Welcome Address

Drug review procedures and drug development strategies are changing rapidly as a result of the “The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use” (ICH). In particular, the E5 guideline, issued in August, 1998, enable the extrapolation of Western clinical data to new regions of the world. In addition, the availability of pharmacogenomic information is likely to play a prominent role in future new drug development, especially as regards individualized, or tailor-made medicine. The two concepts can lead to profound effect of drug development programs worldwide. It is therefore very important to create a forum for discussing the multiple issues surrounding these concepts.

This symposium – the 2nd Kitasato University – Harvard School of Public Health Symposium on Advanced and Global Drug Development Techniques: Bridging Strategies and Pharmacogenomics – is partially a result of partnership formed in 2000 between the Department of Biostatistics at Kitasato University Graduate School and Harvard School of Public Health. The symposium will address a variety of topics related to bridging strategies and pharmacogenomics, including bridging strategies (overview, the west experience, and practical implementation of E5 guidelines), regional/global clinical trials, and pharmacogenomics (advances in understanding, and clinical & regulatory impact). We have organized the sessions so as to have both the Western and Eastern perspectives.

It is our great pleasure to welcome you to this important meeting.

Stephen W. Lagakos, Ph.D.  
Harvard School of Public Health

Masahiro Takeuchi, Sc. D.  
Kitasato University Graduate School
## PROGRAM
**Monday, October 22**

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<td>9:30-9:40</td>
<td><strong>Opening Remarks and Welcoming Address</strong></td>
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<td>Toshiro Sato</td>
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<td>9:40-9:45</td>
<td><strong>Congratulatory Remarks: What is Expected of the Symposium?</strong></td>
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<td>9:45-10:15</td>
<td><strong>SESSION1: BRIDGING STRATEGIES: OVERVIEW</strong></td>
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<td><strong>chaired by</strong> Yoshio Yazaki</td>
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<td>9:45-10:15</td>
<td>ICH-E5: OVERVIEW AND CURRENT TOPICS</td>
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<td>Mamoru Narukawa</td>
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<td>10:15-10:45</td>
<td>1) Japanese Experience on Bridging Studies through PMDEC Reviews of NDAs</td>
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<td>Yasuhiro Fujiwara</td>
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<td>2) Experiences in Other Asian Countries</td>
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<td>- Bridging Studies in the Asian Pacific Region</td>
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<td>Singapore: Shook-Fong Tan</td>
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<td>Taiwan: Meir-Chyun Tzou</td>
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<td>3) Comments from Academia</td>
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<td>James H. Ware</td>
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SESSION2: BRIDGING STRATEGIES: THE WEST EXPERIENCE WITH BRIDGING

*chaired by* Declan P. Doogan
*Pfizer Inc.*

13:45-14:05

1) Regulatory System in Europe
- Thomas Kuemer
  *Nippon Boehringer Ingelheim Co., Ltd.*

14:05-14:25

2) Practical Issues in Conducting Multi-country Studies
- Kenneth E. Stanley
  *Harvard School of Public Health, World Health Organization*

14:25-15:00

3) Racial Differences in the Response to Drugs?
- Alastair J.J. Wood
  *Vanderbilt University School of Medicine*

15:00-15:45

Q&A session

**discussants**
- Thomas Kuerner
  *Nippon Boehringer Ingelheim Co., Ltd.*
- Kenneth E. Stanley
  *Harvard School of Public Health, World Health Organization*
- Alastair J.J. Wood
  *Vanderbilt University School of Medicine*

15:45-16:00 Refreshment Break

SESSION3: REGIONAL/GLOBAL CLINICAL TRIALS

*chaired by* Stephen W. Lagakos
*Harvard School of Public Health*

DEVELOPING AN ASIAN REGIONAL STRATEGY

16:00-16:20

Significance of Extrapolation of Foreign Data to Asian Countries
- Masahiro Takeuchi
  *Kitasato University Graduate School*

CHALLENGE IN CONDUCTING GLOBAL CLINICAL TRIALS

16:20-16:40

Katsuyoshi Shimatani
*Pfizer Pharmaceuticals Inc.*

16:40-17:40 Panel Discussion

**discussants**
The above speakers plus;
- Shook-Fong Tan
  *Ministry of Health, Singapore*
- Meir-Chyun Tzou
  *Bureau of Pharmaceutical Affairs, Department of Health, Taiwan*
- Suchart Chongprasert
  *Thai Food and Drug Administration, Thailand*
Tuesday, October 23

8:00-8:30 Registration

TV CONFERENCE: TOKYO-WASHINGTON, D.C.
(19:30 - 20:40, October 22, Washington, D.C. Time)

SESSION4: ICH: PRACTICAL IMPLEMENTATION OF E5 GUIDELINES

chaired by Stephen.W. Lagakos
Harvard School of Public Health

8:30-8:50 Regulatory Experience with ICH E5
Robert T. O'Neill -----via TV
U.S. Food and Drug Administration
Robert J. Temple -----via TV
U.S. Food and Drug Administration

8:50-9:20 Panel Discussion
Feasibility of Doing Regional Clinical Trials Across Several Countries
--- What is ethnic variation?
--- Intrinsic and extrinsic factors, which are really important?
--- Genetic polymorphism/Asian pacific region
--- Should there be regional protocol?
--- Will regional protocols accelerate study conduct?
discussants Daisaku Sato
Ministry of Health, Labour and Welfare
Thomas Kuerner
Nippon Boehringer Ingelheim Co., Ltd.
Takenobu Tasaki
Shionogi & Co., Ltd.
Kenneth E. Stanley
Harvard School of Public Health, World Health Organization
Declan P. Doogan
Pfizer Inc.

SESSION5: PHARMACOGENOMICS: ADVANCES IN UNDERSTANDING

chaired by Hiroo Imura
Council for Science and Technology Policy, Cabinet Office
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<td>9:20-9:40</td>
<td><strong>Typical Example for an Approval of Genome Research Compound:</strong></td>
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<td><em>Accelerated Approval of Gleevec (Imatinib Mesylate) for Leukemia Treatment</em></td>
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<td>Martin H. Cohen ------ via TV</td>
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<td>9:40-10:10</td>
<td><strong>Genome Sequencing and Analysis (DNA, cDNA)</strong></td>
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<td><strong>SESSION 6: PHARMACOGENOMICS: IMPACTS - CLINICAL &amp; REGULATORY</strong></td>
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<td><strong>Implication of New Genetic Science (Future for Tailor-made Therapy)</strong></td>
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<td>Kiyoshi Kurokawa</td>
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<td><strong>Applications of Clinical Genetics</strong></td>
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<td>Aidan Power</td>
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<td>11:45-12:30</td>
<td><strong>Panel Discussion</strong></td>
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<td><em>Key words</em>: Life ethics, Genotyping, Genes related to Drug Response; Prediction of AE and D/D interaction, Consultation/Review system in Japan, Resource, Requirement for NDA and PMS, Prevention</td>
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<td><em>discussants</em>: The above speakers, Dr. Woodage, Dr. Arai plus;</td>
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<td>Kazuto Nishio</td>
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<td><em>National Cancer Center Research Institute</em></td>
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<td>Fumitaka Nagamura</td>
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<td>Hiroshi Gushima</td>
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<td>12:30-12:45</td>
<td><strong>SUMMARY AND CONCLUSION</strong></td>
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<td>Stephen W. Lagakos</td>
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<td>Masahiro Takeuchi</td>
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<td><em>Kitasato University Graduate School</em></td>
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FACULTY MEMBERS

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University of Tokyo

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Thailand

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Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Cooperate Officer
Deputy Division Manager of DI&A Japan
PR Site Coordinator
Aventis Pharma Ltd.

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General Manager of Medical Development
Division
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Tokai University
Professor Emeritus of the University of Tokyo

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Harvard School of Public Health

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Instructor
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Deputy Director
First International Organizations Division
Economic Affairs Bureau
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Kazuto Nishio
Drug Resistance Section
Pharmacology Division
National Cancer Center Research Institute

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Center for Drug Evaluation and Research

Aidan Power
Director
Clinical Pharmacogenetics
Pfizer Inc.

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Evaluation and Licensing Division
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Chairman of the Board of Trustees
Juridical Person of Kitasato

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Ministry of Health, Singapore

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Biometric Analysis Department
Shionogi & Co., Ltd.

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U.S. Food and Drug Administration

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Department of Health, Taiwan, ROC

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Frederick Mosteller Professor of Biostatistics
Dean for Academic Affairs
Harvard School of Public Health

Alastair J.J. Wood
Assistant Vice Chancellor
Vanderbilt University School of Medicine

Trevor J. Woodage
Clinical Investigator
Celera Genomics

Yoshio Yazaki
President
International Medical Center of Japan

(Alphabetical order)
Japan is the second largest market for pharmaceuticals in the world, at the same time one of the key players in originating new drugs. Nowadays, many pharmaceutical companies have been extending their operations worldwide, and reorganization of the pharmaceutical industry has been under way. Internationalization and globalization of new drug development is inevitable.

In the summer of 1998, a new policy on the utilization of foreign clinical data in new drug application was adopted by the Ministry of Health and Welfare. It is based on the ICH agreement on Topic E-5, which was achieved through a lengthy process. Now many pharmaceutical companies are forced to drastically re-examine their new drug development strategies.

The guideline points out that the influence of intrinsic and extrinsic ethnic factors on the drug’s efficacy and safety should be evaluated through the development process. And in most cases, sponsors need to conduct a “bridging study” to determine whether or not the foreign clinical data can be extrapolated to the domestic population. “Bridging studies” can be classified roughly into the following three categories, (1) no need for bridging study, (2) controlled pharmacodynamic study, and (3) controlled clinical study. In any case, a study with quality, similarity in its design to the reference foreign studies, and adequate number of subjects would be crucial to the success. As the experience of bridging study accumulates, the need for harmonizing medical practice may be gradually brought to light.

The guideline is expected to contribute towards the solution to the so-called “drug-lag”, a delay of new drug marketing in Japan, though, the situation seems not favorable so far. The introduction of international multi-center trials might be one option to take it a turn for the better. In order to put forward the scheme successfully, further improvement of the infrastructure that enables the practice of clinical trials with quality and speed would be needed. At the same time, it might be necessary to remove the fixed idea that carrying out clinical trials in Japan is difficult from the mind of international manufacturers’ head office.
As of October 1, 2001, following implementation of the ICH-E5 guidance in 1998 (Notification No. 739 of Pharmaceutical and Medical Safety Bureau (PMSB) dated August 11, 1998 and Notification No. 672 of Evaluation and Licesing Division, PMSB dated August 11, 1998), five drugs (fexofenadine, approved September 22, 2000; oseltamivir, approved December 12, 2000; anastrozole, approved December 22, 2000; sumatriptan, approved June 20, 2001; zolmitriptan, approved June 20, 2001) have been approved with a prospectively conceptualized bridging strategy during clinical development. As to the contents of these bridging studies, three (fexofenadine, sumatriptan, zolmitriptan) of five studies were conducted as a randomized, fixed dose, placebo-controlled, dose-response study. As for anastrozole, two studies (a clinical pharmacology study conducted in healthy volunteer subjects and a small-scale (n=30) randomized controlled trial) were designated as bridging studies by the sponsor. As for oseltamivir two randomized placebo-controlled trials (one in a treatment setting (n=316), and one in a prophylaxis setting were designated as bridging studies by the sponsor. I will briefly overview and comment on these study results based on publicly available review reports (in Japanese) from the Internet (http://www.pharamasys.gr.jp/shinyaku/index.html).

The views and opinions expressed in this abstract and the presentation reflect the author’s personal opinion and do not necessarily represent the views of the PMDEC and the MHLW.
Bridging Studies in the Asian Pacific

Shook-Fong Tan
Ministry of Health, Singapore

Singapore is an island state with a population of 4 million people. In the year 2000 there were 5325 doctors, 1143 pharmacists and 15,947 nurses. There are 24 hospitals (public & private) with a total of 11,739 beds.

Conduct of Clinical Trials are not compulsory for drug registration in Singapore but these must be carried out according to the Declaration of Helsinki, Medicines (Clinical Trial) Registration 1978 and its amendment (1998) and the Singapore Guideline for GCP (1998).

In 1998, the Singapore GCP guidelines which adopts the ICH guidelines was launched. This ensured that clinical trials are conducted at internationally acceptable ethical and scientific standards. Initiatives in place included legislation and formation of ethics committees. In preparation for adopting ICH GCP Guidelines there were intensive teachings over 2 ½ years for Principal Investigators, Clinical Research Assistants, Doctors, Nurses, Pharmacists, Laboratory Technicians. These courses were organised by the Ministry of Health, clinical trial centres in the hospitals, the academia and clinical research organisations. The teachings focussed on different sections of ICH GCP and stressed on important points for different groups of people.

The majority of clinical trials conducted in Singapore are Phase III multi centre trials on new drugs. Others include Phase I and Phase II trials for new drugs, Phase IV trials on registered drugs and clinical trials on registered drugs for new indications. A Clinical Trial Certificate issued by the Health Sciences Authority is necessary before a clinical trial can be conducted.

Pharmacokinetics in the different clinical situations such as children, elderly and the pregnant woman are expected to be different. From the pharmacokinetics studies the relevant dose and dosing regimens can be drawn.

Bridging studies on ethnic differences is still new. Bearing in mind the cost and timeliness to registration of drugs, bridging studies need only be carried out for specially identified drugs. The Asia Pacific with a total population of 1.49 billion people is a worthwhile site for consideration of bridging studies. In the selection of a country for bridging studies several considerations such as standards must be borne in mind.
SESSION1

Implementation of Bridging Study-Taiwan’s Experience

Meir-Chyun Tzou
Bureau of Pharmaceutical Affairs, Department of Health, Taiwan, R.O.C.

To face and act to the drastically changing environment of new drug development, the Department of Health (DOH) in Taiwan has made a lot of efforts in various aspects of the regulation and registration of new drugs.

Recent trends in globalization of the new drug developments have urged the needs of the mutual recognition in regulation of new drug registration between regulatory authorities of different countries. In order to eliminate the redundant or unnecessary clinical trials and to understand better the effect of ethnic sensitivities of a new drug, the International Conference on Harmonization (ICH) E5 guidance: Ethnic Factors in the Acceptability of Foreign Clinical Data, is adopted by DOH in Taiwan. Local clinical trials are required for the new drug registration since 1993 (July 7 Announcement) in Taiwan, while DOH has developed lists of registration trial waivers corresponding to the trend of global pharmaceutical development. Recently, An announcement made in December 12, 2000 (also known as Double-Twelve Announcement) clearly stated the scope and principle for implementing the bridging study starting from January 1, 2001. The sponsors are encouraged to consult with DOH in the earliest stage of new drug development. There is a one-year transition period before full implementation. During this period, the sponsor can choose to conduct a local registration trial based on the July 7 Announcement or a bridging study according to the result of evaluation process.

DOH, in conjunction with the effort of Center for Drug Evaluation, has made countless efforts in developing the regulatory process for consultation and evaluation of bridging studies. To closely following the ICH E5 guidance, sharing experiences, developing a sound and practical methodology for implementing the bridging study, a bridging study symposium was held on May 2001. During this symposium, the experts from different backgrounds discussed issues on the ICH E5 guidance, the scientific consideration of bridging study, methodology and statistic model, and procedure of consultation and evaluation of bridging studies. Currently, DOH received 17 bridging study evaluation applications for new drug applications. We sincerely hope that through our efficient and transparent process of evaluation of bridging studies, we can develop sound and practical methodology for implementation of bridging study in Asia-Pacific region to assist pharmaceutical industries in their development strategies for global development of new drugs.
Development of Evaluation and Consultation on Bridging Studies: Thailand Experiences

Suchart Chongprasert
Food and Drug Administration, Thailand

The conceptual framework to address the impacts of ethnic factors on drug’s responses laid out in the ICH E5 has currently brought increased awareness in several countries regarding local trials to be requested. It is widely accepted that the influences of ethnicity on drug’s effects are not a new concept, but the ICH E5 puts this concept into concrete criteria and guideline to build justification whether a local clinical trial is needed and, if necessary, to determine types of the trials. This is a real innovation. Historically, conducting a local clinical trial in Thailand is not a mandatory requirement, but Thailand has experienced requesting a local clinical trial about 5% of the total applications submitted for market approval. It happens when there is reasonable evidence to believe that foreign clinical data might not provide sufficient information regarding safety, efficacy, dose, and dose regimen in Thai population. However, a guideline and criteria to facilitate the judgement for the request of the local trials have not been established. Because one of the major responsibilities of the FDA is to assure the public that quality, safe, and effective drug will be available in a timely manner, it is therefore an urgent need to develop science–based criteria and guideline to assess the influences of ethnic factors and determine if there is a need for and, if necessary, types of local clinical trials. The FDA has recently stated a clear policy to take advantages of the concepts of bridging study established in the ICH E5 to improve our drug registration system. Distinction has been made clearly that local trials needed are classified as either additional study to fulfil the local regulatory requirements or a bridging study to allow extrapolation of foreign clinical data to the population of the new region. The FDA then preliminarily developed three sets of assessment criteria. They are 1) criteria to evaluate the fulfillment of regulatory requirements, 2) criteria to assess drug’s sensitivity to ethnic factors, and 3) criteria to evaluate extrapolability of foreign data. All of these sets of assessment criteria will be presented and discussed. In addition, a schematic diagram showing how to evaluate the need for bridging study in Thailand is presented. Comments, suggestions, criticisms on these assessment criteria are welcomed. In the near future, a series of workshops will be organized to provide an industry-regulatory-academia dialogue forum to brainstorm on the appropriateness of the criteria. Importantly, exploring a statistical approach for the bridging study is also ongoing. The consultation process to promote scientific discussion on bridging study among involved parties is under development. Currently, the FDA is developing a structure and organization of the consultation process. Thus, we are focusing on the development of criteria and guideline to evaluate the need for and types of local trials, if necessary, as well as a
consultation process. It is expected that the FDA would be able to implement a bridging study requirement by the year 2002. However, the FDA emphasizes that a bridging study must not lead to an unnecessary delay or obstruction of a registration process i.e., bridging justification must be rationally built up on strong scientific evidence that the drug is ethnically sensitive, and that sensitivity significantly affects a clinical outcome.
The International Conference on Harmonization has defined bridging as the use of clinical data from one regulatory region to support registration of drugs in another region. A critical issue in bridging is the role of ethnic factors, i.e., differences in efficacy and safety between populations. From a statistical point of view, bridging involves extrapolation of evidence regarding efficacy from one region to another. As does any extrapolation, any use of bridging in the evaluation of drugs requires assumptions, in this case about treatment by region interaction. In the absence of such assumptions, one would be required to develop a complete clinical data package in the new region.

Countries with small pharmaceutical markets face a dilemma when they consider whether to approve drugs based on evidence of efficacy and safety developed primarily in other regions. If they require substantial clinical data within their own country to provide an empirical basis for bridging, the cost of obtaining drug approval may well exceed the potential financial value of approval. If they require little or no clinical data within their country, they run the risk of approving drugs that are either ineffective or have unanticipated adverse effects in their patient population.

This paper argues that this problem can be addressed most effectively by a regional strategy in which countries with some degree of similarity in the ethnic characteristics of their populations develop empirical evidence for efficacy and safety that can be applied simultaneously in the several participating regions. It describes a statistical approach based on empirical Bayes methods that allows pooling of evidence from several regions with allowance for variation among regions in drug efficacy. When the estimates of efficacy are very similar across regions, the region-specific estimates of efficacy will be strongly determined by the average efficacy across regions. When the estimates of efficacy show substantial variation between regions, the region-specific estimates will be based primarily on regional data, with consequent loss of precision.

The approach is illustrated using data on the efficacy of sertraline from Phase III trials with placebo and active controls from around the world.
On July 3\textsuperscript{rd}, 2001 the European Commission adopted a comprehensive package to revise the European pharmaceutical legislation in the near future. The major changes are derived from the past 6 years of experiences with the current legislation. The underlying concept of the proposed revision is to further streamline the procedures for marketing authorization for medicine in Europe.

Among the proposed changes the followings represent the cornerstones:

- the strengthening of the scientific advice for companies provided by the European Medicines Agency’s various committees;
- the introduction of a "fast-track" registration procedure that facilitates patient access to innovative treatments;
- the restructuring of the Agency’s Management Board as well as the establishment of an Advisory Board;
- the legalisation of the "Mutual Recognition Facilitation Group" and its role in resolving differences of opinion among national agencies;
- the shortening of the first assessment;
- the possibility to market a product in a "positive" Member State during the arbitration process;
- the harmonisation of data protection at 10-year for all EU Member States and for both regulatory procedures;
- renewals of marketing authorizations no longer required;
- improvements in "business flexibility";
- enhancements of the pharmacovigilance procedures;
- improved patients access to information on prescription medicines.

Detailed explanation of the existing regulation and the proposed changes will be given with a critical view based on Boehringer Ingelheim’s position as a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA).
Practical Issues in Conducting Multi-country Studies

Kenneth E. Stanley
Harvard School of Public Health, World Health Organization, USA

The conduct of a clinical trial is a complex undertaking involving the collaboration of many disciplines, including medicine, laboratory sciences, quantitative sciences, ethics, politics and regulatory affairs. Involvement of multiple countries in a study significantly increases this complexity. Contrary to the common view that language differences would be a key problem, aspects of standardization and the discipline needed to conduct high-quality clinical research often present the greatest challenges. The following basic principles focus on the key practical issues in designing and conducting such studies.

Basic principles
1. Alternate study leadership; do not share leadership.
2. Standardize, document and periodically check all key study components.
3. Agreeing to disagree is not an option.
4. The discipline of randomization must be established and maintained.
5. MDs are notoriously poor at filling out data forms.
6. Data managers are professionals too.
7. Periodic meetings of key staff with wide-open reviews of performance.
8. Use an Executive Committee with one participant from each component.
9. Use an Independent Data Monitoring Committee (IDMC/DSMB).
10. Only modify an ongoing study if the change is “enthusiastically unanimous”.

Conduct of multi-country studies can yield definitive research conclusions in situations in which single-country studies would be inconclusive. However, such studies may provide a greater legacy by promoting good clinical research methodology and establishing close collaboration within and between countries.
Pharmacogenetics and Bridging Studies

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The purpose of bridging studies is to determine if ethnic differences exist in either or both a drug’s disposition and response. Such differences may translate into differences in the dose required to produce either therapeutic or toxic effects, so that different doses may be required in different populations. In the past, such bridging studies have used randomly chosen individuals in the different populations, often in relatively small numbers with the assumption being that these individuals would be representative of the entire population under study. However, we now recognize that interindividual differences, including ethnic differences, are due to either or both genetic differences and environmental differences. While environmental differences may sometimes be hard to quantify and identify, genetic differences between different ethnic groups are now well described, and include ethnic differences in drug metabolism, drug transporter, and drug receptor genotypes. The implication of these interethnic differences in genotype distribution needs to be taken into account in designing and interpreting gene studies. In the future, bridging studies should not be performed without appropriately matching populations by genotype. Therefore, it is time for a new approach to the design of bridging studies, and to determine when such studies are either appropriate and interpretable.
Significance of Extrapolation of Foreign Clinical Data to Asian Countries

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Drug review procedures and drug development strategies are changing rapidly now due to the “The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use” (ICH), which was initiated in 1990. The ICH seeks to improve the efficiency of development and review process for promising new drugs. In particular, the E5 guideline (extrapolation of foreign clinical data to new regions for new drug applications) has a significant impact on new drug development in Japan.

It has been well known that two aspects - intrinsic and extrinsic factors - should be considered to extrapolate existed foreign clinical data to new regions. Main emphasis has been paid on the extrapolation of Western clinical data to a country, say, to Japan, and several new drugs have been approved through the extrapolation in Japan.

We can apply the same principle among similar racial regions, say, Asian region, by extrapolation of clinical data from one country to other countries with probably lessened conditions. This is due to considerably similar intrinsic factors among the regions. This suggests that it might be possible that Western clinical data can be extrapolated to a large region with several similar countries simultaneously. This indicates that there exist an appropriate way for a global drug development. We investigate necessary conditions from statistical point of view.
Challenge in Conducting Global Clinical Trials

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Since the ICH E-5 guidelines were issued, there have been many attempts to use the bridging concept to incorporate overseas data into Japanese NDAs, and there have in fact been more and more drugs that have been approved as ethical drugs following the acceptance by the MHLW of the extrapolation of their overseas data.

However, up to now the focus has been on studies that have already been conducted overseas, and on conducting similar studies in Japan as bridging studies and evaluating whether or not the results of the two studies are similar. Naturally, the way in which similarity is evaluated varies depending on the drug, since drugs differ widely in terms of their features and therapeutic areas. Consequently, the development in Japan of drugs based on the bridging concept is still being conducted on a trial-and-error basis, and it is therefore still difficult to say what should be studied in Japanese.

The most important issue is what sort of data are necessary in order for an ethical drug to be used appropriately in Japan.

This needs to be discussed in more detail in order to conduct development simultaneously in Japan and other regions, to file simultaneous NDAs, and to receive prompt approval review.

Although the age of individualized therapy based on a person’s own genes is approaching, until that day comes, we must study a variety of appropriate drug development approaches, including the existing bridging concept.
SESSION4

TV Conference: Regulatory Experience with ICH E5

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Approval Summary for Imatinib Mesylate Capsules in the Treatment of Chronic Myelogenous Leukemia

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*The views expressed are the result of independent work and do not necessarily represent the views and findings of the United States Food and Drug Administration.

**Purpose:** Chronic myelogenous leukemia (CML) results from the Bcr-Abl fusion gene product, a constitutively activated tyrosine kinase involved in cell division and apoptosis. Imatinib mesylate (Gleevec™) is an orally administered inhibitor of that kinase. This report summarizes the preclinical profile of imatinib and describes its clinical activity.

**Experimental Design:** Animal toxicology and biopharmaceutical data are described. Results of Phase 1 and Phase 2 clinical studies in patients with chronic myelogenous leukemia in blast crisis, in accelerated phase and in chronic phase disease resistant or intolerant to alpha interferon are summarized. The basis for United States Food and Drug Administration marketing approval and post marketing commitments by the pharmaceutical company are discussed.

**Results:** Toxicology studies in the rat dog and monkey show imatinib hematologic, renal and hepatobiliary toxicity. Pharmacokinetic studies in patients with chronic myelogenous leukemia demonstrate 98% imatinib bioavailability. The elimination half-lives of the parent drug and the major metabolite, CGP74588, from plasma are approximately 18 and 40 hours, respectively. Approximately 81% of the drug is eliminated in 7 days, 68% in the feces and 13% in the urine. Cytochrome P 450 3A4 (CYP3A4) is the main enzyme responsible for imatinib metabolism.

Phase 1 and 2 clinical studies were conducted. The Phase 1 study, in 83 CML patients, evaluated oral imatinib doses from 25 to 1000 mg/d. Dose limiting toxicity was not observed. The three phase 2 studies, in CML chronic phase after failure of interferon therapy (CML-CP), CML accelerated phase (CML-AP) and CML blast crisis (CML-BC) enrolled 1,027 patients. CML-CP patients received imatinib 400 mg/d while CML-AP and CML-BC patients generally received imatinib 600 mg/d. Primary study endpoints were cytogenetic response rate (CML-CP) and hematologic response rate (CML-AP and BC). The cytogenetic response rate for CML-CP patients was 49%. The hematologic response rate of CML-AP and BC patients was 63% and 26%, respectively. Follow-up duration was too short to determine response durations or survival for any
CML disease category. The most common imatinib adverse events were nausea, vomiting, myalgia, edema and diarrhea. Elevated liver enzymes and/or bilirubin were reported in 27 patients (2.6%).

**Conclusion:** On May 10, 2001, imatinib mesylate (Gleevec™), manufactured and distributed by Novartis Pharmaceuticals, East Hanover, N.J., received accelerated approved by the United States Food and Drug Administration (FDA) for the treatment of Chronic Myeloid Leukemia in three clinical settings: blast crisis, accelerated phase, and chronic phase after failure of interferon-alpha therapy.
Applications of Whole Genome Shotgun Sequencing and Analysis

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Much of the progress made in biomedical science in the past century has been due to an increasingly sophisticated understanding of the cellular and molecular mechanisms underlying disease processes. Deciphering the nucleotide sequence of the human genome represents a major milestone in our ability to understand these processes. Formally initiated in 1990, efforts to sequence the human genome were markedly accelerated in 1998 when Celera Genomics pioneered the use of a strategy known as whole genome shotgun sequencing and a new generation of automated DNA sequencing instruments. Far ahead of the initial schedule, both Celera and the international, publicly-funded Human Genome Project jointly announced that they had completed versions of the human genome sequence in June 2000, with publications describing these efforts appearing in February 2001. Knowledge of the human genome sequence will help us understand the structure and function of the proteins and RNA molecules that control the developmental programs and functions of human cells in both health and disease. In addition to determining an assembled reference genome sequence, Celera has identified over 3 million mapped single nucleotide polymorphisms (SNPs) providing the most comprehensive view available of the patterns of sequence variation throughout the genome. Celera has also produced a draft sequence of the mouse genome and is developing sophisticated comparative genomics approaches aimed at identifying important conserved coding, and non-coding sequence elements. One of the major challenges facing geneticists, other biomedical scientists and clinicians over the next decade will be to develop an understanding of the ways in which DNA sequence changes correlate with risks for developing common diseases. Perhaps just as important, will be the search for patterns of SNPs that are associated with efficacy and toxicity of drug treatment. Tests based on such information offer the chance to offer truly personalized approaches to medicine in which individually tailored treatment programs or lifestyle interventions are aimed at preventing the development of serious consequences of disease.
Translation of Genomic Information into Drug Discovery and Early Clinical Development

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Until very recently, about 500 genes have been listed as targets of drug discovery. Wealth of information provided by human genome analysis has dramatically expanded the number of candidate genes for drug discovery targets. How to find disease related and/or therapeutic genes become key agenda having scientific and economic significance for academic research and pharmaceutical industry. SNP analysis and expression profiling of RNAs and proteins using microarray technology and proteomics offer great promise from diagnostic aspect. However, in view of extremely high cost necessary for drug development, additional tools are necessary to develop more creative approach in translating genomics into drug discovery and clinical development. Progress of molecular and cellular biology and biotechnology in the last decades has altered the traditional concept of drug based on organic chemistry. In addition to low molecular weight compounds, proteins (biotech drugs), peptides, DNAs, RNAs (gene therapy) and cells (cell therapy) have been added to drug catalogues. How to select and/or combine various therapeutic approaches optimized to particular diseases and to individuals is important for tailored medicine. Since many countries/economies do not have enough resources for costly drug development, it is important to develop technology platform for genomic medicine which is open to international community. I will discuss the role of translational research in bridging discovery/innovation and creation of new industry/medicine.
Tailor-Made Medicine; Dream or Nightmare?

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The advances in life science research has led, at the dawn of the new century, to analysis of human genome sequence and a variety of gene technologies which opened a gateway to a new paradigm for health care and medical practice. Combining with new generations of computing power, it has become possible to decipher genomic messages, to make genetic diagnoses for a wide variety of disorders/diseases, to discover and create gene- and protein-based new drugs, and to identify individual susceptibility and efficacy for drugs. Other possibilities include embryonic stem (ES) cells for cell and tissue re-generation and re-engineering, cloning of organs and even whole organisms including humans. Ethical issues will become critical for society with participation of professionals in different disciplines, scientists, the public and the policymakers. The national policy for research and development investment must be implemented carefully, wisely, and strategically as the resources are limited and the return could be unpredictable, but could be more than significant. International competition has become even harder as the results of life science research could become a significant component of national economic power and health care policy. I will discuss some key issues in these and other aspects of life science research and policies in Japan and elsewhere.
In this presentation I will discuss some of the ways in which new genetic discoveries will have an impact upon the future of medicine. The pace of the science and the technology in the field of genetics has led to many promises about how it will change the face of medicine. I will discuss how genetics is integrated into the research programmes of a large pharmaceutical industry and how this is designed to make use of emerging technologies and scientific approaches, in certain areas helping to improve the design of clinical trials and improve the process of drug discovery and development. I will illustrate with examples of data from the literature how pharmacogenetics has already had an impact, often helping to understand much better how to interpret ethnic differences in drug response. This is particularly important in the area of drug metabolism particularly with respect to the CYP family of enzymes emphasising the key individual differences that contribute to variability in drug response. However, it is clear that examples are now beginning to emerge in the literature of variability in genes that have a key effect upon the pharmacodynamic response to prescribed drugs. Our understanding of genetics will have a considerable impact upon the practice of medicine in the future but there are many issues to be faced before the final place of genetics in medicine is known.