



EMERGING MARKETS:

ACCEPTABILITY OF DATA GENERATED
FROM FOREIGN CLINICAL TRIALS
AND ETHNIC FACTORS IN DRUG
DEVELOPMENT

WORKSHOP
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Geneva, CH

WORKSHOP REPORT

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Acceptability of data generated from foreign clinical trials and ethnic factors in drug development

Section 1: Overview and Executive Summary

Background to the Workshop

The majority of medicines are not currently developed for exclusive use in one country, and there is a continuing debate on how best to use clinical data that are obtained from global studies so as to avoid duplicative testing, delayed availability, and increased cost of development.

As the regulation of medicine should be based on scientific principles, it is these that should be at the forefront of any discussion on acceptability of foreign data. When considering foreign clinical data, regulators will be checking to see that

- the data are relevant to their country's environment from a clinical perspective;
- studies have been conducted to appropriate standards;
- the evidence package is sufficient to meet the regulators' criteria for a registration of a new medicine;
- and that there are no issues of differing response relating to the ethnicity between the population studied and the local population.

There are a number of countries that require local clinical trials for registration as a pre-requisite for marketing the drug in the country, such as China and India, as well as countries that require bridging studies, such as Japan, South Korea and Taiwan. The International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5 Guideline was intended to establish a framework through which agencies could assess whether efficacy or safety data from other countries could be used to make regulatory evaluations in their own jurisdictions. It has now been over 10 years since the ICH E5 Guideline (Ethnic Factors in the Acceptability of Foreign Clinical Data) was signed off under the auspices of ICH and the guideline is still interpreted differently by different countries.

Many countries are actively investigating the relevance of ethnic factors to the way medicines are used by their constituents. Currently Japan

is being proactive in looking to encourage companies to include Japan in global trials. There is also an initiative to evaluate clinically relevant differences between Asian populations, with China, Japan and South Korea in discussion about undertaking studies to identify if there are any clinically relevant differences in data generated from patients in their respective countries. In Taiwan and South Korea, the agencies have identified which products require bridging studies and for which ones a company can obtain a bridging waiver.

In the future, there are concerns that individual countries might increase their requests for additional data to be generated in their country or region. As more companies undertake trials outside of Europe and USA, these regulatory authorities are becoming more conscious that companies may be submitting dossiers that will predominantly include data from clinical studies conducted outside the ICH countries. Matching the regional sensitivities with the limitations of global clinical programmes will be a challenge to be overcome.

This Workshop was held to move forward the discussion on this topic, not just to evaluate 10 years of the E5 guideline, but to understand the current perspectives of agencies and companies on the use of foreign data and to look to the future and identify the framework that agencies should be using when interpreting foreign clinical data.

Workshop Highlights

Speaking on behalf of **Dr Robert O'Neill**, *Director Office of Biostatistics, CDER, FDA, USA*, **Dr Paul Huckle**, *Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA* explained that the FDA is receiving increasing numbers of applications based on clinical trials that were conducted either entirely or partially outside of the United States. Although he regards the E5 as still fit for purpose, he suggested that more attention should be paid at the trial planning stage to the sources of variation and potential heterogeneity in responses, treatment effects, and identifying the best outcomes to characterise treatment effects. Prior evaluations must be made of the impact of genomic and response profiles on the chosen study design.

Before 1998, individualised country pharmaceutical development strategies and a lack of cooperation between regulatory agencies resulted in a lag in the development of medicines in East Asia. **Dr Sue Forda**, *Vice President, International Regulatory Affairs, Eli Lilly and Company Ltd, UK* told the Workshop that the E5 Guideline, with significant support from the regulatory agencies, has facilitated global drug development including that in East Asia, resulting in optimisation of resources utilisation. It remains true, however, that intrinsic and, most especially, extrinsic factors may influence the applicability of foreign data in a particular geographic setting. Encouraging developments in East Asia include the increased collaboration and alignment among regulators and increased acceptance of common East Asian ethnicity assessments. Work is still needed to shorten clinical trial approval timelines for innovative products and to remove predefined patient allocation targets in some regions.

Professor Mamoru Narukawa, *Associate Professor, Division of Pharmaceutical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Japan* discussed the significant impact that the ICH E5 Guideline has had on the strategy of new medicine development in Japan and the resulting accumulation of experience in utilising and evaluating foreign clinical data. Japan requires bridging studies for about 70% of drug applications based on non-Japanese data. They have initiated a programme of collaboration with other Asian regions, forming a research group for the study of the pharmacokinetics of ethnic factors that might impact the relevance of clinical data for East Asian populations.

The ICH E5 experience in Chinese Taipei was presented by **Dr Meir-Chyun Tzou**, *Director, Division of Pharmaceutical Chemistry, Bureau of Food and Drug Analysis, Department of Health, Chinese Taipei*. In Chinese Taipei, sponsors are required to conduct clinically meaningful bridging studies only when ethnic issues are identified through a bridging evaluation carried out in accordance with the ICH E5 Guideline. Bridging study requirements have not only resulted in labelling changes in Chinese Taipei and worldwide, but have also lent an independent Asian regulatory voice to the globalisation of drug development, registration and marketing.

Dr Jung Yun Chang, *Deputy Director, Korea Food and Drug Administration, South Korea*, explained

that major regulatory changes relevant to clinical trials have recently taken place in South Korea, including the Korean Good Clinical Practice revision for harmonisation with the ICH Guideline E6. With the new pre-Investigative consultation process, sponsors can determine whether a clinical trial protocol is appropriate and obtain advice on the development plan before embarking on the final safety and efficacy confirmatory clinical trial. Bridging study waivers for non-Korean trial data are granted in the review of orphan drugs, drugs for life-threatening diseases, diagnostic reagents, radiopharmaceuticals or those drugs with no significant systemic effects.

Currently, 70% to 80% of trials in Singapore are multinational or global trials sponsored by pharmaceutical companies or contract research organizations. Fifty to 60% are multinational or global trials (phase II-III) to support new drug applications. **Dr Huei-Xin Lou**, *Deputy Director, Pharmaceuticals and Biologics Branch, Health Sciences Authority, Singapore*, specified that all clinical drug trials conducted locally have to comply with legislation for oversight of clinical drug trials, which includes the Medicines Act, Medicines (Clinical Trials) Regulations and Singapore Guideline for Good Clinical Practice. In addition, regulatory requirements in Singapore specify that all clinical trials require Clinical Trial Certificates from the Health Products Regulation Group, Health Sciences Authority.

Dr Jane Lin, *Senior Medical and Regulatory Affairs Director, Baxter (China) Investment Co Ltd, China*, stated that there are growing opportunities for conducting global clinical trials in China. However, for successful simultaneous international drug development, involvement with China should be initiated early in clinical development, with consideration of local medical practice while developing study protocols. Inclusion of a sufficient number of Chinese patients should be planned to satisfy regulatory requirements. Furthermore, it is a good regulatory strategy to have science-based discussions with Chinese agency reviewers, thereby facilitating and promoting the international exchange of information and expertise among stakeholders.

Dr Fergus Sweeney, *Head of Sector, Inspections, European Medicines Agency, UK*, defined the challenges faced by the European Medicines Agency (EMA) in the acceptance of clinical trial data from non-European countries as falling into the two broad categories of acceptability and

applicability. EMA requirements for good clinical practice, ethics, quality and safety apply to all clinical trials conducted in countries included in a marketing authorisation application submitted in Europe. European treatment guidelines and European epidemiologic databases and statistics are factors that are complementary to ICH E5 that should be taken into consideration during the design of global studies. To obviate the influence of extrinsic factors as much as possible, it is necessary to address the implications of these in a more structured fashion during the period of scientific advice.

Although differences in intrinsic and extrinsic factors and study conditions exist both within and between regions, evidence coming from multiple regions can be acceptable. **Rob Hemmings**, *Statistics Unit Manager, Medicines and Healthcare products Regulatory Agency, (MHRA), UK* explained that it is important to identify, control and investigate the relevant factors. Failure to prospectively consider potential regional differences, and to plan for evidence to address potential heterogeneity, represents a risk to the drug developer.

Ray Harris, *Senior Director, Biostatistics, Eisai, UK*, outlined the risks for regional randomisation within global clinical trials, including resulting differences in efficacy due to subjective assessment, differences in language and lack of validation of scales. There may also be differences in safety because of different standards of reporting and other factors. Risks, however, can be mitigated through protocol development that includes good planning, study initiation and monitoring.

In his presentation *The Myth of Culture: A Research Ethics Perspective on Ethnic Differences in Global Clinical Research*, **Francis Crawley**, *Executive Director, Good Clinical Practice Alliance – Europe (GCPA), Belgium*, said that common public

good and contributions to public health can be achieved through industry research with government oversight. A certain polarity exists, however, in the ethics of clinical trials conducted in countries with less developed pharmaceutical markets. The need to protect trial participants and their communities against exploitation can exist at odds with the recognised need for, and contribution of, clinical trials to public health.

In the opinion of **Dr Pol Vandenbroucke**, *Vice President, Development, Emerging Markets, Pfizer Inc, USA*, the quality of the institutional board review and informed consent for clinical trials in the Emerging Markets might be improved if ethical considerations would be specifically addressed in a separate section of the clinical trial protocol and a system to publish IRB/EC trial reviews established.

Dr Murray Lumpkin, *Deputy Commissioner, International Programs, Food and Drug Administration, USA* concluded the Workshop with his presentation on the challenges to the FDA in the use of foreign data for drug authorisation. Increased requirement for worldwide GCP inspections require increases in resources, capability assessments, knowledge of various medical qualifications and medical practice legislation and interactions with international regulatory counterparts. Regional ethical standards, ethics committees, and documentation represent additional FDA challenges, including individual versus population ethics, properly applying the definition of “exploitation”, and the resulting disqualification of data from poorly planned studies.

Section 2: Syndicate and Panel Discussions

Workshop participants formed two syndicate groups to discuss the following topics:

How to ensure acceptance of foreign clinical data at time of registration

What are the arguments for and against individual countries requiring data to be generated in their country or region?

The Chairpersons and Rapporteurs for the groups follow:

Syndicate 1	Chair:	Dr Petra Dörr , Head of Management Services and Networking, Swissmedic
	Rapporteur:	Dr Simon Larkin , Head of Product Development, Celgene International, Switzerland
Syndicate 2	Chair:	Professor Robert Peterson , Chairman, Canadian Expert Drug Advisory Committee (CEDAC); Clinical Professor, University of British Columbia, Canada
	Rapporteur:	Julie Dennis , Senior Director, Asia Region, Worldwide Regulatory Strategy, Emerging Markets Pfizer Limited, UK

In order to inform the Syndicate participants regarding current perceptions of the acceptability of foreign data, a brief survey was undertaken to explore experiences and views of Institute member companies. Ten of the sixteen companies participating in the Workshop were able to provide data.

Survey objectives

Within their companies, participants were asked to identify:

- How the E5 Guideline is being used in global drug development
- Perceptions of where bridging/local studies have been required and whether these have been justified
- Perceptions of foreign data acceptance in registration of new medicines and how extrinsic and intrinsic factors play a role in characterising ethnic differences
- Perspectives with regard to how ethnic differences will affect the use of foreign data in the future

Survey results

Although the majority of companies responding to the survey are looking forward to undertaking a single integrated global development programme for their new medicines, the main concepts of the E5 Guideline are still not imbedded in all companies. In fact, the majority

of participants do not believe the E5 Guideline is clear, well understood and interpreted in the same way by all agencies. Respondents indicated, however, that the majority of ethnic factors as cited by E5 can be identified and addressed in protocols prior to undertaking clinical work.

Responses further indicated that it is anticipated that from 2015 to 2020, the percentage of foreign clinical data will increase in dossiers submitted to the US and EU to eventually reach approximately 75%. All respondents believe that regulatory acceptance of foreign data will mainly be on a case-by-case basis and eight out of nine responding companies have had the acceptability of foreign data questioned in the past. Key issues looking forward are around data quality, study design and the ability of the data to be applied to local populations.

Syndicate 1: How to ensure acceptance of foreign clinical data at time of registration

Background

The starting premise of this topic was that the majority of medicines are not currently developed for their exclusive use in one country and, therefore, dossiers will contain data derived from multiple countries. The acceptability of the “foreign” clinical data presented in a regulatory dossier should be based on scientific principles and not regional perceptions of potential ethnic or extrinsic differences.

Therefore, the focuses of this syndicate were 1) a discussion of the challenge for companies to determine the impact that ethnic factors have on the activity of individual medicines and 2) to outline, based on current experience and future needs, what key principles companies and agencies will need to work within to ensure regulatory acceptance of foreign clinical data.

Outcome of Discussion: Syndicate 1

Because the global pharmaceutical market and the execution of clinical trials are changing, the collection and flow of data are also changing, with foreign data within dossiers becoming the norm. Intrinsic ethnic factors are becoming well understood through scientific observation and can be objectively assessed and managed, but their importance depends on the specific nature of the medicinal molecule and the geographic location of the test population, which will determine the potential scope for within-group differences and group response homogeneity.

As the regional diversity broadens, however, so does the treatment landscape, and the extrinsic factors that influence diagnosis and disease management are becoming of greater importance, harder to identify, and more difficult to reconcile across regions. Now and in the future, bridges between diverse data sources and local populations will need to be built and requirements for that bridging satisfied. Data requirements include, adaptability, acceptability according to recognised standards, applicability or the local “fit”, and familiarity and trust gained through experience.

The consensus approach has been to rely on the E5 Guideline as the map for determining the acceptability of data that could be affected by ethnic factors. But is the E5 Guideline still fit for purpose? The suitability of the intrinsic elements specified by the Guideline depend on the situation – for example, the homogeneity of the local population in Japan versus that of Singapore. Current standards of interpretation seem reasonable for short-term exposure to a new medicine, but longer term effects and variations remain unknown. Extrinsic elements listed in the Guideline involve much greater potential diversity; and lack of familiarity with both standards and content can be problematic. Regional differences in standards are addressable, but differences in medical practice and therefore measures, endpoints, and standards of care remain significant challenges.

Critical Issues

- Failures of compliance with a rational framework

- Differences in medical practice
- Standards of diagnosis and treatment, concomitant medicine, behavioural factors, social welfare
- Objective versus subjective outcomes, ratings and scales
- One size doesn't fit all: in an era of personalised medicine, we should not expect to depersonalise populations

Strategies

- Continue to build in good clinical practice at the very beginning
- Engage in training and sharing of best practice on what actually matters
- Where possible, seek internationally agreed upon treatment goals and measures up front with stakeholders
 - Common endpoints and confirmations
 - Suitable treatment benchmarks for comparison, rather than single “standards” of care
 - Due diligence and consensus
- Determine which regional factors matter in a disease and which don't: aetiology, natural course, treatment options, treatment aims, outcomes
- Develop objectivity through validation of scales and ratings
- If a medication does not fit into the current local paradigm, it must be adapted or withdrawn

SYNDICATE 1 RECOMMENDATIONS

- Allow a step-wise approach: develop local >> national >> regional >> internationally recognised standards of evaluation and enforcement
- Define common treatment goals and therefore endpoints for common diseases, and suitable benchmarks as opposed to standards of care
- The Institute to conduct systematic research on population behaviours, such as the placebo effect
- Anticipate and select “best fit” populations, starting at a regional level

Syndicate 2: What are the arguments for and against individual countries requiring data to be generated in their country or region?

Background

The starting premise for this Syndicate was that there is a continuing debate on how best to use clinical data that are obtained from global studies so as to avoid duplicative testing, thus reducing delay in availability of medicines and the cost of development. Despite the widespread acceptance of the E5 Guideline, often, regional agencies will request that local experience with the new product be obtained with patients from that country in order to confirm that there will not be unforeseen issues due to intrinsic or extrinsic ethnic factors. The need to conduct local studies is sometimes waived in lieu of bridging studies and these may or may not be helpful in identifying ethnic differences in response.

Therefore, the focus on this Syndicate was a discussion of the role played by and relevance of extrinsic and intrinsic ethnic factors in the clinical evaluation of medicines. The group was also asked to consider how to establish confidence within regulatory agencies that the appropriate benefit-risk decisions for the local population can be determined without the need for a local clinical trial if the medicine is considered from prior experience to be ethnically insensitive or has been tested on a similar population. Conversely, is there still a role for conducting local clinical trials for certain medicines? Which scientific criteria need to be met to include a medicine in this category?

Outcome of Discussion: Syndicate 2

Critical issues

- Identification of multiple factors that lead to individual country requirement for local clinical trials
- Ethnicity needs to be specified on intrinsic and extrinsic factors
- Studies addressing intrinsic and extrinsic factors need to be proactively defined
- Health technology assessment (HTA) requirements need to be factored into local/regional studies

Strategies

- Confirm the reasons why countries require these data and how will it be evaluated by them.
 - Political (desire to create research capacity)
 - Economic (seeking R & D investment)
 - Scientific
- Gain experience to satisfy academia and key opinion leaders
- Validate measurements in other populations
- Extrapolate results to local population
- Negotiate around the timing of local studies designed to meet political, economic, or academic requirements
- Establish criteria for local/bridging studies based on intrinsic and extrinsic factors
- Determine if there are accepted global criteria
- Determine when a bridging study would be required to determine appropriate dosing?
- Study to examine a unique safety issue, for example, HLA marker
- Validate tools used to measure extrinsic factors, for example, Alzheimer's questionnaire

SYNDICATE 2 RECOMMENDATIONS

- Conduct a survey of countries that require local/bridging data, confirm the reasons why countries require these data and how they are evaluated
- Make a retrospective analysis of local/bridging studies and their influence on the final regulatory decision
- Conduct a review (Workshop) of those submissions that were either approved or rejected in order to understand if the reasons were reliability or extrapolability of the studies, also include studies submitted to EMA

Panel discussion

A reflection from UK MHRA, Health Canada and Australian TGA on the outcome of the syndicate discussion on acceptance of foreign data/need for local data in drug registrations for their jurisdictions

Professor Sir Alasdair Breckenridge

Chairman, Medicines and Healthcare products Regulatory Agency, (MHRA), UK

Although the ICH E5 Guideline has been implemented for 10 years and has served its stakeholders very well, it now needs to be decided if it continues to be the best framework to be used in the new paradigm of global drug development.

Because *ethnicity* does not seem to be a very useful term from a regulatory perspective, the term *regionality* could be substituted, as it is not ambiguous and does not convey the aspect of pharmacogenetics present in *ethnicity*. There are, for example, 57 ethnic groups in China, and similar characterisations could be made of Europe and the United States, but the clinical relevance of these categorisations remains to be determined through comprehensive ethnopharmacologic analyses. However, as discussed at this Workshop, the ways in which regional differences have influenced dosing in Asia may be more of a reflection of the clinical approaches to dosing typically recommended in the West as opposed to inherent biologic differences in Asian patients.

There must be a more thorough consideration of whether regional studies are required to satisfy scientific, political or social needs. Regulators must be able to justify their requests for studies in local populations based on scientifically valid precepts, if they believe that non-regional data cannot be extrapolated to their population. As the majority of clinical trial populations shift from traditional settings in the West, it will be interesting to observe the shift in regulatory requests for local or bridging studies.

Reimbursement is also a global concern, and for far too long regulators and Health Technology Assessment agencies (HTAs) have operated in distinctly separate silos. Regulators need to be involved in HTA assessment because they must perform benefit-risk analysis of a medicine throughout its life cycle. It is important to define HTA assessment, however, as a comparison of clinical and comparative effectiveness in real user populations. By comparison, the measure

of cost-effectiveness is often predicated by local economic considerations.

Audience response

- The missing stakeholder in our discussions here is academia. In cases of significant unmet medical need, treatment practices are often driven by publications and academic collaborations. Academicians can be utilised to great effect to validate international treatment standards, as they have been in the development of guidelines in chronic lymphogenous leukaemia.

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Canada

For a number of years, regulators in Canada have seen a shift in the locations of clinical trials used to support new drug applications. In the past, pivotal trials for new drugs in Canada were typically conducted in Europe and North America, with the use of trials conducted in other regions to bolster recruitment as needed. Currently, entire development programmes may be conducted in areas outside of those traditional regions. Despite this global mix of patients, the data from most clinical trial subjects are indeed relevant to Canada's extremely heterogeneous population (perhaps with the exception of the First Nation community, who remain severely underrepresented in clinical research inside and outside of Canada).

From the regulatory perspective, the critical factor is the "robustness" of the data package to support the sought-for indications in the population that regulators are mandated to protect. In general, because people are more similar than they are different, regulators are more often confronted with challenges in the basic quality of the data from foreign sources rather than with issues of the effects of ethnicity or regionality. While it is true that there are areas, such as dosing, in which there may be some relevant differences among selected populations, this is the exception rather than the rule. Furthermore, most of these differences have surfaced as a result of post-hoc subgroup analyses rather than a priori results observed through careful study design.

Regulatory requirements for pivotal trials used in Canadian applications can be highly individualised depending on the drug being investigated, the patient populations and indication, and the standard of care for

comparison. Although the requirements needed to address these issues are best determined in early-stage development, Canadian regulators generally do not have the benefit of these discussions with sponsors until the time of, or shortly prior to application, at which point the minimum requirements necessary for additional data or analysis are discussed.

Finally, regulators have observed a knowledge gap for generalisable data, such as that for the placebo response. Meta-analyses by academic institutions of such generalisable data that can be applied globally across products would be helpful for regulators seeking to extrapolate global data to their local populations.

Audience response

- It is not placebo response that needs academic meta-analyses, but trial response, or the effect of trial participation and health care practitioner interaction on subjects, which applies to all treatment groups and which varies by region.
- New rigorous methodologies have evolved for indirect comparisons that are common in the evaluation of new medicines. Strenuous tests need to be performed to determine the homogeneity of a population, the similarity in study objectives, and the consistency of outcomes. The reality is that the placebo effect changes regionally and these differences will not be easy to dismiss.

Dr Ruth Lopert

Principle Medical Adviser, Therapeutic Goods Administration, Australia

As in Canada, Australian regulators have had to adapt to and accommodate many varied sources of clinical trial data. Also as in Canada, the need for additional data and analyses in studies conducted outside of Australia is highly situation-dependent.

However, even though intrinsic factors can be fairly well characterised, use of the term *regionality* to describe these factors may not be the best substitute for *ethnicity*. Furthermore, while the reasons for requiring additional local trial data should theoretically be scientifically justified, often the impetus for requiring these studies may be less based on science than on regional perceptions of the need for local data.

Because it is likely that there will always be a role for bridging studies to increase regulators' confidence about the activity of a new product in the local population, it may be advantageous to consider these studies as opportunities to better inform both a regulatory and HTA decision. Clinical and comparative effectiveness evaluations often require local data, particularly for those issues that concern quality of life and a bridging study may provide insights into validating subjective measures that will be assessed in a larger real-world population.

Workshop Programme

Session 1: Acceptability of foreign data in a globalised world: What are the principles?	
Ethnic factors, ten years on from adoption of the E5 Guideline: What have we learned and is E5 fit for purpose in the changing global development landscape?	
Regulatory perspective	Dr Robert O'Neill , <i>Director Office of Biostatistics, CDER, FDA, USA</i>
Company perspective	Dr Sue Forda , <i>Vice President, International Regulatory Affairs, Eli Lilly and Company Ltd, UK</i>
Ethnic Factors and the E5 Guideline: What has been learnt about ethnic differences based on experience	
The Japanese experience	Dr Mamoru Narukawa , <i>Associate Professor, Division of Pharmaceutical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Japan</i>
The Chinese Taipei experience	Dr Meir-Chyun Tzou , <i>Director, Division of Pharmaceutical Chemistry, Bureau of Food and Drug Analysis, Department of Health, Chinese Taipei</i>
The South Korean experience	Dr Jung Yun Chang , <i>Deputy Director, Korea Food and Drug Administration, South Korea</i>
Acceptability of data generated in global studies: How are agencies and companies ensuring credible and reliable clinical trials so that the data generated are robust enough for global regulatory scrutiny?	
A perspective from Singapore	Dr Huei-Xin Lou , <i>Deputy Director, Pharmaceuticals and Biologics Branch, Health Sciences Authority, Singapore</i>
A perspective from China	Dr Jane Lin , <i>Senior Medical and Regulatory Affairs Director, Baxter (China) Investment Co Ltd, China</i>
What are the key regulatory principles that will give confidence to regulators for acceptance of foreign clinical data to be used as pivotal in the assessment of new medicines for approval?	Dr Fergus Sweeney , <i>Head of Sector, Inspections, European Medicines Agency, UK</i>
Session 2: Global clinical research: are ethnic differences effectively covered?	
Chairman's introduction	Dr Murray Lumpkin , <i>Deputy Commissioner, International Programs, Food and Drug Administration, USA</i>
Regulatory perspective	Rob Hemmings , <i>Statistics Unit Manager MHRA and CHMP, Medicines and Healthcare products Regulatory Agency, (MHRA), UK</i>
Company perspective	Ray Harris , <i>Director of Biostatistics, Eisai, UK.</i>
An ethics expert perspective	Francis Crawley , <i>Executive Director, Good Clinical Practice Alliance – (GCPA) Europe, Belgium</i>
Company perspective	Dr Pol Vandenbroucke , <i>Vice President, Development, Emerging Markets, Pfizer Inc, USA</i>
An FDA reflection on the acceptability of foreign data and future issues that need to be addressed.	Dr Murray Lumpkin , <i>Deputy Commissioner, International Programs, Food and Drug Administration, USA</i>

Section 3: Workshop Presentations

Session 1: Acceptability of foreign data in a globalised world: what are the principles?

Chairman: Dr Paul Huckle

*Senior Vice President, Global Regulatory Affairs,
GlaxoSmithKline, USA*

Some reflections on the ICH: E5 Guideline after 10 years

Dr Paul Huckle for

Dr Robert O'Neill

Director Office of Biostatistics, CDER, FDA, USA

Key Principles of E5

The International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E5 Guideline was intended to establish a framework through which agencies could assess whether efficacy or safety data from other countries could be used to make regulatory evaluations in their own jurisdictions. It allows all regions to request additional or bridging studies if evidence relevant to that region is considered not convincing or relevant to local populations,

and provides a cap for the amount of additional data that can be requested in a region. Although this provision is rarely used by the US FDA, there are examples of its use in psychiatry and neurology product evaluations.

The E5 also specified the classification of intrinsic and extrinsic factors to be considered in product evaluations. The intrinsic factor focus of the Guideline is of the most current interest, relating genomic profiles to differential benefit or risk or dosing paradigms, and evaluating the differential prevalence of such genomic profiles for different ethnic and racial groups. The E5 Questions & Answers addendum clarified some points of ambiguity and stimulated new thinking in the initial Guideline and introduced the multiregional trial concept for bridging, highlighting the need for early agreement on protocols. The multiregional trial concept is very prevalent today and is potentially problematic to interpret if not planned or conducted well.

The FDA has primarily applied E5 in the evaluation of multiregional multicenter studies and typically evaluates results from inside and outside the United States or North America and then overall. On occasion, after the evaluation of a foreign study performed entirely in an area unfamiliar to the agency, the FDA may request an additional study if results are in question.

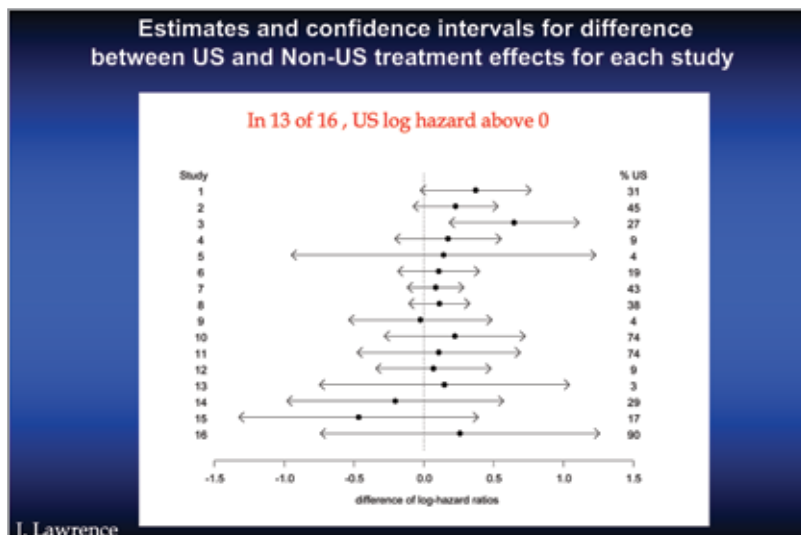
The FDA is receiving increasing numbers of clinical trials that are either conducted solely in a foreign region or are combined foreign and domestic. Of 1,926 clinical trials evaluated by statisticians from 2001 to 2007: 41% were domestic; 50% foreign-domestic; and 9% foreign. Of all patients enrolled in these trials: 30% were from the United States; 63% domestic and foreign; and 7% foreign. The review of the trials generally involves evaluating study results according to region or country, which are often difficult to interpret. The agency evaluates the study data and conduct and key metrics of quality, and prepares statistical displays of key sources of variation, bias and uncertainty. Regional and site outcomes are evaluated including dropouts, differences in response rates, outcomes, covariates, exposures and follow-up. Individual patient profiles nested within sites are assessed, including which sites and which patient records to evaluate in more detail. Of a selected sample of 22 NDA submissions whose decisions depended upon

**Of 1,926 clinical trials evaluated by statisticians during FY01-FY07:
41% were domestic; 50% foreign-domestic; and 9% foreign.**

**Of all subjects enrolled in these trials:
30% were U.S.; 63% domestic-foreign; and 7% foreign.**

	# Trials (%)	# Subjects (%)
Domestic (U.S. & Canada)	788 (40.9%)	320,221 (30.1%)
Domestic-Foreign	958 (49.7%)	668,572 (62.8%)
Foreign	180 (9.3%)	75,430 (7.1%)
Total	1,926	1,064,223

analysis and interpretation of treatment effects in multiregional trials: 4 were not approved because of regional heterogeneity; 9 were approvable but required more because of regional heterogeneity.



Differences in treatment effects are expected, but too much heterogeneity is problematic. The question is 'are these treatment differences real and are they systematic; that is, are the treatment effects consistently better or worse in the United States?' A study of major cardiovascular outcome trials over the last 10 years was undertaken by FDA statisticians to evaluate the possibility of systematic regional differences. In these 16 independent studies, treatment region was never a pre-specified factor for statistical evaluation. In 13 of the 16 studies, there was a demonstrated overall systematic effect, resulting in an overall statistically positive result for US treatment.

While intrinsic factor identification and possibly genomic studies to elucidate pharmacokinetic/ pharmacodynamic or responsiveness/ sensitivity may be conducted prior to later phase studies, in Dr O'Neil's opinion, the emphasis exists now as it should be, at the study design and analysis stage. Recognising that extrinsic factors will contribute a source of variability there should be planning for heterogeneity of treatment effects. Accordingly, the value of bridging studies seems less relevant.

Suggestions for the future

Dr O'Neil believes that the E5 remains fit for purpose. Clinical studies with many country sites are now being conducted in places not initially part of the ICH regions. The quality of the study, and its design and conduct are important to understand and control for the results to be interpretable and open to extrapolation. New regions with less experience will continue to be scrutinised closely as they gain experience with study conduct, quality, and investigators. Finally, more attention should be paid at the trial planning stage to the sources of variation and potential heterogeneity in responses, treatment effects, and the best outcomes to characterise treatment effects. In therapeutic areas where mechanisms of actions have been characterised, evaluations must be made of the impact of genomic and response profiles on the chosen study design.

Ten years on from the adoption of the E5 Guideline: What have we learned and is the E5 fit for purpose in the changing global development landscape?

Dr Sue Forda

Vice President, International Regulatory Affairs, Eli Lilly and Company Ltd, UK

The Past

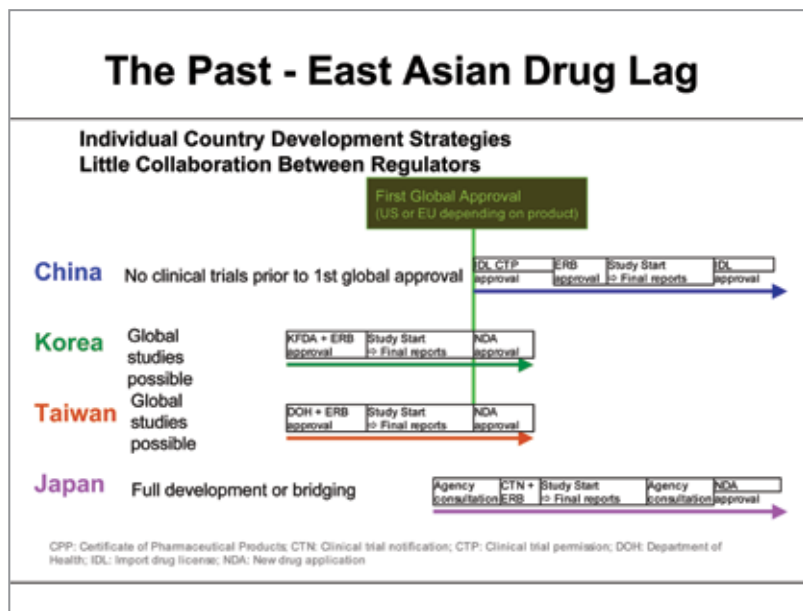
Before 1998, individualised country-specific pharmaceutical development strategies and a lack of cooperation between regulatory agencies resulted in a lag in the development of medicines in East Asia. Delays were not as pronounced in Korea and Taiwan, where participation in global development programmes was encouraged, but in China, the clinical trial approval process, which could take up to 15 months, was not even initiated until the first approval in a reference country was received. And in Japan, a completely separate clinical development process was often required. Consequently, the resulting lag time for approvals in these two countries ranged from 2 to 7 years as compared with the US and Europe.

framework for evaluating the impact of intrinsic and extrinsic factors on the efficacy and safety of a product, focussing in particular on the concept of the *bridging study*, in which a new region may request to determine whether data from another region are applicable to its population. This guideline brought great change in the strategy of drug development for Japanese, US and European pharmaceutical companies.

The E5 has continued to evolve, and in 2003 and 2006, E5 Questions & Answers were issued to further clarify the guideline. Meanwhile, in 2007, *Basic Principles on Global Clinical Trials* was published in Japan, which recommended the inclusion of that country in global drug development to eliminate the drug lag. The document encourages a case-by-case approach through consultation with the Japanese Pharmaceutical and Medical Devices Agency (PMDA) on study design, data handling and conduct of a global clinical trial. It additionally specifies that safety and pharmacokinetics should ideally be investigated via single-dose tests in a Japanese population prior to commencing joint international clinical trials; and that trials should include enough numbers of Japanese patients to show consistent results. According to the *Basic Principles*, all countries in global trials must be Good Clinical Practice-(GCP-) compliant, with Japan performing GCP site inspections as needed; preliminary investigations must be conducted for those factors that may affect the efficacy and safety of the drug; and social differences and clinical trial implementation conditions in each facility must be characterised.

The influence of extrinsic factors, such as disease definition and diagnosis and medical and therapeutic practice may be critical to determine the acceptability of a global clinical trial programme in Japan. Traditionally seen as the manifestation of ethnic differences, dose decisions in Japan are made through an integrated high-level evaluation of data including biology, toxicology, absorption, distribution, metabolism and excretion (ADME), clinical pharmacology and clinical efficacy and safety from both Japanese and foreign sources, but may not be only scientifically driven. Of 32 medicines approved in Japan after approval in the United States from 2003 through 2008, 20 were approved at the same dosage as the United States, 10 were approved at lower doses, and two at higher doses.

Great strides have been made in the past 10 years in the determination of the genetic



In 1998, the ICH issued the E5 Guideline, with the objective of facilitating the acceptance of foreign clinical data. The E5 recommended a

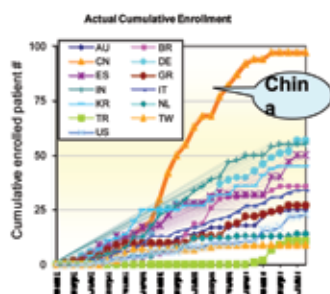
impact of therapeutics. Phase I studies remain key to establishing inter-ethnic, metabolic and biomarker profiles and target interactions, and many companies have dedicated clinical research units in Asia where there is access to full range of human variation. As a result, important studies have recently determined the similarity of metabolism and transporter genes between Chinese, Japanese and Caucasian subjects.

East Asia in Global Trials – Oncology

Increasing contribution to global studies due to high productivity

- Asia share about 12 % of patients in global US/EU registration studies (2007)
- ↑ enrollment rate & ↓ dropout

Example: Asian countries (especially China) in a global Oncology study



How drug development has changed

The previous default strategy for the generation of clinical data in different regions had been clinical development in Europe and US together followed by Japan and other Asian countries separately. The current clinical development strategy, however, leverages capability and capacity in Asia to meet parallel or staggered development programmes, taking into account complex development plan considerations such as timing and ethnic assessment.

There has been a shift from local to multiregional clinical trials in the Asian region, but there are problems conducting clinical trials in Japan, including the observation that trials are run slower than in other countries and often at a higher operational cost per patient; furthermore, there remains the possibility of differences in dose-response between patients in Japan and the United States and Europe.

Lilly's Asia CT experience

Currently, Eli Lilly initiates Asian clinical trials much earlier than previously. The company

prefers conducting a single phase III study for registration and the drive to reduce Asian drug lag has resulted in a reduction in the average timing of approval from its former range of 2.0 to 3.3 years to its current range of 1.5 to 2 years after the first regulatory approval. There is an increasing East Asian contribution to global studies due to high productivity in this region. China particularly has comparatively high patient enrolment and low patient dropout rates. Significantly, 24% and 38% of patients enrolled in two current Lilly global clinical trials are from East Asia.

Success in global drug development

Dr Forda pointed to the recent successful simultaneous submission and approval of tadalafil, a PDE5 inhibitor for pulmonary arterial hypertension (PAH) as a recent success in global drug development. A randomised, double-blind, 16-week placebo-controlled study was conducted in 405 patients with PAH, with a mean age of 54 years and with the majority of patients being Caucasian (81%) and female (78%). Aetiologies were predominantly idiopathic PAH (61%) and related to collagen vascular disease (24%) and the majority of subjects had a World Health Organization (WHO) functional class III (65%) or II (32%). Despite the challenges in identifying this very specific population type worldwide, the global plan proceeded efficiently and tadalafil was approved in the US in May 2009 and in Japan and the EU in October of that year.

Challenges in global drug development

Obstacles for global development have also emerged outside of Asia. In April 2008, in response to the fact that approximately 500 foreign studies are submitted to the US FDA each year that were not conducted under an investigational new drug exemption, the FDA updated its requirements for these studies; specifically, the studies must conform to GCP, subject rights must be protected, and the FDA must be permitted to validate the data through an on-site inspection.

Likewise, a reflection paper recently published by the Committee for Medicinal Products for Human Use (CHMP) stated that research has been performed on a number of medicinal products for which extrapolation of study results to a EU population has been challenged.¹ The paper identifies several extrinsic factors that may influence the extrapolation of study data such as medical practice, disease definition, study population, lifestyle, and genetic factors.

Accordingly, the solicitation of EU scientific advice is encouraged and an in-depth, prospective analysis of potential ethnic factors is recommended. Depending on the outcome of such analyses, it will be decided whether foreign clinical trials would be relevant to the EU setting or if additional studies in the EU are necessary. Indeed, there have been several recent instances in which insufficient data in European patients was cited by the CHMP as a rationale for negative opinions on new drug applications, despite approvals granted by regulatory agencies in the United States and Canada for those same medicines.

The future

Asia continues to move toward global development, with a continually evolving flexibility for product registration allowing efficiency and acceleration and integration with US and EU development programmes. Encouraging developments include increased collaboration and alignment among East Asian regulators and increased acceptance of common East Asian ethnicity assessments.

Work is still needed to shorten clinical trial approval timelines for innovative products and to remove predefined patient allocation targets. The E5 Guideline, with significant support from the regulatory agencies, has facilitated global drug development, resulting in optimisation of resources utilisation; however, intrinsic and, most especially, extrinsic factors may influence the applicability of foreign data to each geographic region. It is therefore essential to ensure that consideration and evaluation of the intrinsic and extrinsic factors is scientifically driven and an in-depth, prospective analysis of potential intrinsic and extrinsic factors is performed before proceeding with multiregional clinical trials.

Reference

1. Committee for Products for Human Use. A Reflection Paper: *The extrapolation of results from clinical trial studies conducted outside Europe to the EU-population*. Available at <http://www.emea.europa.eu/pdfs/human/ewp/69270208en.pdf>. Accessed December 2009.

Ethnic factors and the E5 Guideline: What has been learnt about ethnic differences?

The Japanese Experience

Professor Mamoru Narukawa

Associate Professor, Division of Pharmaceutical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Japan

Japanese policy for foreign data before and after E5

In 1985, the Japanese Ministry of Health Labour and Welfare (MHLW) published a notification of Japanese policy on the handling of foreign clinical data, which stated that foreign clinical data with credibility and quality were acceptable as a component of new drug application (NDA) data in Japan. The notification also specified, however, that pharmacokinetic and dose-response studies, as well as well-controlled trials to demonstrate the drug's efficacy and safety should in *principle* be conducted in Japan, which effectively negated the acceptability of foreign data for registration purposes in Japan.

In 1998, a new notification of policy was published by the MHLW, which was based on the ICH E5 Guideline and which stated that foreign clinical data prepared according to GCP were acceptable as NDA data in Japan. It further specified that the extent and content

of domestic clinical data (bridging study data) to assess the possibility of extrapolating the foreign data to the Japanese population should be decided based on the ICH E5 Guideline. Desirable conditions for the utilisation of foreign data in Japan include the use of internationalised diagnostic criteria, therapeutic approaches and trial practices and the controllability of the influence of ethnic factors in drug development and evaluation.

Since this publication, the number of new medicines approved in Japan through the use of foreign clinical data has grown substantially. Dose response bridging studies were conducted for 35% of those medicines, uncontrolled studies were conducted for 21% and other types of bridging studies were conducted for 14%; perhaps more importantly, no bridging studies at all were required for 30% of new medicines such as orphan drugs and HIV therapies.

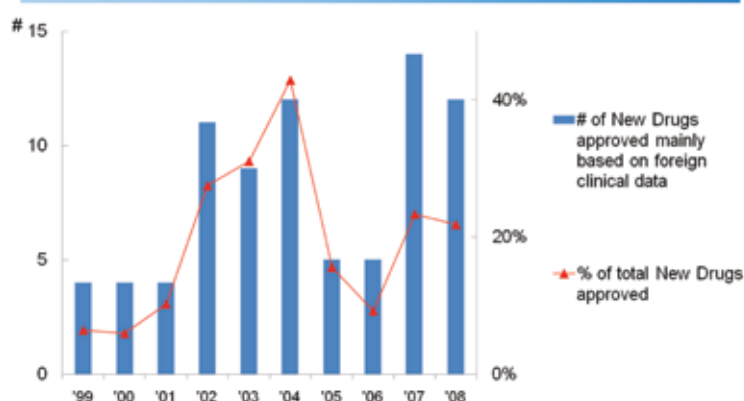
Bridging studies: 3 case examples

In the first of three bridging case studies presented by Professor Narukawa, a dose-response bridging study was conducted for a HMG-CoA reductase inhibitor after pharmacokinetic studies revealed that systemic exposure of the drug was approximately double in Japanese relative to Caucasians, possibly owing to involvement of transporter polymorphism. The results of the bridging study showed that one half the dosage specified for Caucasians was safe and effective in Japanese. Accordingly, that half dosage was recommended for Japanese, along with a requirement for intensive post-marketing surveillance. In fact, the following qualification was subsequently added to the US labelling: "... Dosage in Asian Patients: Initiation of ... 5 mg once daily should be considered for Asian patients." [The usual recommended starting dose is 10 mg].

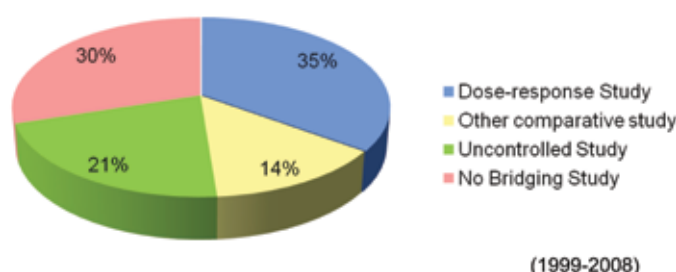
The second case study concerned triptans for migraine headaches, for which pharmacokinetic profiles were similar between Japanese and Caucasians yet the placebo response rate seemed higher in Japanese. However, considering the fact that the internationalised diagnostic criteria were applied, and that good dose-response relationship and superiority to placebo were shown in the bridging studies, the foreign data were judged to be extrapolatable to Japanese.

The final case study exemplified the failure of a poorly designed bridging strategy. A bridging study for a humanised IgG monoclonal antibody for severe persistent asthma in Japanese

Number of New Drugs Approved in Japan by Utilizing Foreign Clinical Data



Characteristics of Bridging Studies in Japan



2

patients was prematurely terminated because of slow enrolment. It was felt that patient accrual problems were likely to have originated because the protocol was designed based on the US protocol, through which concomitant medication was too severely restricted in light of Japanese medical practice.

As mentioned in Dr Ford's presentation, the MHLW has also published *Basic Principles on Global Clinical Trials* in 2007¹ with the goal of synchronising new drug development in Japan with that of Europe and North America to shorten or eliminate the so-called "drug-lag." These principles, consisting of twelve questions and answers for planning and conducting global clinical trials, specified that Japan should join in global clinical development from its early stages and that trials should be designed to obtain consistent results among regions and populations. This new strategy is expected to lead to a decrease in the number of new medicines that are approved in other countries

before Japan and a shortening of the overall drug lag. The number of multiregional clinical trials taking place in Japan is also growing steadily: in 2007, 38 of 508 trials were MRCTs and in 2008, 82 of 524 fell into this category.

Japan has also initiated a programme of collaboration with other Asian countries or regions, forming a research group for the study of pharmacokinetics of ethnic factors of clinical data of East Asian populations, retrospectively examining clinical trial data provided by the Japan Pharmaceutical Manufacturers Association, the Pharmaceutical Research and Manufacturers of America, the European Federation of Pharmaceutical Industries and Associations and from published literature. Although this programme is expected to bring scientific knowledge of value, Professor Narukawa stressed the importance of paying attention to the influence of "extrinsic" ethnic factors such as medical practice in seeking to utilise foreign clinical data.

Conclusions

The ICH E5 Guideline has significantly changed the strategy of new medicine development in Japan and has led to an accumulation of experience in utilising and evaluating foreign clinical data. All Japanese stakeholders are proactively planning to conduct and participate in global clinical trials. New drug development strategies aimed at global pharmaceutical market and the cultivation and maintenance of a healthy environment for research and development are keys to success.

Reference

1. The Japanese Ministry of Health Labour and Welfare. *Basic Principles on Global Clinical Trials*; 2007. Available at <http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf>. Accessed December 2009.

Ethnic factors and the E5 Guideline: What has been learned about ethnic differences?

The Chinese Taipei experience

Dr Meir-Chyun Tzou

Director, Division of Pharmaceutical Chemistry,
Bureau of Food and Drug Analysis, Department of
Health, Chinese Taipei

Dr Tzou discussed the evolution of bridging study regulations in Taiwan, where prior to 1993 there were no requirements for the inclusion of Asian patients in clinical trials used for new drug applications. By 2001, a bridging study evaluation (BSE) of the ethnic sensitivity potential of a proposed medicine was required to address ethnic-related issues with statistical meaning, and the inclusion of Asian data from early clinical development was strongly encouraged.

Trend of Multi-national Trials in Taiwan Involving Korea, Japan and HK / China

	2006			2007			2008		
	Japan	Korea	China (including Hong Kong)	Japan	Korea	China (including Hong Kong)	Japan	Korea	China (including Hong Kong)
The Multinational trials conducted in TAIWAN also in	6	53	37	19	62	53	26	75	58
* Sponsored by JP	*1			*3			*6		
# Multinational trials conducted in TAIWAN	100			125			155		

* From CDE database

2/33

In Taiwan, disease epidemiology is determined through its incidence, aetiology, natural course, prognosis and response to other medications. The ethnic sensitivity for BSEs is determined by a drug's characteristics in relation to the epidemiology of its intended indication, yielding its clinical impact to the local population in terms of benefits and risks. Certain pharmacokinetic, pharmacodynamic and clinical properties are used to assess a medicine's ethnic sensitivity including:

- Non-linear pharmacokinetics
- Pharmacodynamic curve for both efficacy and safety at the recommended dosage
- A narrow therapeutic dose range
- Highly metabolised, especially through a single pathway
- Metabolised thorough genetically polymorphic enzymes
- Administration as a prodrug
- Inter-subject variation in bioavailability
- Likelihood for use in a setting of multiple co-medications
- Likelihood for inappropriate use
- Epidemiologic difference in the indication between the reference and Taiwanese population
- Other important ethnic sensitive factors

Since implementation of the BSE regulations, major categories of trials for which bridging studies have not been waived include those for which the data were judged to be insufficient for evaluation such as those with incomplete efficacy or safety information or a lack of sufficient Asian data. For other trials in which BSEs were not waived there were questions regarding optimal dosing for the local population. For example, where there has been a demonstrated difference in systemic exposure between Caucasians and Asians, but lack of clinical data to determine the dosing information for the local population.

Bridging study waivers have been granted, however, for specific drugs. Examples include a drug for which the active ingredient was the purified enantiomer of a medicine already marketed in Taiwan, a drug under a rigorous monitoring program by specific physicians with local ongoing clinical trials, and a medicine already marketed in multiple Asian countries with no efficacy and safety issues observed for Asians.

Sponsors are required to conduct clinically meaningful bridging studies only when ethnic issues are identified through a bridging evaluation carried out in accordance with ICH E5 Guideline. They are encouraged to submit a complete clinical data package (includes phase I, II, III results) for the BSE before or with the new drug application. For most of BSE Asian data are required, Taiwanese data are preferred and a dosage adjustment for local use could

be requested should any dose-response issue identified. "If the bridging study is not waived, the sponsor can appeal the evaluation with more data or can conduct the required bridging study or studies.

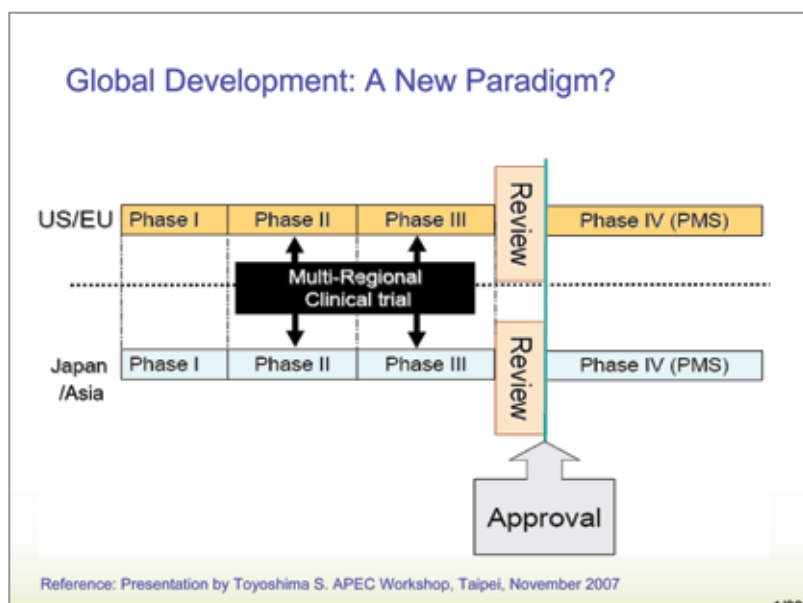
Results

Required bridging studies have resulted in labelling changes in Taiwan and worldwide. The registration trial of the fixed combination 200 mg dipyridamole/25 mg aspirin twice daily for prevention of recurrent stroke demonstrated a higher headache rate for Philippine patients compared with Caucasian patients, resulting in the request for a Taiwan bridging study. In this bridging study, a reduced 2-week dose followed by a full 2-week dose was associated with a 6.7% rate of headache compared with the 16.3% rate experienced with a full 4-week dose. The resulting reduced dosage label for Taiwan was also later adopted in the United States. Following required bridging studies, rosuvastatin was approved in Taiwan at half the initial proposed dose. The HLA-B*1502 and Steven-Johnson syndrome labelling warning for carbamazepine that was first required in Taiwan after required local studies was later also required by the FDA.

Ethnic concerns, risk management plan and critical path initiatives for regulatory science call for global partnership in harmonisation. Other regulatory viewpoints are required in addition to those of the FDA and EMA, especially considering ethnic factors and different local benefit-risk perspectives. Bridging study requirements have resulted in an independent Asian regulatory voice and a globalisation in drug development, registration and marketing. It is envisioned that multiregional trials could be conducted for the purpose of bridging in the context of a global development program designed for near simultaneous world-wide registration.

Through the assessment of foreign clinical data for sensitivity to ethnic differences, Taiwan regulators hope to ensure a favourable benefit-risk ratio in their target population and to develop a feasible risk management plan for any potential clinical impact in that population. They also seek to advance clinical research activities and the regulatory science environment, with the ultimate goal of timely access to new therapies for the people of Taiwan.

Recent cooperative activities to assess clinical data compatibility have resulted in the establishment of the Asian Clinical Trial Network to encourage information/experience exchange and to benchmark trial performance. The sharing of these data is expected to improve trial efficiency. In the ideal multiregional clinical trial, primary endpoints will be defined and accepted in all individual regions and data will be collected under a common protocol. Results will be examined for persuasive evidence in the pre-specified region and be compared between the regions with the intent of establishing ethnic sensitivity. Pan-Asian collaborations will provide effective and safe drugs expeditiously to all patients in Asia.



Evaluation of bridging data in Korea

Dr Jung Yun Chang

Deputy Director, Korea Food and Drug Administration, South Korea

Currently experiencing double digit yearly growth, Korea has the tenth largest pharmaceutical market in the world. Dr Chang explained that there is strong government support for clinical research, with an investment for 15 regional clinical trial centres expected to reach \$60 million in 2010. Global trials are conducted by experienced investigators and trained staff under an efficient institutional review board process. Regulatory review is conducted with open sponsor communication and clear review timelines.

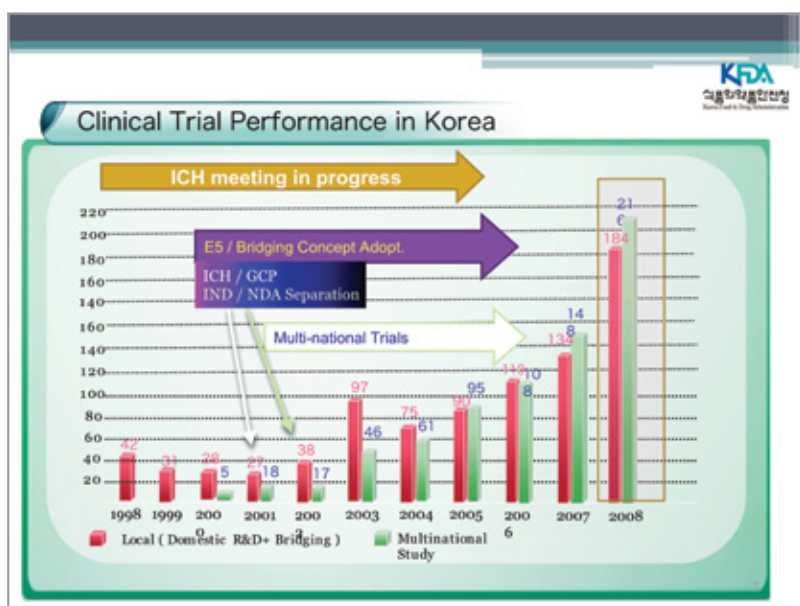
Reflecting this strong development, major regulatory changes relevant to clinical trials have recently taken place, including implementation of the Korean Good Clinical Practice revision for harmonisation with ICH Guideline E6. This revision clarified the responsibility of the investigator and the functions of the institutional review boards. With Korea's adoption of the E5 bridging concept, diverse bridging strategies were permitted. Expansion of mutual recognition among IRBs has also taken place in Korea, with more opportunities for specialised hospitals as accredited clinical institutes. Improvements have also occurred in record retention and

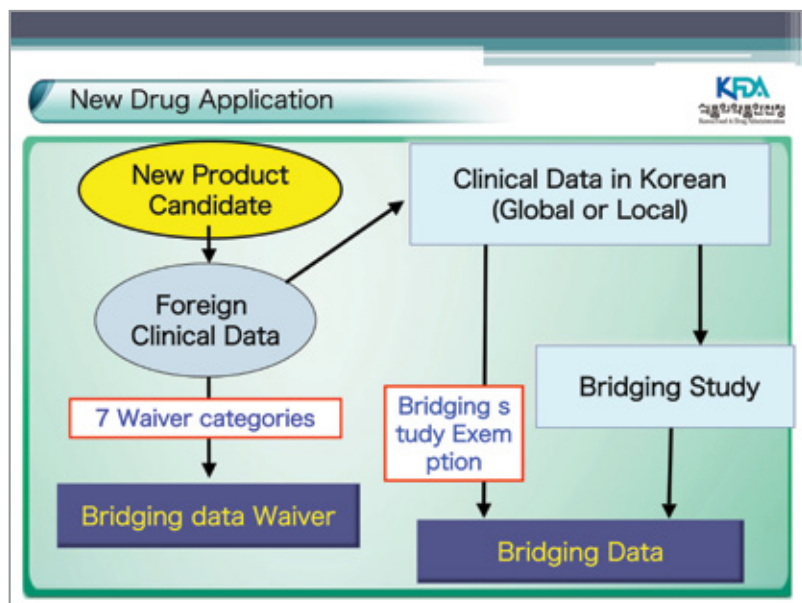
in the quality of the manufacturing facilities for investigational products. With the pre-Investigative new drug consultation process, sponsors can determine whether the clinical trial protocol is appropriate and obtain advice on the development plan before starting the final safety and efficacy confirmatory clinical trial. If no objections are raised, the Korean Food and Drug Association (KFDA) reviews the application for new drugs in less than 30 days.

Bridging study waivers for non-Korean trial data have been granted in the review of orphan drugs such as zoledronic acid, verteporfin, indinavir, and imatinib or for drugs for life-threatening diseases such as caspofungin, voriconazole, tegafur, and gefitinib or for diagnostic reagents, radiopharmaceuticals or those with no systemic effects.

Bridging case studies

- Pioglitazone hydrochloride is indicated for glycaemic control in patients with type 2 diabetes mellitus and considered to potentially be less sensitive to ethnic factors. Recommended dosage and administration in the United States was for 15, 30, or 45 mg once daily as monotherapy or 15 or 30 mg as combination therapy. A pharmacokinetic study with 24 healthy Koreans supported 15 and 30 mg as efficacious doses, resulting in an adjusted recommended monotherapy dosage in Koreans of 15 mg and 30 mg and combination therapy dosage of 15 mg.
- The first recommended dosage in the United States and Europe for rosuvastatin calcium in primary hypercholesterolemia was 10 to 20 mg per day. Bridging study pharmacokinetic data revealed AUC and C_{max} levels were doubled in Japanese subjects compared with those of Caucasians at the same dose. The US FDA subsequently changed the labelling to specify a starting dose for Asians of 5 mg /day. The adjusted dosage approved in Korea was 5 to 20 mg once daily.
- Sitagliptin, indicated for glycaemic control in patients with type 2 diabetes mellitus showed similar pharmacokinetic and pharmacodynamic properties in Japanese and western subjects. The required bridging study demonstrated similar efficacy and safety results between Koreans and Caucasians and the application was approved by the KFDA without a change in dosage.





South Korea is committed to a programme of international cooperation through participation in organisations such as the Global Cooperation Group (GCC) of the ICH, the Asian Pacific Economic Cooperation (APEC) group and APEC

Harmonization Center (AHC), the Pan-American Network for Drug Regulatory Harmonization (PANDRH) and the Life Science Innovation Forum (LSIF). In addition South Korea is participating in a Korea/China/Japan collaboration network for sharing clinical data.

In 2009, Seoul hosted the Asia Pacific Economic Cooperation (APEC) Multi-Regional Clinical Trial Workshop. Approximately 600 delegates, including those from Malaysia, Peru, Philippines, Thailand and Vietnam developed long-range recommendations for clinical trial globalisation. These included:

- Develop guidance for multi-regional clinical trials
 - Perform prospective research and data collection
 - Create principle documents
- Create repository of Information
 - Guidelines for the better understanding of diverse regulations
 - Consider common language

Acceptability of foreign clinical trial data in drug applications: Singapore's Perspective

Dr Huei-Xin Lou

*Deputy Director, Clinical Regulatory Unit,
Pharmaceuticals and Biologics Branch, Health
Sciences Authority, Singapore*

Clinical Trial Requirements

Regulatory authorities in Singapore seek to ensure credible and reliable clinical trials so that the data generated are robust enough for global regulatory scrutiny. Before any clinical trials of medicinal products can be conducted in Singapore, the investigator must obtain both ethics and regulatory approvals. All clinical drug trials conducted locally have to comply with legislation for oversight of clinical drug trials including the Medicines Act (Chapter 176, Sec 18 and 74), Medicines (Clinical Trials) Regulations and Singapore Guideline for Good Clinical Practice.

Regulatory requirements in Singapore specify

that all clinical trials on medicinal products conducted require Clinical Trial Certificates (CTC) from the Health Products Regulation Group (HPRG), Health Sciences Authority (HSA). Applications for CTC are to be made by the sponsor, which should be a locally registered company. Upon completion of the trial, the sponsor must submit the clinical trial status report and the final clinical study report, synopsis or publication. Import of clinical trial test materials into Singapore requires the approval of the HSA. Application must be made by a local sponsor or third party and include submission of proof of good manufacturing practice.

Pre-clinical trials conducted by testing facilities must comply with the requirements of good laboratory practice (GLP). The Singapore GLP programme was developed and is being administered by the Standards, Productivity Innovation Board Singapore (SPRING) in collaboration with HSA and other agencies. In 2009, Singapore was accepted into the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data framework.

Singapore GCP, implemented in 1998, was adapted from the ICH Guideline for Good Clinical



Regulatory Requirements

- All clinical trials on medicinal products conducted in Singapore requires Clinical Trial Certificates (CTC) from the Health Products Regulation Group (HPRG), Health Sciences Authority.
- Applications for CTC are to be made by the sponsor, which should be a locally registered company.
- If a trial is not completed upon the expiry of the CTC, the sponsor has to make a written request for an extension of the CTC and submit an interim clinical trial status report to support the request.
- Upon completion of the trial, the sponsor must submit
 - The Clinical Trial Status Report
 - The Final Clinical Study Report/ Synopsis/ Publication

Practice (GCP E6) and sets ethical and scientific standards for the conduct of clinical trials and serves as an assurance that results obtained from clinical trials are credible. Three types of GCP inspections are possible in Singapore. Routine GCP inspections are performed for ongoing clinical trials, triggered GCP inspections may occur as a result of requests, complaints or reports to HSA regarding ongoing or completed clinical trials, and pre-marketing approval application inspections that apply to completed clinical trials.

Approval from the respective Institutional Review Board (IRB) or Domain-Specific Review Board is required prior to initiation of clinical trials, and

these are issued independently of regulatory approval. The IRBs in the major healthcare institutions specify the minimal training required of the investigators and trial personnel.

There are multiple programmes for the training for clinical trial personnel including an on-line training programme, the Collaborative Institutional Training Initiatives (CITI) training programme on GCP. In addition, in-house training is organised by individual healthcare institutions and joint training is organised by the National University of Singapore, healthcare institutions, HSA, and contract research organisations (CROs).

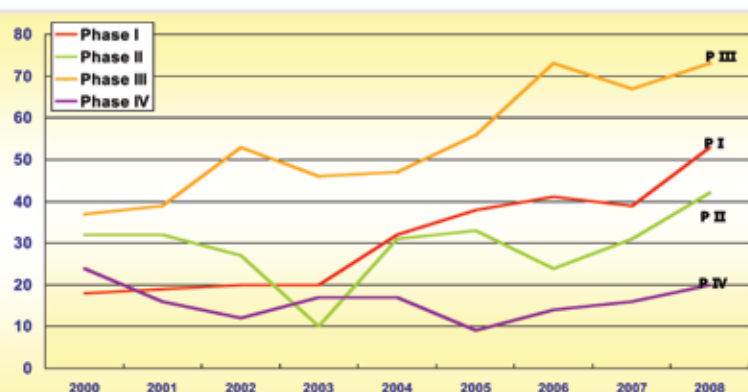
Regulators' Roles and Responsibilities

The roles and responsibilities of regulators in Singapore include safeguarding public health, implementing regulations, guidelines, systems and procedures. They must make an assessment of the benefit-risk ratio of new medicines, ensuring appropriate standards of safety, quality and efficacy. In addition, regulators are responsible for ensuring that compliance with regulations and responsibilities of the sponsor and investigator are maintained through GCP inspections. Regulators have also assumed responsibility for an educational outreach programme with stakeholders to train clinical researchers and investigators and to improve the quality of industry activities. In strengthening ties with regulatory alliances, Singapore regulators strive for enhanced collaborations to enable exchange of critical information and shared experiences and to facilitate timely alerts on non-compliance issues and investigation follow-ups.

Currently, 70% to 80% of trials in Singapore are multinational or global trials sponsored by pharmaceutical companies or CROs. Fifty to 60% are multinational or global trials (phase II-III) to support new drug applications to major regulatory agencies. Phase I clinical pharmacology studies are growing, currently representing 20% to 25% of trials and a total of six phase I centres have been established in Singapore, half owned by the healthcare institutions. Singapore's Biomedical Sciences programme is key in enabling multinational companies to set up dedicated phase I centres in Singapore to conduct early phase clinical drug development. Singapore will continue to support more of such studies to complement and strengthen strategies in knowledge-driven research.



No. of Approved CT Applications



Acceptability of data generated in global studies: How are agencies and companies ensuring credible and reliable clinical trials so the data generated is robust enough for global regulatory scrutiny? : A perspective from China

Dr Jane Lin

*Senior Medical and Regulatory Affairs Director,
Baxter (China) Investment Co Ltd, China*

Tremendous changes have occurred in China over the past three decades; and the same is true for pharmaceutical industry and clinical research. There were few, sporadic multinational clinical trials during the late 1980s and 1990s, and from the 1990s through 2000, most multinational trials were phase IV and IIIb. By 2000, however, there were an increasing number of phase III trials conducted as part of global development programmes and by 2005, many major pharmaceutical companies set up development-oriented centres and were establishing specific drug development strategies for China.

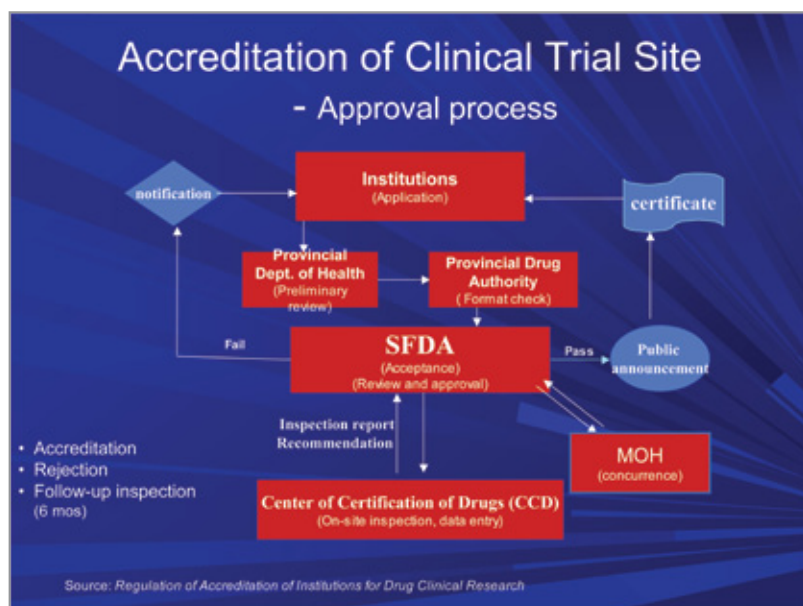
The third version of China's Good Clinical Practice, which was issued in 2003, closely resembles the GCP of the ICH. An accreditation programme for clinical trials was organised by the State Food and Drug Administration (SFDA) and Ministry of Health (MOH) in 2004. By October 2009, 260 institutions had been accredited. Because accreditation is specific to

a specialty or department in a hospital and one hospital typically has more than one specialty/department accredited, there are currently 1908 specialty-sites accredited in those institutions. Each accreditation is subject to re-evaluation every three years and the SFDA has recently published the procedures for such re-evaluation. The SFDA has also begun a programme for the regulatory inspections of clinical trials. All clinical trials conducted in China are subject to a registration inspection. All trials may additionally be inspected on a for-cause basis generated by an abnormal clinical trial process or result, a public report to regulatory authorities, or by issues found in the process of drug registration.

Although only eight US FDA GCP inspections had taken place in China by 2009, investigators involved consider the inspections valuable learning experiences. The most common deficiencies found in these inspections related to inadequate or inaccurate record keeping or inadequate drug accountability. There was only one instance of failure to report an adverse drug reaction.

Extensive consideration has been given to the establishment of quality in the study initiation, monitoring, and site management by China's pharmaceutical industry. Intensive training is provided in general GCP topics, study-specific issues, informed consent procedures, and adverse event reporting. Study tools such as brochures, posters, and newsletters are also supplied and periodic study investigator meetings are held. Quality control resources are dedicated within clinical research organisations, with training and sharing of best practices.

FDA inspection data suggest that the quality of clinical trials in China is comparable to that of the developed world. There are growing opportunities for conducting successful simultaneous global drug development in China; however, China should be involved early in clinical trial planning, with consideration of local medical practice while developing study protocols. A sufficient number of Chinese patients should be planned to satisfy regulatory requirements. Furthermore, it is a good regulatory strategy to have science-based discussions with the Chinese agency reviewer, thereby facilitating and promoting international exchange of information and expertise among stakeholders.



Regulatory principles guiding acceptance of clinical trials from non-EU countries

Dr Fergus Sweeney

Head of Sector, Inspections, European Medicines Agency, UK

Dr Sweeney defined the challenges faced by the European Medicines Agency (EMA) in the acceptance of clinical trial data from non-European countries as falling into the two broad categories of acceptability and applicability. That is, it must be determined if the ethical requirements of the trial and quality of the resulting data are acceptable by EMA standards and if those data are capable of being applied through European medical practice to European populations. It must further be decided if the data are sufficient in themselves or if bridging studies or other supporting data will be required.

Acceptability

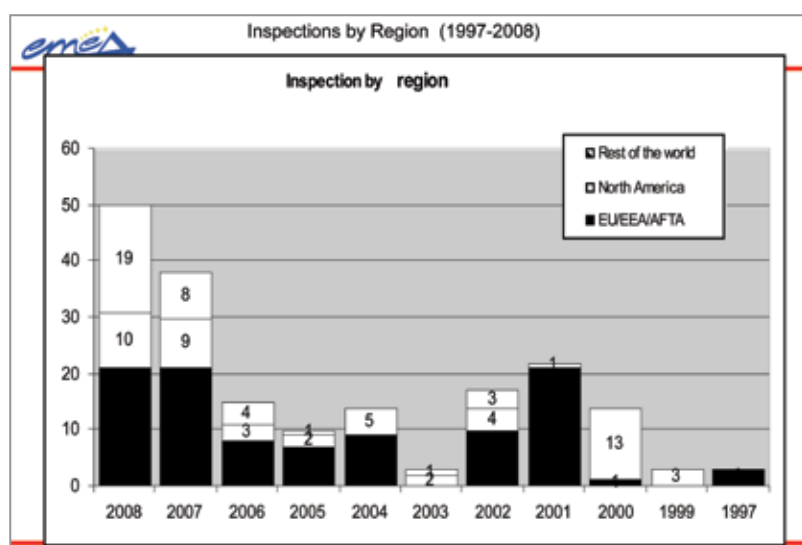
Europe has established programmes of regulatory exchange with other nations. Confidentiality arrangements exist between Europe and the United States, Canada, Japan and Australia, and bilateral discussions take place between the European Commission and China, India and Russia. This international cooperation assists in the development of standards and requirements, the building of expertise and systems, the reduction of the duplication of effort and the filling in of gaps in the global network.

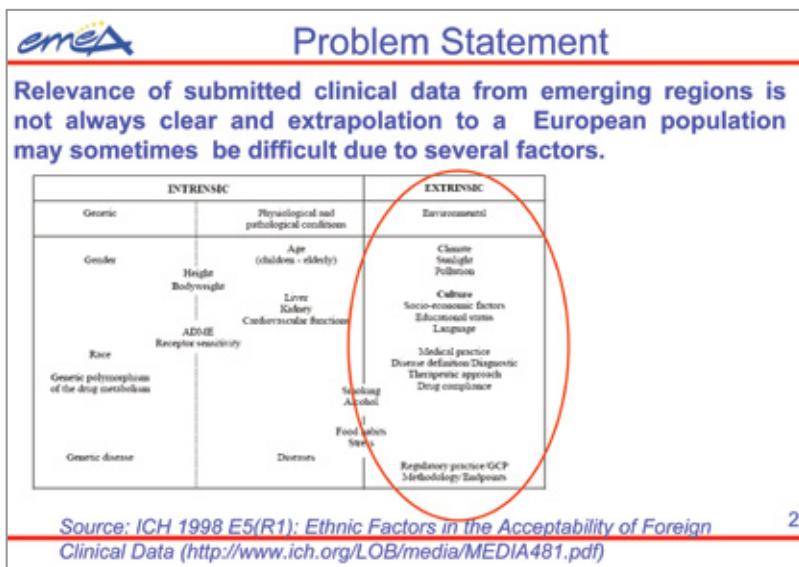
EMA requirements for good clinical practice, ethics, quality and safety apply to all clinical trials conducted in third countries that are included in a marketing authorisation application (MAA) submitted in Europe. These requirements apply regardless of the route of application (that is, Centralised, Mutual Recognition, Decentralised) and regardless of the third country involved.

Role of EMA/Committee for Human Products for Human Use (CHMP)

The EMA and CHMP provide global assistance in the form of development of guidelines and provision of scientific advice, paediatric investigation plans and orphan designation. MAAs are evaluated and offered tools include advice, guidance, assessment and inspection. EMA GCP protects subjects who participate in clinical trials or patients who will be treated with marketed medicinal products.

In 2008, the EMA published a strategy paper – *Acceptance of clinical trials conducted in third countries, and submitted to the EMA, in support of Marketing Authorisations*.¹ A three-year plan of activities was outlined to increase influence on the process of clinical development not only at the time of MAA (by which time the pre-authorisation clinical trials have mostly been completed) but at earlier stages before and during the conduct of the clinical trials, starting with the early activities such as Scientific Advice, Orphan Designation and Paediatric Investigation Plan and continuing through the finalisation of opinions on initial MAAs and clinical trials conducted post-authorisation. Action areas identified within the scope of EMA responsibilities, and in the context of other initiatives being undertaken by the European Regulatory Network and the European Commission, include planning and development and practical application. A Working Group has been formed to develop practical proposals for tasks and procedures and guidance in the action areas identified in the strategy paper. The objectives of the Working Group are to clarify the practical application of ethical standards for clinical trials, in the context of EMEA activities; determine the practical steps to be undertaken during the provision of guidance and advice in the drug development phase; determine the practical steps to be undertaken during the marketing authorisation phase; and achieve international cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area. Next steps are public consultation in 2010 and a Workshop in mid-2010.





Applicability

The ICH E5 Guideline (*Ethnic Factors in the Acceptability of Foreign Clinical Data*) focussed on bridging studies to determine a medicine's sensitivity to ethnic factors. It identifies the basic problem statement surrounding the acceptance of foreign data: "Relevance of submitted clinical data from emerging regions is not always clear and extrapolation to a European population may sometimes be difficult due to several factors."²

An EMA reflection paper has been drafted, *Reflection Paper on Extrapolation of Results in Clinical Studies conducted outside EU to the EU-Population*, presenting a background study of a number of applications for which the interpretation of the data for EU had been found to be difficult. It specifies characteristics

used to identify intrinsic and extrinsic factors impacting the extrapolation of clinical data. The paper finds that differences in extrinsic and intrinsic factors also exist within the (enlarged) EU, and the influence of extrinsic factors both within and between regions will play an increasing role during the assessment of new applications/variations.³ The factors, which are complementary to ICH E5, and which should be taken into consideration during the design of studies are European treatment guidelines and European epidemiological databases and statistics. To obviate the influence of extrinsic factors as much as possible, it is necessary to interpret these in a more structured fashion during Scientific advice.

The ultimate goals of EMA policies and procedures in respect to the acceptability of foreign data are that patients participating in trials are fully protected – wherever the trial takes place and that the availability of safe and effective new medicines, as early as possible, with data relevant to all regions is ensured.

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Session 2: Global clinical research: Are ethnic differences effectively covered?

Chairman: Dr Murray Lumpkin

*Deputy Commissioner, International Programs,
Food and Drug Administration, USA*

Subgroup analysis: What are the strengths and weaknesses of this approach in interpreting global clinical trials and identifying ethnic differences? A regulatory perspective

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While acknowledging the “cautiously inclusive guidance” provided by the CHMP reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population, ¹ Mr Hemmings explained that the use of non-EU data in the regulatory review of medicines for use in Europe is best considered on an indication-specific, case-by-case basis. In these considerations, intrinsic (individual) and extrinsic (societal) factors are identified

and differences in regional standard such as endpoints or controls and the applicability or generalisability of data are evaluated.

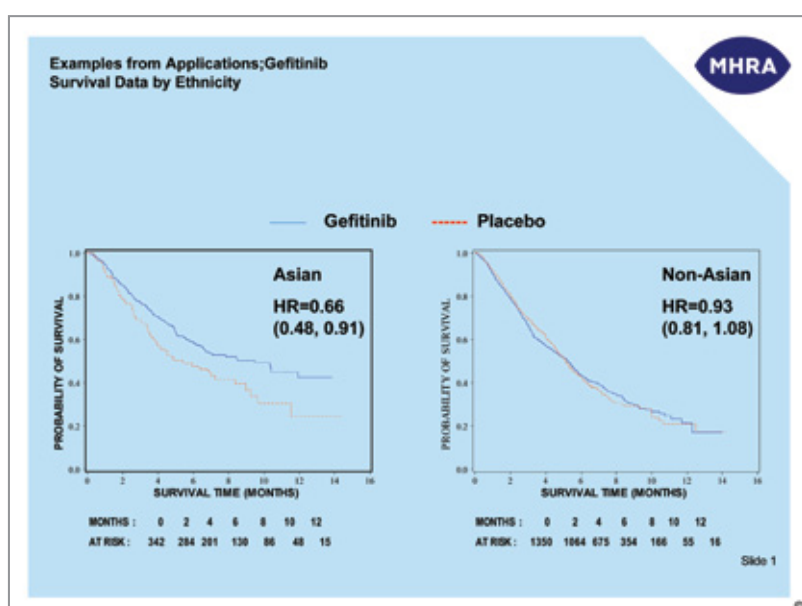
Subgroup analyses

Two common reasons for conducting subgroup analyses include the “rescue” of a failed trial and the investigation of internal consistency. However, no specific regulatory guidance has been provided on subgroup analyses, and regulators typically express a lack of confidence in the findings of post-hoc rescue analysis. On the other hand, if a subgroup analysis for internal consistency is negative, this result is regarded as credible and may result in a restriction of indications for a new medicine. These standards of evaluation do not represent a scientific divergence, but rather an exhibition of the precautionary principle. That is, whilst subgroup analyses can be a source of additional data, there is an attendant risk of misleading results, and the strength and consistency of the data observed and the biological plausibility are critical. For example, in the ISIS-2 trial ($n = 17,000$), aspirin use in patients who had suffered heart attacks was associated with statistically compelling positive effects. One publication, however, suggested that a subgroup analysis of patients born under the astrologic signs of Gemini and Libra showed that these patients experienced adverse rather than a beneficial effects.² This facetious example demonstrates that subgroup analyses must be treated with caution and interpreted responsibly. Whereas differences in cardiovascular disease prevention by star sign are implausible, differences in non-small cell tumour biology between Asian and Caucasian patients are entirely plausible.

Having multiple pivotal trials to estimate effects in the relevant subgroup is extremely helpful. Divergence often argues for a chance finding, but repetition is hard to ignore, even if biological plausibility is not strong. Subgroup analyses by region, where differences are plausible, are mandatory and interpretation can be quantitative as well as qualitative.

Examples

When a new indication was proposed for the antithrombotic clopidogrel, the application was based on the results of one small study in 6,000 primarily Caucasian patients and a larger study of 46,000 patients entirely conducted in China. Overall results of the larger trial showed that clopidogrel treatment was associated with a beneficial effect; however, subgroup



analyses revealed that the beneficial effect was not evident in patients also treated with beta-blockers. Because almost all patients with this diagnosis are given beta-blockers in Europe, there were concerns that the results from the large Chinese study may not be relevant to European patients and this trial was considered to be a supportive rather than pivotal study by the Committee for Medicinal Products for Human Use (CHMP).

In another example, because initial clinical trial data for the tyrosine kinase inhibitor gefitinib in non-small cell lung cancer refractory to other therapies suggested a higher response in Asian patients, an additional large study was conducted. This later trial confirmed a positive survival effect in Asian patients but not in Caucasians. The reason for the difference in response was undetermined, but gefitinib was approved in Japan but not in the EU. Further studies revealed that gefitinib is predominately effective in mutation- positive tumours, which are more prevalent in Asian patients (40% versus 10%). It was further determined that gefitinib is effective in Caucasian patients with non-small cell mutation-specific lung cancer.

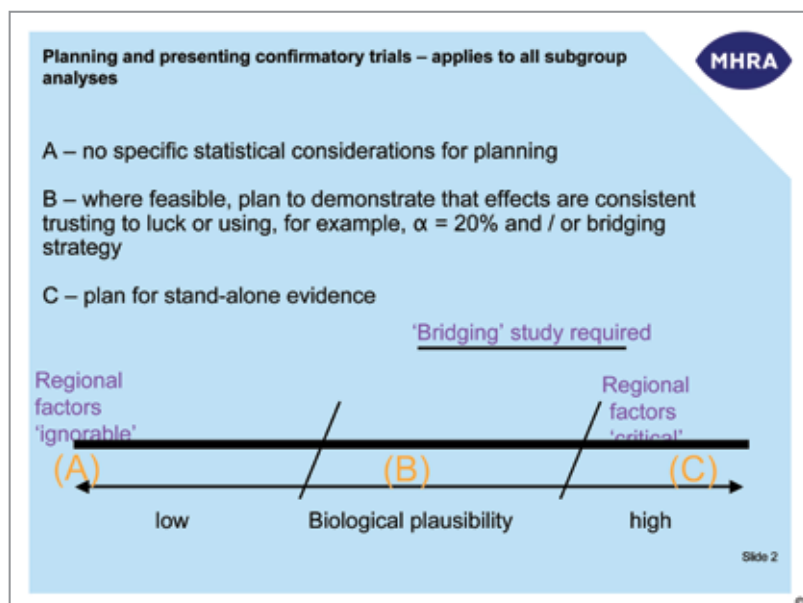
Finally, an application for a new indication for an antipsychotic drug already approved for the treatment of schizophrenia was made based on 2 studies. One fixed dose study and one flexible dose study in which 71% of patients were US and 54% were ex-US. Although there was a significant effect in Asian patients in the fixed dose study, and in Russian and Ukrainian patients in the flexible dose study, the CHMP concluded that it was questionable whether the positive findings were relevant for the majority of European patients suffering from an acute episode of mania because of the differences in race or medical and social environment. The application was withdrawn.

Confirmatory trials should be planned for all subgroup analyses to determine the plausible reasons for heterogeneous regional effects of treatment by region. Potential differences in effect should be discussed in the trial protocol and randomisation stratification considered a priori. Sponsors should seek scientific advice if there are concerns about regulatory interpretation. If there is biologic plausibility for regional heterogeneity, sponsors should plan on demonstrating that differences are consistent to chance occurrence using a bridging study and if the regional differences are considered critical, there should be a plan to develop stand-alone evidence.

Evidence coming from multiple regions can be acceptable. Consider regional standards as well as the generalisability of the trial findings. Differences in intrinsic/extrinsic factors and study conditions exist both within and between regions. It is important to identify, control (where possible) and investigate relevant factors. Failure to prospectively consider potential regional differences, and to plan for evidence to address potential heterogeneity, represents a risk to the drug developer.

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Global Clinical Research: Are Ethnic Differences Effectively Covered? A Company Perspective

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According to the ICH E9 directive *Statistical Principles for Clinical Trials*, randomisation “provides a sound statistical basis for the quantitative evaluation of clinical trial evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of known and unknown prognostic factors are similar.” Therefore, treatment comparisons within a study will be sound, but there may be other effects on the data that need to be considered, such as ethnic differences.

Within a pharmaceutical clinical development programme, there should be a consistent definition of region. It should also be remembered that countries within the European Union may not be homogeneous and may therefore not be considered a single region. If a treatment population is stratified for randomisation within a trial, by region, for instance, this factor must be incorporated in the analysis of the trial results. The number of patients required for inclusion per region should be investigated during sample size calculations.

Risks for regional randomisation include resulting differences in efficacy due to subjective assessment, differences in language and lack of validation of scales. There may also be differences in safety because of different standards of reporting and other factors. Studies are not usually powered to show differences within regions, and having only a small number of patients in a region is associated with a greater risk of influential anomalous data. Other risks include opening sites in emerging countries with developing clinical standards as well as differences and inconsistencies between countries.

Risks, however, can be mitigated through protocol development that includes good planning, study initiation and monitoring. Recruitment should be managed and trial sites in new countries should not be added later in the study. Data should be reviewed as they accumulate during the study (as permitted by the statistical analysis plan), and, upon completion, statistical analysis applied to explore regional effects using models that include terms for region. Outliers and anomalous countries may present problems for interpretation. Other influential information related to region may be observed through data patterns, although there is unlikely to be enough data to fully address regional differences. Results may also be confounded by extrinsic differences in treatment such as co-medications. In the long term, trial data can be added to consolidated database to better understand effects, but summaries from the entire database may not reflect a local population.

Reducing Risks

- Protocol addresses potential issues
- Good planning
- Good initiation of a study, followed by good monitoring
- Manage recruitment
- More than one study
- Do not add sites in new countries later in the study
- Review accumulating data during the study

Eisai

The Myth of Culture: A Research Ethics Perspective on Ethnic Differences in Global Clinical Research

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Patients and communities want to have their proper identities recognised in science and health. Health is not only a matter of science and technique, but also requires an approach to the individual within their familiar and cultural contexts. Health research, in both its public and private forms, provides a common public good, contributing to public health. This public good is strengthened and secured by appropriate government oversight. With the rise in the number of foreign clinical trials contributing to drug registration globally, it is incumbent upon researchers and government oversight authorities to appreciate the importance as well as the limitations of culture on clinical trial design, implementation, and data appreciation. While culture may form only a limited part of the ethnic differences we might be concerned with in foreign clinical trial data, it carries a particular identity that cannot easily be discarded or discounted.

Increasingly we are aware of a certain polarity that exists in the ethics of clinical trials: On the one hand, research ethics places a high priority on the need to protect trial participants and their communities from unacceptable risk and exploitation. On the other hand, health science cannot advance without necessarily carrying out experiments on new interventions in selected populations.¹ The use of foreign clinical trial data to justify the marketing of a medicinal product for public usage heightens our concern with the validity of the data for the domestic population while also increasing our sensitivity to the extent of risk and possibility of exploitation in foreign populations, especially when there is less clarity between the extrapolation of data from this population and the eventual use and availability of the product in the foreign population.²

Numerous guidelines and declarations have been developed in an attempt to find an ethical basis for global research, particularly concentrating on the need to protect vulnerable persons and populations. The ICH E5 Guideline frames the discussion, particularly from a regulatory perspective, stating that “All regions acknowledge the desirability of utilising foreign clinical data that meet the regulatory standards and clinical trial practices acceptable to the region considering the application for registration. However, concern that ethnic differences may affect the medication’s safety, efficacy, dosage and dose regimen in the new region has limited the willingness to rely on foreign clinical data.”³ It is a considerable challenge for the sponsor and researcher to demonstrate the validity of foreign data for justifying the use of a medicinal product in a domestic population. It is an even greater responsibility for the regulatory authority to ensure that the data is not ‘corrupted’ by pre-existing cultural or biological differences.

The South African Good Clinical Practice Guideline is particularly sensitive to the potential exploitation of its populations with the purpose of generating data to be used in foreign marketing applications. It specifies that “Researchers must respect the cultures and traditional values of all communities.” This is further supported by its requirement that “A research ethics committee must be satisfied that the protocol gives adequate consideration to participants’ welfare, rights, beliefs, perceptions, customs and cultural heritage.”⁴ There exists something of a cultural justification for research, at home and abroad, of which we are increasingly aware and from which it is more and

The Polarity in the Ethics of ‘Foreign Clinical Trials’

- A need to **protect** trial participants (individuals and communities)
– the fear of exploitation; a sense of vulnerability
- A need to **promote** health and research
– the (recognised) need for, and contribution of, clinical trials (for public health)



more difficult to extrapolate pure scientific data.

Recently the sensitivities around the use of foreign clinical trial data for domestic purposes were sharpened with the US Food and Drug Administration (FDA) ruling on GCP for foreign clinical studies not conducted under an investigational new drug application. The ruling essentially substitutes a requirement to follow GCP for the earlier requirement to follow the 1989 *Declaration of Helsinki*. This is the result of several years of tensions between US research authorities and the World Medical Association, and the inability to find a common position on shared ethical concerns in clinical research. Moreover, and generally overlooked, it is also the result of the FDA trying to reshape US regulation to meet the realities and demands of globalised clinical trials where foreign clinical trial data are increasingly represented in applications for marketing authorisation in the United States. An editorial in *Nature* criticised the move, accusing the government of turning a blind eye to ethics, writing “if the FDA jettisons Helsinki . . . it risks sending a message that ethical considerations are expendable when research subjects live half a world away.”⁵ Similar positions have since followed. For example, Kimmel et al criticise the FDA ruling on three grounds, 1) asserting that the Declaration of Helsinki has a moral authority that GCP lacks, 2) that the Declaration of Helsinki has a breadth and depth that GCP lacks, and 3) that the move could undermine the FDA’s stated goals of clarity and regulatory harmonisation.⁶

The *Nature* editorial and Kimmel et al appear to represent a large part of the research ethics

community, which has for so long focused on the vulnerabilities and rights of persons from different cultures while doing little to promote an ethics that addresses suffering due to the specific lack of research tackling urgent medical needs and the appropriate responsibilities of those undertaking the research. Increasingly the research community (academia and industry alike), including the community of ethics committee/institutional review board members, are ‘voting with their feet’ by insisting on following guidelines that are comprehensive, giving consideration to ethics and science in their common activities, as well as to the roles and responsibilities of all parties to the research. Not only has the US FDA chosen for a higher authority by acting on GCP as a framework respected and implemented near globally, but it is also taking a more comprehensive approach to harmonisation at home and internationally. GCP provides a framework that promotes needed research, addresses suffering caused by health deficits, and is comprehensive in ethics without the muddle involved in vilifying or polarising parties with shared interests in a common good.⁷

The culture surrounding foreign data has been generally supported within a framework of human rights. International organisations have struggled to impose a philosophy of human rights linked to culture within the field of health research. In 1997, the United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declaration on the Human Genome stated that “The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity.”⁸ UNESCO pushed the idea of associating human biology with culture, suggesting a correlation between genetic coding and cultural identity. In an attempt to promote the idea of universal human rights and inherent cultural rights, in its 2006 Universal Declaration on Bioethics, UNESCO went further by stating that “a person’s identity includes biological, psychological, social, cultural and spiritual dimensions.”⁹ From such a point of view in research ethics, it is near impossible to disassociate foreign clinical trial data from the cultural setting in which it is obtained. For many research ethicists it appears that human biology and culture are mutually identifying attributes of a person’s fundamental identity.

Culture increasingly achieves a mythic proportion among research ethicists in international clinical trials. Concerns that the rights of all

WHO Ethics Committees Guidelines (2000)

‘Justice requires that the benefits and burdens of research be **distributed fairly among all** groups and classes in society, taking into account age, gender, economic status, **culture**, and **ethnic** considerations.’

(2. The Role of an EC)



patients be protected are reflected in Guidelines issued in 2002 by the Council for International Organizations on Culture (CIOMS): “Many people in all cultures are unfamiliar with, or do not readily understand, scientific concepts such as those of placebo or randomization. Sponsors and investigators should develop culturally appropriate ways to communicate information.”¹⁰ The Declaration of Helsinki (2008) requires that “Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.” (paragraph 17) At the same time, Helsinki also wants to insist that “Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research. (paragraph 5)”¹¹ Increasingly we are realising that research is a priority for health and access to research should not be limited by culture or other factors. Indeed there is a growing recognition of the interdependence between populations, cultures, and regions in the development of medicinal products.¹²

It is not enough for health science to use only the parameters of hard data when evaluating the role and contribution of foreign clinical trial data to the domestic assurances of safety and efficacy; we also need to ask if these data also represent adequately the derivation of health parameters from the larger picture people of have themselves, their communities and their identities. At the same time we should be cautious in believing that culture is so fundamentally differentiating and isolating that we can no longer appreciate and benefit from what is similar and uniting in the foreign and domestic. As a selected group of global experts in research ethics wrote in 2000 when developing WHO guidelines for health research, “Justice requires that the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture, and ethnic considerations.”¹³ It is incumbent on researchers and government oversight officials alike to ensure that foreign clinical trial data are derived meaningfully from participants and researchers as well as interpreted meaningfully for decisions regarding its application the domestic use of medical products.

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Globalisation of clinical research: A company perspective

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An increasing number of clinical trials are being performed outside the traditional geographies, and although the pharmaceutical industry is committed to apply the same standards for the conduct of clinical trials globally, concerns have been raised over the movement of clinical trials to emerging countries. These concerns have focused both on the rationale and standards for quality and oversight applied to these studies.

Rationale for Clinical Trials in Emerging Markets

There are many different reasons to perform clinical trials in Emerging Markets, including the fact that 88% of the world's population lives in these regions, which are associated with a potential for huge economic growth. Furthermore, although there is an increasing prevalence of diseases of the West, trials in these areas permit the study of region-specific diseases, the assessment of safety in different ethnic groups and the recruitment of difficult-to-enrol patients. In comparison to trials in more traditional markets, these trials can be associated with shorter development timelines, lower cost and often better quality. Industry

can take advantage of available frameworks for the globalisation of clinical development and the regional adoption of The ICH Good Clinical Practice Guidelines while advancing the potential for global regulatory harmonisation.

Despite these advantages in conducting these clinical trials, specific issues remain to be addressed including developing region-specific protocols, appropriate informed consent, and Ethics Committee (EC) review; data monitoring and endpoint adjudication committees and safety reporting; investigator training and selection; and monitoring and use of contract research organisations.

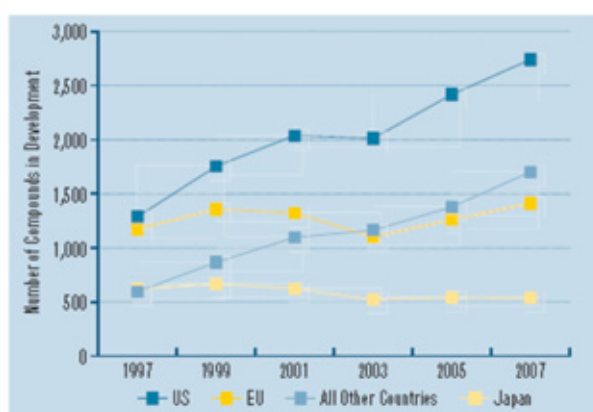
Protocol, Informed Consent and Ethics Committee Review Issues

Selecting an institutional review board (IRB)/EC or ensuring that an IRB/EC review is adequate in an Emerging Market can be challenging. Local norms vary, and often the selection of the EC is specified under local law. Training and expertise of the local IRB/EC members may be deficient or unknown. Lack of standardised guidelines for IRB protocol review and ongoing oversight of trials may be further complicated by the lack of a standardised approach to development of the protocol for submission and review by the IRB. Centralised IRB/EC review may be preferable in certain circumstances but cannot substitute entirely for local IRB/EC reviews. Stakeholders can and should collaborate on the development of guidance, and other standards for the design and operation of clinical trials in specific regions. IRB/EC review can be improved by support for accreditation and public registration of IRBs and their qualifications. The quality of the IRB review and the quality of the informed consent might also be improved if ethical considerations would be specifically addressed in a separate section of the protocol and a system to publish IRB/EC trial reviews could be established.

Data Monitoring and Endpoint Adjudication Committees and Safety Reporting Issues

Members of independent data monitoring committees (IDMCs) should be knowledgeable in the scientific aspects of the clinical trials they are monitoring, but there is typically an absence of formal training in safety signal analysis, and getting all relevant information to the committees in a timely manner for their decision process can be challenging. Furthermore, there can be an overlap in IDMC and IRB scope; a central IDMC may be better placed to monitor trials, but establishing multinational

Number of Compounds in Clinical Trials in Emerging Countries is Increasing



Pfizer Emerging Markets

PhRMA, 2009

representation can be difficult when the trial involves multiple geographies with markedly different time zones. Industry stakeholders can and should enhance standards for IDMCs through such methods as the establishment of standard charters. Apprenticeship learning for IDMC members could be developed through the use of one or two non-voting positions for trainees to participate and gain experience. Roles and responsibilities for the IRB and the IDMC should be established for example, by having the IRB focus on the protocol design and ethical issues and the IDMC on matters of patient safety.

Investigator Training and Selection

Skills required to serve as a clinical investigator for clinical trials can be very different from those needed for clinical practice, and there is a lack of well-qualified and trained investigators, especially in some emerging geographical areas.

for the assessment of new investigators. There is enormous potential value in investing in research in emerging countries that already have basic research training and infrastructure.

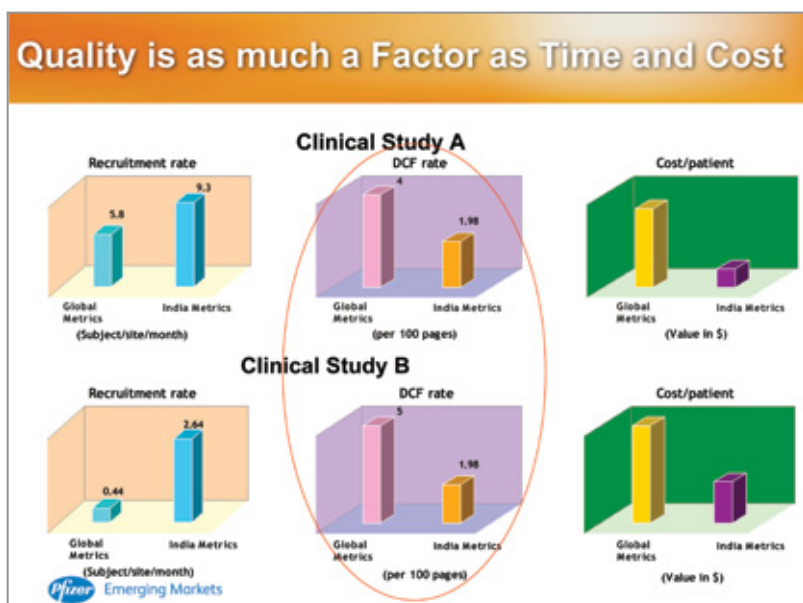
Monitoring and Use of Contract Research Organisations (CROs)

Whilst monitoring is critical to ensuring quality and optimal investigator and site performance, it cannot serve as a substitute for good protocol design and careful investigator selection. It is undeniable that there is a worldwide need for better training standards for new monitors and the high turnover rate of these positions presents challenges to quality assurance. The global reach and expertise of CROs can be uneven and sponsor oversight can be difficult when multi-national trials are wholly outsourced.

Global standards for monitoring, consensus about the monitor's responsibilities, standard certification with global applicability could be developed and validated. Sharing of audits and inspection findings should be consistent with applicable laws. There should also be a sharing of information about the qualifications and experience of CROs and monitors in different geographies. Different CROs could be used for various aspects of the trial such as data management and monitoring.

Conclusions

There is growing recognition that the large majority of the world's population lives in emerging countries and that their growth outpaces that of the rest of the world. Trials conducted in Emerging Markets can surpass those of established markets in terms of speed and quality, but several concerns have been identified and need to be addressed to ensure ethical design and conduct of clinical trials. We all have a shared responsibility for addressing these issues and only by working together can we effect meaningful changes. A collective dialogue with all stakeholders is needed so that we have a common understanding of the problems, their root causes, and the possible solutions



Furthermore there is a lack of uniformly accepted standards or approach in investigator training programs run by governments, industry and academic medical centres and sponsors must assess the qualifications and competency of investigators' clinical knowledge rather than just GCP training. Stakeholders can and should work together to develop a recognised investigator certification and training programmes. This certification might incorporate fundamentals of medicine as well as trial ethics and concepts about clinical trial design and understanding protocols, with a standardised examination

Challenges in the use of foreign data for drug authorisation

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Globalisation has fundamentally changed the environment for regulating food and medical products and created unique regulatory challenges for the US FDA. More foreign manufacturing facilities and clinical trials sites are supplying the United States and there is an increasing volume of imported products and data. Along with this rise in imported products and data, the US FDA has seen a rise in the incidence of opportunities for economic and data fraud. The US FDA regulations on the acceptability of foreign data include, for example, those that govern the qualification and training of investigators; the availability of trial sites for inspection, the use of GCP and the maintenance and use of an independent ethics committee. The conclusions of the data must additionally be applicable to the US population and medical practice.

In addition to the many positive aspects to the globalisation of clinical trials, there are significant challenges. Although most data in FDA marketing authorisation applications still come from non-emerging economies, the globalisation of clinical research is a growing reality.

Increased worldwide GCP inspections require increases in resources, capability assessments, knowledge of various medical qualifications and medical practice legislation, and interactions with international regulatory counterparts. Regional ethical standards, ethics committees, and documentation represent additional FDA challenges, including individual versus population ethics, the definition of “exploitation” and the resulting disqualification of data. The definition of standard of care, the impact of the regional unavailability of therapies, and the social context and perspective surrounding patient consent must also all be determined.

The relevance of the treated population in the clinical trial to the US population and medical practice is not a new issue. ICH E5 has grappled with this issue for years, and bridging studies have been one proposed solution. Comparator products and appropriate primary endpoints, especially in trials involving biomarkers are a concern and it must be decided if biomarkers need to be population validated. Underlying illnesses, concomitant therapies, cultural issues – food, dietary supplements, herbals, concomitant traditional medicines play roles in the applicability of trial data to medicines used in the United States. This is the well-discussed “intrinsic” versus “extrinsic” factors that play into decisions regarding the comparability of clinical trials populations with the population in the country in which the manufacturer is seeking marketing authorisation.

Finding ways to address these diverse and constantly changing challenges remains the shared goal and responsibilities of regulators, sponsors, patients and their advocates.

