 312.23 if ANY of the following apply

1. *The test results will be used for decision making in any clinical trial, or in an animal trial used to support safety. (For example, the results will affect dose selection, entry criteria, safety monitoring, or subject stratification.)*
2. *The sponsor is using the test results to support scientific arguments pertaining to, for example, the safety, effectiveness, dosing and pharmacology of the drug.*
3. *The test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known valid biomarker for a safety outcome in animal studies. If the information on the biomarker (example, human P450 2D6 656 status) is not being used for purposes 1 or 2 above, the information can be submitted to the IND as an abbreviated report.*

Submission to an IND is NOT needed, but voluntary submission is encouraged (i.e., information does not meet the criteria of § 312.23) if

4. *Information is from exploratory studies or is research data, such as from general gene expression analyses in cells/animals/humans, or single nucleotide polymorphism (SNP) analysis of trial participants. 662*
5. *Information consists of results from test systems where the validity of the biomarker is not established*

Regulatory Perspectives; FDA Draft Guidance



Reports of pharmacogenomic investigations should be submitted to the NDA in the following formats:

1. Provide reports on pharmacogenomic investigations intended by the sponsor to be used in the drug label or as part of the scientific database being used to support approval as complete submissions (not in the form of an abbreviated report, synopsis, or VGDS), including information about test procedures and complete data, in the relevant sections of the NDA or BLA. If the pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

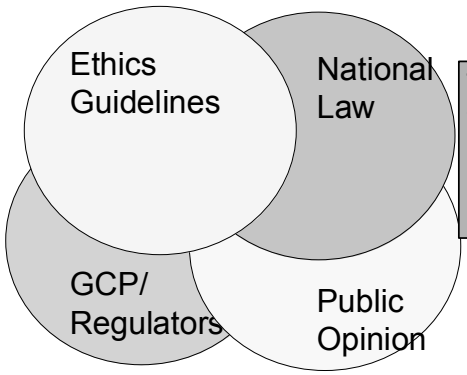
The following examples would fit this category.

- Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection, or effectiveness
- Pharmacogenomic test results that the sponsor proposes to describe in the drug label
- Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label

Reports of pharmacogenomic investigations should be submitted to the NDA in the following formats:

2. Submit reports of pharmacogenomic test results that constitute known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species, but that the sponsor is not relying on or mentioning in the label, to the Agency as an abbreviated report (not in the form of a synopsis or VGDS). (If a pharmacogenomic test of this type was conducted as part of a larger overall study, the reporting of the pharmacogenomic test results can be incorporated into the larger study report.)
3. Submit reports of pharmacogenomic tests that represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species to the NDA or BLA as an abbreviated report. (If the pharmacogenomic testing of this type was conducted as part of a larger study, the abbreviated report can be appended to the report of the overall study.)
4. There is no need to submit detailed reports of general exploratory or research information, such as broad gene expression screening, collection of sera or tissue samples, or results of pharmacogenomic tests that are not known or probable valid biomarkers to the NDA or BLA. Because the Agency does not view these studies as germane in determining the safety or effectiveness of a drug, the submission requirements in §§ 314.50 or 601.2 will be satisfied by the submission of a synopsis of the study. However, the Agency encourages the voluntary submission of the data from the study in a VGDS submitted to the NDA or BLA.

Constraints for PGx research



The constraints for pharmacogenetic research are of the same type as for all clinical trials

- but with an extra level of sensitivity

FDA Perspectiveson Genotypin & Clinical Efficacy/Safety Trials

- Familiar with “enrichment” study
- Genotype can be used in PoC, individualization, dose modification, and retrospective association possible (Abacavir)
- Need prospective confirmation
- If a treatment cannot be limited to genotyped population, true risk/benefit need to be assessed

EMEA CPMP Perspectives

- Concerns on post hoc association studies
  - Reliability & reproducibility
  - Need to confirm in a prospective study for sensitivity and specificity of genetic marker
- EMEA CPMP PGx Expert Group
- CPMP Position Papers:
  - PGx Terminology
  - Briefing Meetings
- Continuing discussion between industry and EMEA
  - EMEA Seminar June 2000
  - EMEA EFPIA DIA PGx meeting, Oct 2003

Pharma view: Submission of Genomics Data to regulators

- Rules for submitting research data are not established
- Pharma may be reluctant to submit data for fear of misinterpretation or over-interpretation
- Some companies actually avoid conducting genomics studies
- Both pharma and regulators limit their knowledge
- Ongoing constructive dialogue between regulators and pharma to reach a practical solution……..

Hurdles/Challenges to the Implementation of Pharmacogenetics

- Predictive power of genetic testing in relation to drug response
- Cost, availability, utility of diagnostics
- Societal responses
  - public attitudes
  - regulatory/legal frameworks

Conclusions

- PGx has great potential for the development of better, safer drugs
- PGx has become an integral part of drug and diagnostic development and considered in all phases of drug development
- Greater clarity on the most appropriate applications of genetic biomarkers is need
- Good co-operation between industry, academia and regulatory scientists is needed

Session 2

The Impact of Bridging Studies in Asia

CARLY ANDERSON, PhD

Project Leader, Centre for Medicines Research International Ltd.

ABSTRACT

One of the major uncertainties when registering new medicines in the emerging markets of Asia is whether local clinical trials will be needed and the type of studies that may be requested. The International Conference on Harmonisation (ICH) (E5) guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data offers a potential solution by setting criteria for the use of bridging studies that allow the extrapolation of pivotal clinical trials from one ethnic population to another. In 2001, CMR International conducted a survey of 17 companies on the implementation of ICH E5 in the three ICH regions and of 13 companies on its implementation in Asian countries (other than Japan). The study found that, although Asian authorities outside the ICH regions have not officially implemented the ICH guideline they were requesting that companies conduct bridging studies as defined by E5. Companies are in favor of the wider implementation of the guideline to facilitate the acceptance of foreign clinical data but there were concerns relating to the impact on resources and timelines, and the need for better understanding of the scientific basis and the implementation of the guideline.

Full publication available in: Drug Information Journal*, Supplements to Vol. 37, No 4 pp. 107–116, 2003 • 0092-8615/2003*

The Impact of Bridging Studies in Asia

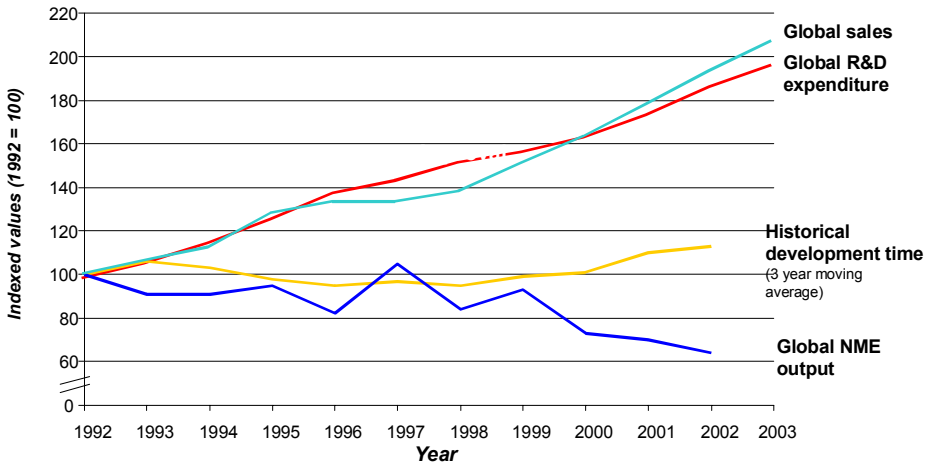
Dr Carly Anderson
CMR International Institute for Regulatory Science

Overview

- Global pharmaceutical environment
- Background
- CMR studies
- Results
- Conclusions

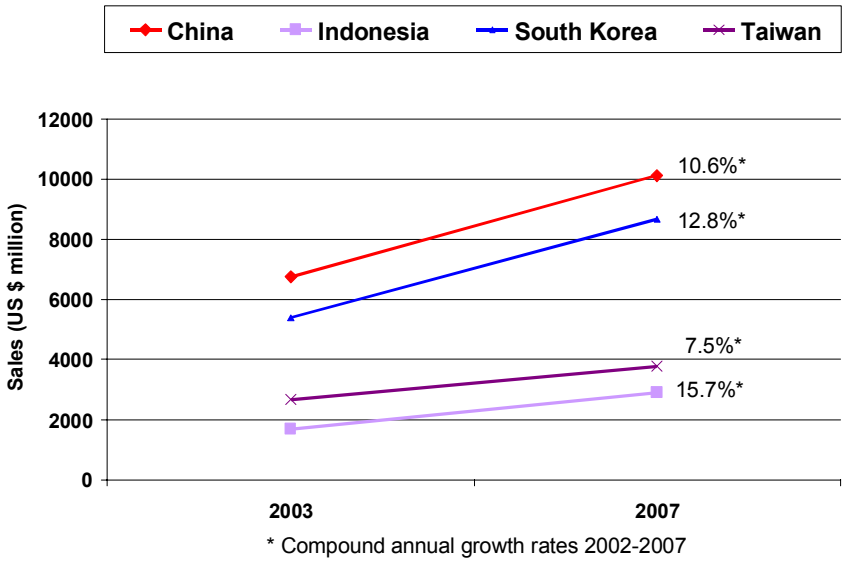
The global pharmaceutical industry

Global ethical pharmaceutical R&D expenditure, historical development time, NME output and sales 1992-2003



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 3

Predicted 2003 and 2007 sales in East and Southeast Asia



* Compound annual growth rates 2002-2007

Source: IMS Market Prognosis Global Audited data Confidential Slide No. 4

Background

- Emerging markets of Asia offer considerable potential for growth
- Recent trends in the globalisation of new drug development have encouraged the need for greater harmonisation of procedures & requirements in Asia
- Regulatory systems in Asia are rapidly evolving to:
  - Enhance best practice
  - Bridge the gap between ICH and Asia
  - Avoid duplication & unnecessary delays
- To facilitate these developments, some authorities have adopted, among other ICH initiatives, the ICH E5 guideline
- E5 has the potential to replace the routine requirements for local clinical trials, which are regarded as one of the major hurdles to achieving efficient and effective registration

CMR studies of Asia Pacific

- Study conducted among 13 companies in late 2001 to look at:
  - Utilisation, strategies and regulatory acceptance of the E5 guideline
- Study updated among 16 companies in November 2003 to look at:
  - Development strategies, authority negotiations & hurdles to using the E5 guideline
- Asia Pacific focus includes: China, Korea, Singapore, Taiwan & Thailand

Participating companies in 2003

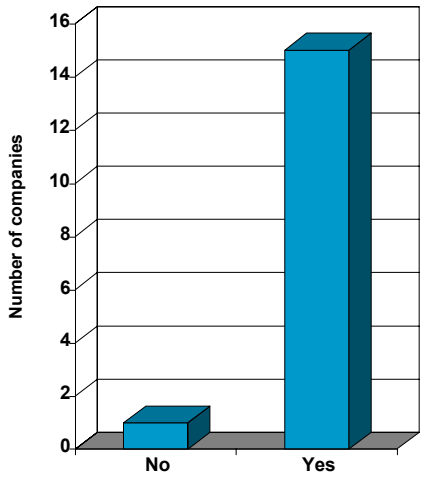
- Abbott Laboratories
- AstraZeneca Pharmaceuticals
- Aventis Pharmaceuticals Inc
- Bristol-Myers Squibb Company
- Chugai Pharmaceutical Company
- Eisai Company Ltd
- F Hoffmann-La Roche Ltd
- GlaxoSmithKline
- Kyowa Hakko Kogyo Co Ltd
- Lilly Research Laboratories
- Merck & Company Inc
- Merck KGA
- Novo Nordisk A/S
- Pfizer Global R & D
- Takeda
- RW Johnson PRI

Impact of bridging in the Asia Pacific region

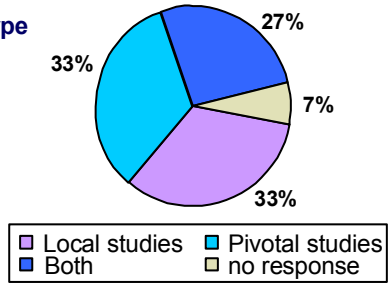
- Development strategies
- Interactions with the regulatory authorities
- Hurdles & benefits to using the ICH E5 guideline

Conduct of clinical trials in Asia Pacific

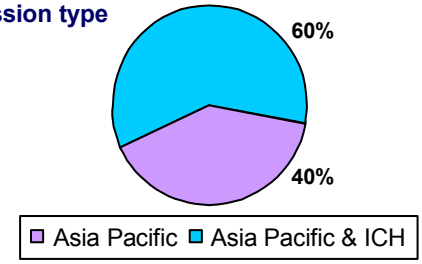
Does your company routinely conduct clinical trials in Asia Pacific?



Study type

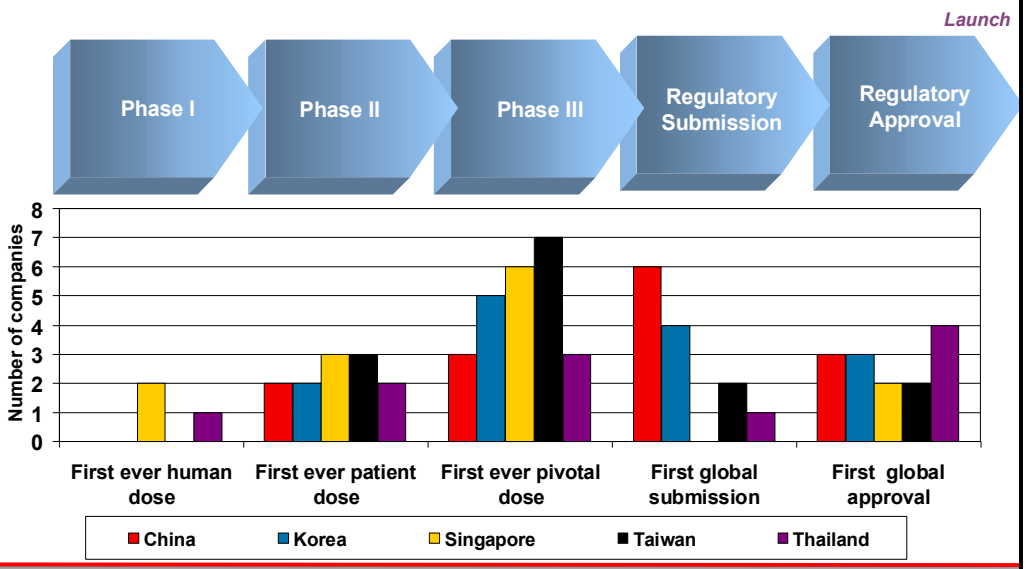


Submission type



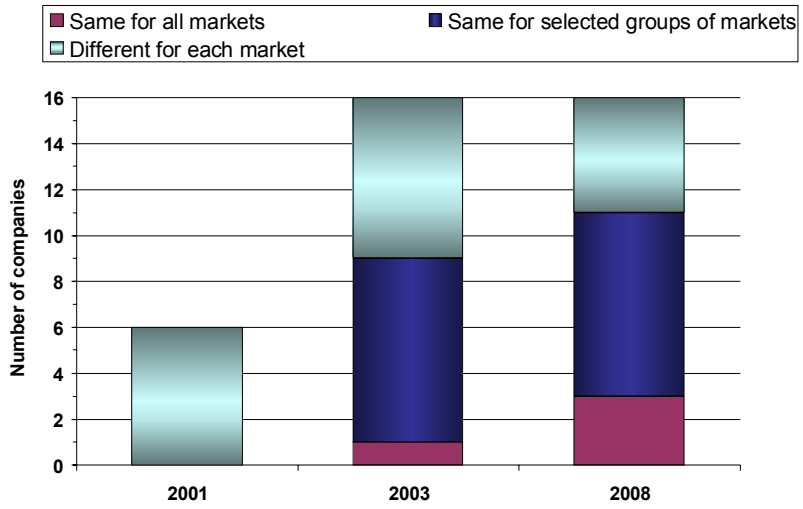
Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 9

At what stage of global development is clinical research conducted in Asia Pacific



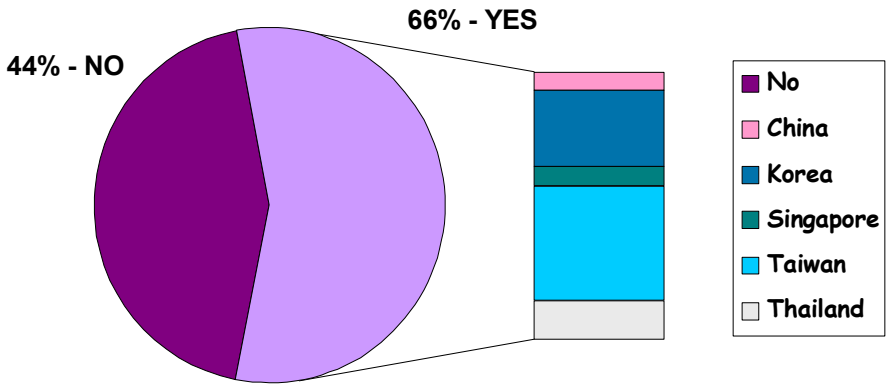
Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 10

Where do you believe your company development strategy for Asia Pacific markets is at present? And in 5 years time?



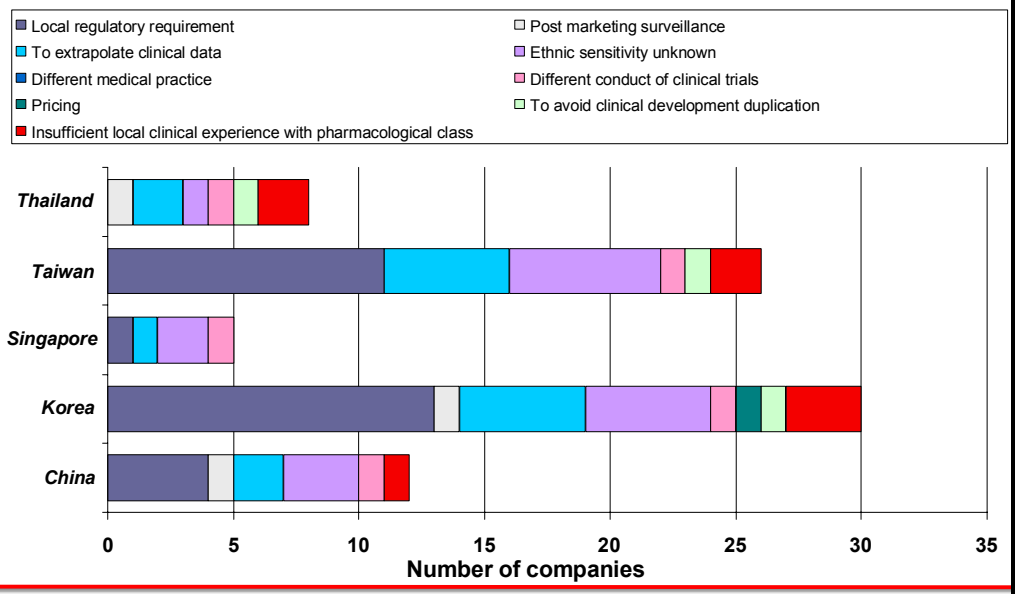
Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 11

Successful use of bridging strategies to register NASs in Asia Pacific



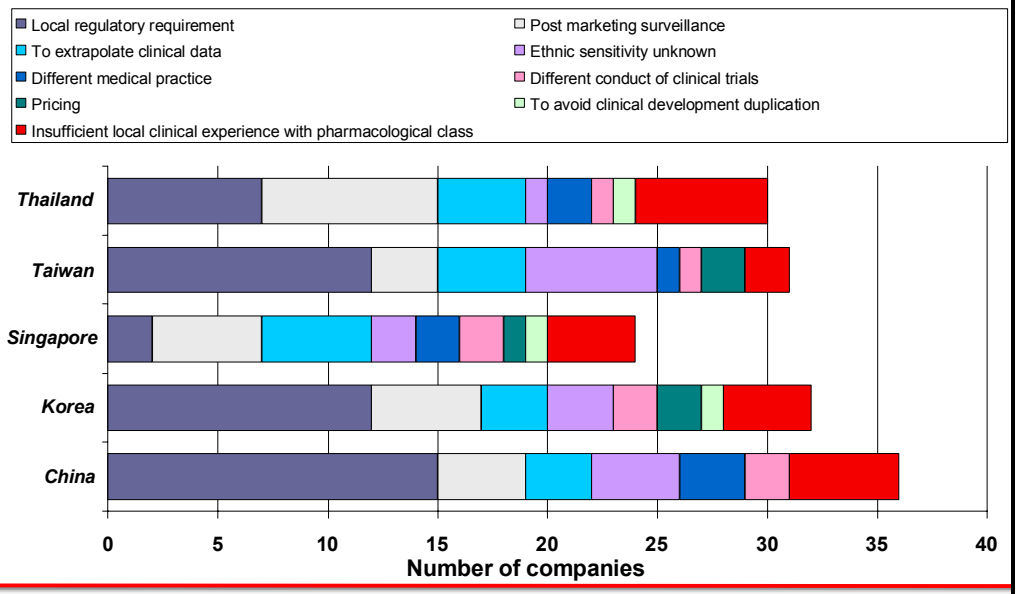
Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 12

Companies' top 3 reasons for conducting bridging studies in Asia Pacific



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 13

Companies' top 3 reasons for conducting local studies in Asia Pacific



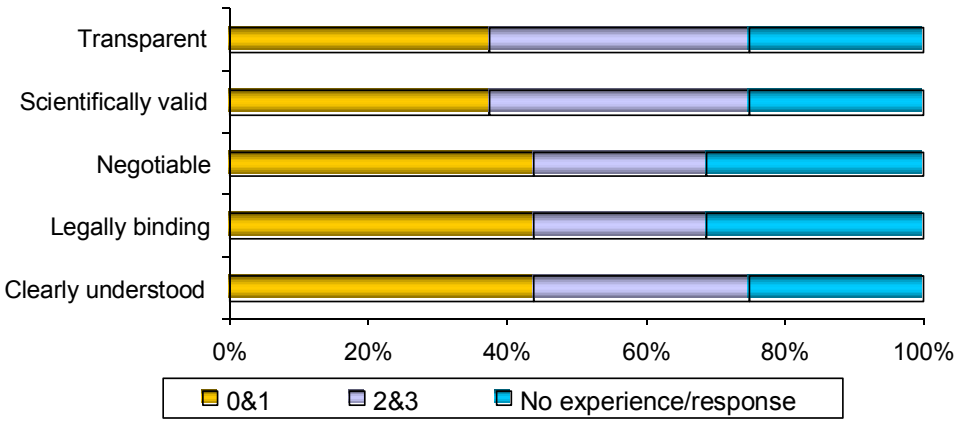
Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 14

Impact of bridging in the Asia Pacific region

- Development strategies
- Interactions with the regulatory authorities
- Hurdles & benefits to using the ICH E5 guideline

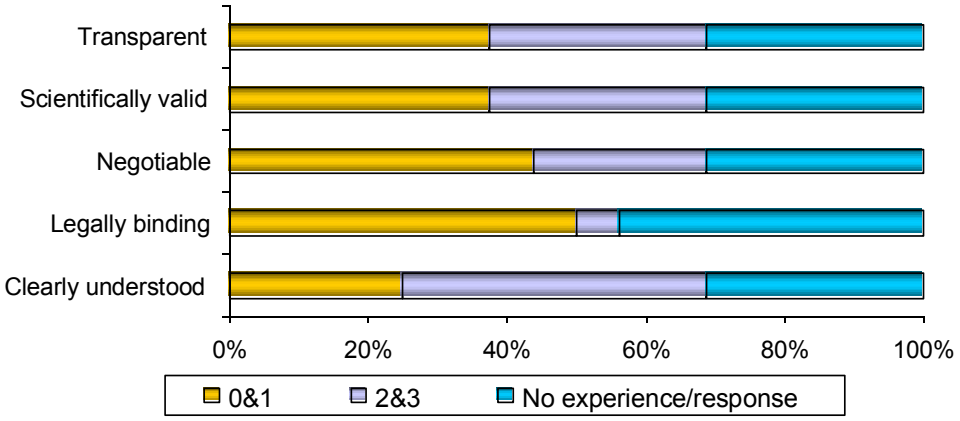
Negotiations with regulatory authorities: CHINA

Rate the characteristics that describe the advice your company received from regulatory authorities during consultation in China. 0=poor and 3=excellent



Negotiations with regulatory authorities: KOREA

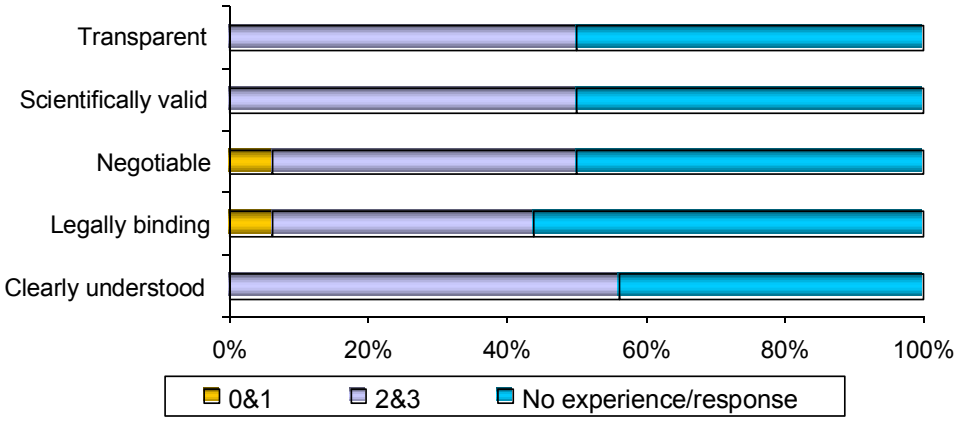
Rate the characteristics that describe the advice your company received from regulatory authorities during consultation in Korea. 0=poor and 3=excellent



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 17

Negotiations with regulatory authorities: SINGAPORE

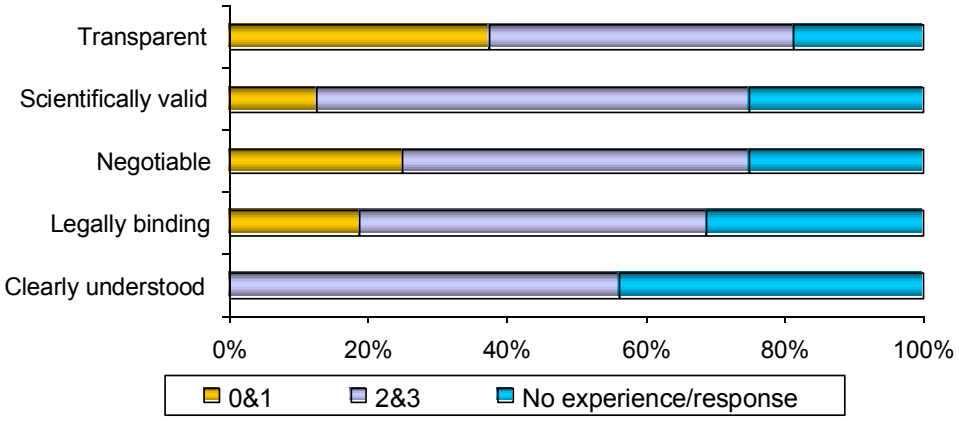
Rate the characteristics that describe the advice your company received from regulatory authorities during consultation in Singapore. 0=poor and 3=excellent



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 18

Negotiations with regulatory authorities: TAIWAN

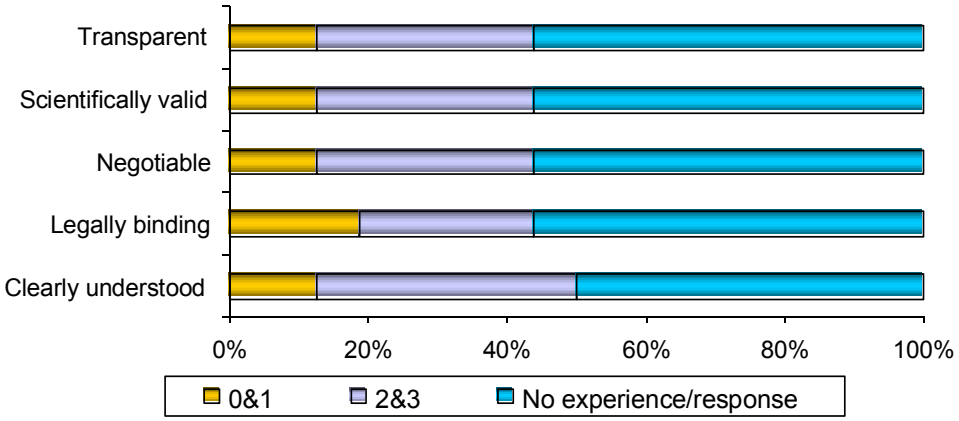
Rate the characteristics that describe the advice your company received from regulatory authorities during consultation in Taiwan. 0=poor and 3=excellent



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 19

Negotiations with regulatory authorities: THAILAND

Rate the characteristics that describe the advice your company received from regulatory authorities during consultation in Thailand. 0=poor and 3=excellent



Source: CMR International Institute for Regulatory Science Audited data Confidential Slide No. 20

Impact of bridging in the Asia Pacific region

- Development strategies
- Interactions with the regulatory authorities
- Hurdles & benefits to using the ICH E5 guideline

Major hurdles identified in 2001 to using ICH E5 guideline in Asia Pacific

- Resource constraints
- Misinterpretation, with bridging becoming routinely requested
- Lack of GCP compliance
- Lack of understanding, experience and knowledge of authorities, with difficulties in negotiation
- Increased development times and costs in the short term
- Increased registration times

Major benefits identified in 2001 to using ICH E5 guideline in Asia Pacific

- Minimum duplication of studies - particularly of small local trials
- Enabling Asian markets to be included in global development plans
- Faster approvals, parallel filings, lower development costs
- Authority transparency & greater product experience
- Better defined, planned and efficient clinical development
- Authority assurance that drug response is similar in local population

The Way Forward...

- Companies are currently active in Asia and expect to become even more so over the next five years. Some intend to integrate development in Asia into global strategies

- Although some Asian authorities have implemented the ICH E5 guideline some have not and are still requesting companies to conduct local studies

The Way Forward...

- Companies are in favour of these authorities implementing the ICH E5 guideline to:
  - facilitate the acceptance of foreign clinical data
  - provide scientific justification for studies conducted locally
  - promote and facilitate dialogue
  - improve authorities education, understanding and transparency
- There needs to be continued dialogue and agreement across the Asian authorities on a common E5 guideline, its application and interpretation

Session 2

Good Review Practice is the First, but not the Least, Step for the KFDA

HOWARD LEE, MD, PhD

Assistant Professor, Center for Drug Development Science, Dept. Pharmacology, Georgetown University Medical Center

ABSTRACT

The Good Clinical Practice (GCP) enactment in 1995, followed by the International Conference on Harmonization standard and the introduction of new clinical trial regulations in 2001, has prompted pharmaceutical companies in Korea to introduce new quality clinical research systems [1]. However, the Korea Food and Drug Administration (KFDA) has failed to implement these new regulations into practice[2], which has long been the source of criticism from pharmaceutical companies. Therefore, the original expectation that the new clinical trial regulations would benefit new drug review process is not evident, and the KFDA still lacks quality review systems, thus delaying timely and efficient introduction of innovative medicines to Korean patients [3]. There is no doubt that this lowers health standards of the Korean public, simultaneously adding unnecessary financial burden to the Korean pharmaceutical industry.

Quality in the drug regulation is no longer confined to the section of the dossier dealing with manufacturing, specifications and stability data [4]. Likewise, quality assurance is not just for the production plant or laboratory, but is now built into the preparation of the dossier, most notably exemplified by

GCP for the planning, conduct, and reporting of clinical trials [5]. However, quality concepts should also be extended to the drug review process by the regulatory agency. To reflect this notion, there has been a great deal of interest from many regulatory agencies as to how the regulatory review process can be streamlined on the basis of quality assurance [4;6]. The US Food and Drug Administration (FDA) is one agency that has embraced the concept of Good Review Practice (GRP), and appears to have outperformed their initial goals.

Quality review entails correct format, scientific reliability, legal and scientific consistency, procedural predictability, timely results, and transparency [7]. GRP can be defined as the reviewers' adherence to explicit and detailed standards, enabling standardization of reviews across divisions and disciplines [8]. The GRP guidance will document the parts of an application that are most important to evaluate, and what to expect when evaluating them [8]. Therefore, GRP ensures that important information is captured in the review, enabling consistent assessment over the drug development period, and is expected to have the highest impact on the quality of the review process [4;6].

Since launched in late 1994[4], the GRP initiative in the US FDA has seen many new developments, such as; the implementation of the Question-Based Review as the review standard for the Clinical Pharmacology and Biopharmaceutics Reviewers (1999)[9], the release of the Reviewer Guidance (Draft) Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (1996)[10], the Guidance for Reviewers Pharmacology/Toxicology Review Format (2001)[11], the establishment of the Review Standards Staff (2001)[12], and the finalization of the GRP template for clinical reviewers (2001)[13].

However, GRP can not be complete unless approached by a total quality assurance framework. This implies that, without establishing, administering, and documenting explicit training requirements for review staff, coupled with strong commitment by management teams and resource allocation, the GRP initiative is

likely to fail. This is why the US FDA has tried to establish the systems of professional training, employment qualifications, supervisory mentoring, and annual performance reviews to ensure that the review staff possesses the knowledge, skills, and abilities to perform their assigned duties [8].

Given that the KFDA reviewers have not prepared anything similar to the review document *per se* and there are few, if any, experts who can perform quality clinical review, the introduction of GRP may be regarded as too early or too hard to implement. However, this deficiency can be used as an opportunity as it will create a new level of urgency in the regulatory agency for quality review standards that would not otherwise be achievable. In this sense, GRP is the first, but not the least, step forward for the KFDA. However, because the current KFDA review system is not prepared for this kind of new initiative, the only practical solution for the KFDA is to create a new third-party review body operated on the user fee scheme. Pilot trials involving one or a few therapeutic categories, followed by gradual implementation, are also recommended.

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(5) ICH HARMONISED TRIPARTITE GUIDELINE E6: Good Clinical Practice consolidated Guideline (Step 4). 1996.

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Good Review Practice is the First, but Not the Least, Step Forward for the Korea Food and Drug Administration

Howard Lee, MD, PhD

March 31, 2004

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Acknowledgement

- Nancy D. Smith, Ph.D.
  - Director, OTCOM, CDER, FDA
  - Recent update on the GRP initiative
  - For her insightful comments

공자가 죽어야 나라가 산다?

子曰, " 道之以政하고 齊之以刑이면 民免而無恥니라. 道之以德하고 齊之以禮이면 有恥且格이니라" (論語, 二編 爲政)

법과 제도로써 백성을 지도하고, 형벌로써 질서를 유지시키면, 백성들은 법망을 빠져 나가되 이를 수치로 여기지 아니한다. 그러나 덕으로 백성을 인도하고 예로써 다스리면 백성들이 부끄러움을 알고 선에 이르게 될 것이다.

H. Lee, *New Millennium of Clinical Drug Development*, KSCPT Annual Meeting, 1999, Seoul, Korea

An Old Norm

… The Master said, "If the people be led by laws (i.e., systems), … they will try to avoid the punishment, but have no sense of shame."

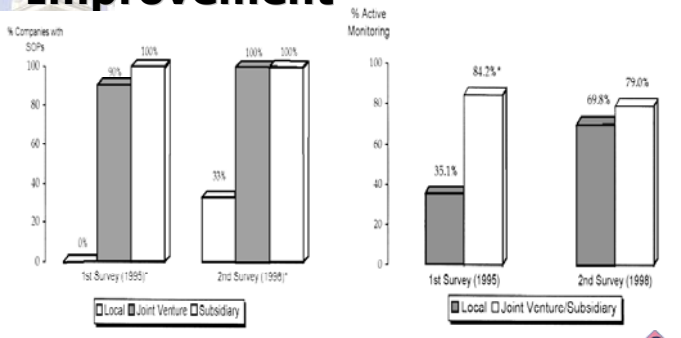
"However, if they be led by virtue, … they will have the sense of shame, and moreover will become good."

Confucian Analects, Chapter II

What is Wrong with Confucius?

- Paradigm shift
  - Get your work done by system rather than relying on personal commitment
- No quality systems, no quality products
  - GCP based clinical research system and quality clinical dossier

Sponsors Showed a Big Improvement



Adapted from Lee, Kim & Shin, *Drug Info J.* 2001, 35:203-10

Motivation

- The regulatory agency is not exempt from quality system
- The implementation of Good *Review* Practices is the key

Topics

- Introduction to Good Review Practices
- GRP initiative in the US FDA
- Implications to the Korean drug regulatory system
- Suggestions

Drug Review: An Anecdote

- Served as Guest Medical Reviewer
  - May-August, 2001
  - Division of Cardio-renal products, CDER, FDA
  - Reviewed two NDAs
- Similar to residency training
  - "A-mentor-showed-how-to-do-it-then-I-copy-exactly-what-he-or-she-did" approach
  - Review documents used as textbook

Drug Review

- A process and a document
- Science and art
- Historically taught by master to apprentice
  - Pros
    - Attention to detail
    - Immediate feedback
  - Cons
    - Very time consuming
    - Highly individual review document
    - Lack of consistency

Adapted from N. Smith, *Good Review Practices*, Progress in Clinical Trials, Tokyo, Japan, February 14, 2004

What is Quality Review?

- Scientifically sound
- Legally and scientifically consistent
- Procedurally predictable
- Meeting time targets
- Correct format
- Transparent

Adapted from Risa Larick, *Giving your NDA Submission the Best Chance of Approval: The importance of Presentation*, Drug Information Association 37th Annual Meeting, 2001, Denver, Colorado

Quality is knowing and meeting your customer's expectation!

Quality Review Does Not Mean

- Hiring many new staff with no training provided
- Doing the same old thing faster with inconsistency and non-transparency remaining
- Focusing only on review contents with no process development

Adapted from N. Smith, *Good Review Practices*, Progress in Clinical Trials, Tokyo, Japan, February 14, 2004

Bad Review Practices

- Copy and paste
  - Review ≠ summary
- Not disclose the rationale for approval or disapproval
- Consider only information that the reviewer wants to see
- Treat individual study separately*
  - No organization or integration across studies
- A "box checking" review*
  - The least desirable

*Lesko and Williams, *The Question-Based Review, A conceptual Framework for Good Review Practices*, Applied Clinical Trials 8(6):56-62, 1999

Good Review Practices

- Reviewer's adherence to pre-specified standards for
  - Content (what to review)
  - Process (how to review)
- Standards should be
  - explicit and detailed
  - Transparent and kept updated
- GRP guidance documents
  - The parts of an application that are most important to evaluate
  - What to expect when evaluating them
- Review templates strongly encouraged

Adapted from *Report to the FDA Commissioner from the Task Force on Risk Management*, May, 1999

GRP Example: *Question Based Review*

- Reviewers ask, in a clear and explicit manner, a set of questions that are deemed important to them
- Current review standard, Office of Biopharmaceutics and Clinical Pharmacology, CDER, FDA

Adapted from Lesko and Williams, *The Question-Based Review, A conceptual Framework for Good Review Practices. Applied Clinical Trials* 8(6):56-62, 1999

3 Steps in QBR

- Systematically review submitted studies
- Thoroughly describe and analyze the data from those studies
- *Pull out the important questions to be asked and judge whether or not the data in the application address them*

Adapted from Lesko and Williams, *The Question-Based Review, A conceptual Framework for Good Review Practices. Applied Clinical Trials* 8(6):56-62, 1999

QBR: Important Clin Pharm Questions

- What is the dose-systemic exposure relationship for the drug substance and its metabolites? (PK)
- What are the exposure-response relationship for efficacy or adverse effects? (PK-PD)
- How dose exposure change in the presence of intrinsic and/or extrinsic patient factors? (Covariates, special population)

Adapted from Lesko and Williams, *The Question-Based Review, A conceptual Framework for Good Review Practices. Applied Clinical Trials* 8(6):56-62, 1999

QBR Example: *Clinical Review Template*

- Executive Summary
  - Recommendations --- approvability, phase IV commitments, risk management issues
  - Overview of clinical program
  - Summary of clinical findings --- orientation to the review, stand-alone document
  - Efficacy and safety
  - Brief (5-6 pages), language understandable to the educated reader

Clinical Review Template

- Clinical Review
  - Background
  - Clinically relevant findings from other disciplines
  - Pharmacokinetics, pharmacodynamics
  - Clinical data description and source
  - Clinical review methods
  - IRE, IRS
  - Dosing, regimen, administration
  - Special populations
  - Conclusions/recommendations

Implications of GRP

- GRP ensured
  - Standardization of reviews across divisions/disciplines
  - Capture of important information
  - Consistent assessment
  - Integrated review and analyses
  - Effective communication between the sponsor and FDA
- The highest impact on the quality of the review process

FDA: Pre-1992

- Chronic under-funding for drug review program
- No imposed deadline for new drug reviews
- Few training opportunities for reviewers
- Low morale, high turnover, burnout

Prescription Drug User Fee Act (PDUFA) of 1992

- Five year program
- Sponsors pay money for drug review
- FDA hires more qualified reviewers/staff
- Goals
  - Primary focus to reduce drug review times (e.g., 12 months for standard drugs)
  - Eliminate the backlog of overdue applications
  - *More predictable, streamlined review process*

Adapted from N. Smith, *Good Review Practices*, Progress in Clinical Trials, Tokyo, Japan, February 14, 2004

GRP Initiative

- Launched in 1994
- Goals
  - Improve the *review process*
  - Improve the *review document*
  - Develop good *data handling practices*
  - Develop plan for *education* of regulatory reviewers

Adapted from N. Smith, *Good Review Practices*, Progress in Clinical Trials, Tokyo, Japan, February 14, 2004

Good Review

Comprehensive Approach

- Centralized Center-level support for development
  - GRP Central Coordinating Committee
  - Provides a multi-tiered and cross-disciplinary voice and feedbacks
  - Fosters CDER as a evolving, learning, and participatory community that supports the improvement of public health

Adapted from M. Ortwerth, *The CDER 2001, Good Review Practices Initiative. A General Overview*, Drug Information Association 37th Annual Meeting, 2001, Denver, Colorado

Good Review

GRP Accomplishments

- 1994: Consensus action plans for clinical and statistical reviewers, 11 tracks prioritized
- 1995: OTCOM established
- 1996: Reviewer Guidance (Draft). Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review
- 1997: Reviews Evaluation & Education Project
- 1998: GRP Clusters 1-5 began
- 1999: Question-Based Review
- 2000: Guidance for Reviewers. Pharmacology and Toxicology Review Format
- 2001: Review standards staff established
- 2004: General Clinical Review Template

Good Review

GRP Benefits

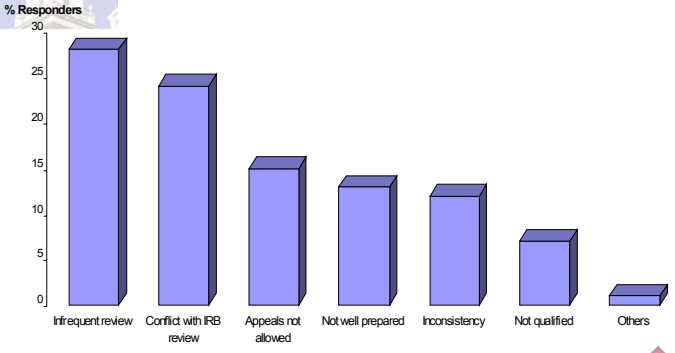
- Higher quality drug reviews
- More information available to the public
- Improved public health

Adapted from N. Smith, *Good Review Practices*, Progress in Clinical Trials, Tokyo, Japan, February 14, 2004

KFDA: Past & Present

- No review documents prepared or available
- No qualified in-house clinical reviewers
  - Expert works reviewed by unqualified personnel
  - Heavy reliance on outside experts, e.g., Central Pharmaceutical Affairs Council (CPAC)

CPAC Is Not an Alternative!



H. Lee et al., *Kor J Clin Pharmacol Ther*, 1998; 6(1): 11-28

Why GRP for KFDA?

- Will create a new level of urgency in the regulatory agency for quality review standards that would not otherwise be achievable
- KFDA announced GRP as new review policy (March 18, 2004)
- Great minds think alike!

향후 심사개선방향 (II)

Good Review Practice (GRP)

KFDA 식품의약품안전청

기준 및 시험방법, 안전성 • 유효성 검토서

유효성자료

- 효력시험자료 요약서
- 일반약리시험자료 요약서
- 일반약리시험자료 Check Lis
- 흡수분포대사배설시험자료 요
- 임상시험자료 요약서
- 임상시험계획승인신청서 검토
- 안정성시험자료 요약서

안전성자료

- 독성시험자료 총괄표
- 단회투여독성시험자료 요약서
- 반복투여독성시험자료 요약서
- 생식발생독성시험자료요약서(I)
  - 수태능 및 초기배자 발생시험
- 생식발생독성시험자료 요약서(II)
  - 배•태자 발생시험
- 생식발생독성시험자료 요약서(III)
  - 출생전후 발생 및 모체기능시험
- 유전독성시험자료 요약서
  - 복귀돌연변이시험
- 유전독성시험자료 요약서
  - 염색체이상시험, 마우스 림포마시험
- 유전독성시험자료 요약서
  - 소핵시험
- 항원성시험자료 요약서
- 피부감작성시험자료 요약서
- 발암성시험자료 요약서

- 제출한 자료요약서 및 검토서 작성하여 심사함 (투명성, 공정성, 일관성,
- 양식을 책에 부록으로 첨부, 우리청 홈페이지에서 다운받을 수 있도록 함
  (심사의뢰시 동 양식을 작성하여 제출)

Adapted from Tae Moo Yoo, March 18, 2004, KFDA

검토서 양식 (Review Form)

KFDA 식품의약품안전청

기준 및 시험방법 및 안전성 • 유효성 검토서

(**최초, 변경**)

2004. 3.

담당자	연구관	과 장

① 신청자		② 문서번호	의약품안전과- †††호 (2004. 1.20.)
③ 제품명	??? (제조회사명)	④ 분류번호	
⑤ 원료약품 분량(주성분)			
⑥ 제조방법			
⑦ 효능•효과 ⑧ 용법•용량			
⑨ 저장방법 및 유효기간			
⑩ 기원및개발의 경위			
⑪ 약리작용 기전			
⑫ 국내외사용현황			
⑬ 관련조항			
⑭ 검토결과	적합/ 시정적합/ 보완		
	보완사항/ 시정사항		
※ 참고사항			

Adapted from Tae Moo Yoo, March 18, 2004, KFDA

의약품 허가지연 개선, 업계 숙원 풀린다
식약청, 검토결과 공개-허가절차 명확화 등 추진

"허가 후 심사 정보 공개는 그동안 업계가 지속적으로 요구했던 사안을 적극적으로 반영, 외국의 SBA (Summary Basis of Approval) 시스템을 도입 …

이를 위해서 GRP의 양식을 공개하고 업계에서 민원 접수시에 가능하면 이 GRP양식을 이용해 줄 것을 권장 …"

데일리 팜, 2004년 3월 20일,
http://www.dreamdrug.com/Users/News/NewsView.html?ID=38996&nSection=1

Great Minds Think Alike?

- SBA is neither a review document nor a GRP component [21 CFR 314.430 (e)(2)(ii)]
  - A summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process
  - *Applicant* or FDA may prepare the SBA

The Real Serious Issue

- A simple review form is not GRP unless coupled with
  - Agency wide policy & management commitments
  - Documented system & defined processes
  - Qualified people
  - Continuous audit, evaluation, and feedback
  - Ongoing training and education of reviewers

Reality Check

- Less likely to recruit quality clinical reviewers under the present system
- The destination is clear, but the path is unclear
- What you get is what you pay for

Paradigm Shift: *Third Party Clinical Review*

- An independent & non-government review body
  - Established in an academic medical institution affiliated with major hospital units
  - Operates under the user fee scheme (i.e., self-supporting)
  - High ethical standards
  - Provides quality clinical review services binding on KFDA's final approval decisions

Third Party Review Body

- Will implement GRP
- Starts with one therapeutic category, followed by extension to other areas
- Committed to training and education of regulatory scientists and process development
- May provide drug development consulting services binding on KFDA's regulatory decisions

Organization: Third Party Review Body

- Director
- Full time reviewers
  - 1-2 subject matter experts (e.g., cardiologist)
  - 1 clinical pharmacologist
  - 1 MS level biostatistician
- Full or partial professorship

Nothing is New Under the Sun

- Third party review, CDRH, FDA, USA
- Center for Drug Evaluation (CDE), Taiwan, as an independent and non-government review organization

Take Home Message I: "It's not Too Late to Start"

"The FDA in the late eighties was exactly what you describe about the KFDA today."

C. Peck, MD, Former CDER Director, Founder and Director of CDDS, Georgetown University

Take Home Message II: "Quality People is Always the Key"

"A wise man has great power, and a man of knowledge increases strength. (Proverbs, 24:5, NIV)"

Biographical Sketchs

- **John Hall, Quintiles**
- **Cynthia Wang, Merck Research Laboratory**
- **Edmund Tsuei, Asia Roche**
- **In-Jin Jang, Seoul National University**
- **Carly Anderson, CMR International Ltd.**
- **Howard Lee, Georgetown University**

Biographical Sketch

John M Hall, PhD

Dr John Hall has over thirty years' experience in the pharmaceutical, chemical and consulting industries. He has worked in a variety of research and development posts in the United Kingdom, France, Belgium and the United States. His responsibilities have included pharmaceutical product research and development, strategic planning, technology transfer, acquisitions, facilities management, marketing development and international contract research.

Dr. Hall graduated in Pharmacy with a PhD in Pharmacology from the University of Aston in Birmingham, United Kingdom. His career has taken him to Hoffman-La-Roche, Inveresk Research and Monsanto/Searle. He joined Quintiles as General Manager of the newly acquired Edinburgh Research Centre in 1995

Currently he is Senior Vice President, Corporate Development a role in which he explores and exploits new business opportunities outside of the traditional CRO offering. He is also a non-executive director of Edinburgh Research and Innovation, the technology transfer company of Edinburgh University, a member of the Governing Council of the Roslin Institute and a non-executive director of Scottish Enterprise Edinburgh and Lothian. He is an honorary Teaching Fellow in Management at the University of St. Andrews, Scotland.

Dr. Hall has published in the fields of pharmacology and the management of pharmaceutical research and development

Biographical Sketch

Cynthia Wang, MD

Dr. Wang received her BA from Mount Holyoke College and her MD from the State University of New York at Buffalo, School of Medicine. She is board certified in Internal Medicine with a subspecialty in Infectious Diseases.

Currently, she is Executive director for Regulatory Affairs International at Merck and Co. Inc. based in Rahway, New Jersey. In addition to global drug development, she has particular interest and responsibility for the Asia Pacific region. She is the Chair of the Asia Pacific Technical Committee [APTC] of PhrMA as well as a member of the Board of Directors for the Regulatory Affairs Professional Society [RAPS].

Prior to her joining Regulatory Affairs, she was with Clinical Research at Merck and had done work with imipenem, ivermectin and norfloxacin as well as various compounds in diabetes and cardiovascular diseases.

Edmund Tsuei, PhD

Dr Edmund Tsuei received his undergraduate degree in the United States of America and his doctorate from the University of Sydney in clinical pharmacokinetics.

Ed has many years of drug development experience in the Asia-Pacific region. He is currently Head of Pharma Development Operations, Asia as well as Deputy Head, Pharma Development Operations, Asia-Pacific-South Africa at Roche Products Pty Limited, based in Sydney, Australia. He is also the global clinical team leader for the Pegasys Hepatitis B project.

Ed joined the pharmaceutical industry in 1981 and has been involved in drug development activities in the Asia-Pacific region since 1984. He has experience in setting up global drug development departments and conducting high quality IND studies in ten Asian countries in addition to Australia, New Zealand and South Africa. He is well familiar with drug development globally as well as in the Asia-Pacific region.

Ed has spoken frequently in international and regional meetings on drug development and good clinical practice. In addition to global drug development, Ed's personal research interest is in the areas of both theoretical and clinical pharmacokinetics and has published many papers in that area.

Biographical Sketch

In-Jin Jang, MD, PhD

Dr. Jang is Assistant Professor of Department of Pharmacology, Seoul National University College of Medicine and Director for Clinical Pharmacology Unit of Seoul National University Hospital.

After obtaining degrees of M.D. and PhD in 1987 and 1992 at Seoul National University, College of Medicine (Department of Pharmacology), he was affiliated at Chungbuk National University. He moved to Seoul National University in 1994.

He is a clinical pharmacologist especially interested in the research fields of pharmacogenetics, PK/PD modeling, population PK and early clinical trials methodologies. He worked as a visiting research fellow at Center for Drug Development Science, Georgetown University Medical Center from 1998 to 2000, where he was involve in population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation of clinical trial. At Seoul National University and Hospital, he is responsible for research and education in the field of clinical pharmacology, especially pharmacogenomics and PK/PD. He is in charge of therapeutic drug monitoring consultation and phase 1 clinical trials at SNUH clinical trial center as well as participating in ADR monitoring at SNUH.

Now he is also serving as a secretary general and a member of steering committee of the Korean Pharmacogenomic Research Network. In the network, he is participating in the ADR related pharmacogenomic research group and is doing genotype related drug interaction studies. He is a member of American Society for Clinical Pharmacology and Therapeutics, Korean Society for Clinical Pharmacology and Therapeutics, Korean Society for Pharmacology, etc.

Biographical Sketch

Carly Anderson, PhD

Carly Anderson BSc, PhD is a Project Leader within the CMR International Institute for Regulatory Science, a not for profit division of the Centre for Medicines Research International Ltd. She joined the Centre in 1999 and continues to work on a number of projects in the regulatory area. Carly received an honours degree in Molecular Biology from King's College, University of London and has just completed her PhD studies with the University of Wales, Cardiff.

Biographical Sketch

Howard (Hyeong Ki) Lee, MD, PhD

Howard (Hyeong Ki) Lee, MD, PhD is an Assistant Professor, Center for Drug Development Science (CDDS), Department of Pharmacology, Georgetown University Medical Center, Washington, Dc., USA. Dr. Lee is also a Guest Researcher, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, FDA, Rockville, Md., USA.

Dr. Lee is a graduate of the Seoul National University College of Medicine, Seoul, Korea, where he received the MD (1988), MSc (1991, Epidemiology), and PhD (1998, Preventive Medicine and Epidemiology) degrees. He also has a diploma in Advanced Management Program for Health Industry (1997, Sejong University, Graduate School of Public Administration, Seoul, Korea). Dr. Lee completed an internship and residency training in the Seoul National University Hospital (1988 - 1991), and is board certified in Family Medicine. Dr. Lee undertook a postdoctoral fellowship in CDDS, Department of Pharmacology, Georgetown University Medical Center, under the supervision by Prof. Carl C. Peck, MD, PhD (hon.) (2000 – 2001). During his fellowship at CDDS, Dr. Lee worked as Guest Medical Reviewer for 4 months at the Division of Cardio-Renal Products, Center for Drug Evaluation and Research, FDA, Rockville, Md., USA.

Before joining CDDS, Dr. Lee held a variety of leadership positions, including Chairman, The Korean Society for Clinical Trials (1996 - 1998) and Secretary General and Director of General Affairs, The Korean Academy of Pharmaceutical Medicine (1998 - 1999). He also served as a member of the Advisory Committee of New Drug Reevaluation, Central Pharmaceutical Affairs Council, KFDA (1998 - 1999), and was credited with helping the KFDA to modernize clinical trial regulations in the late nineties.