

CMR International Institute for Regulatory Science

Workshop on
**CLINICAL DEVELOPMENT IN ASIA,
AFRICA AND LATIN AMERICA:**

**Streamlining the procedure for obtaining global
clinical trial approvals**

Singapore, 1-2 December 2008

WORKSHOP REPORT

Final version
March 2009


CMR
International
Institute for Regulatory Science

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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Workshop on Clinical Development in Asia, Africa and Latin America: Streamlining the procedure for obtaining Global Clinical Trial approvals

1-2 December 2008
Intercontinental Hotel, Singapore

Workshop Organisation

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WORKSHOP ON CLINICAL DEVELOPMENT IN ASIA, AFRICA AND LATIN AMERICA: Streamlining the procedure for obtaining Global Clinical Trial approvals

Section 1: Overview

Background to the Workshop

Is the concept of the simultaneous Global Clinical Development of new medicines becoming a reality or is it still a vision for the future?

In December 2008 the CMR International Institute for Regulatory Science (the Institute) hosted a Workshop in Singapore to discuss this goal and whether it has become more achievable since the Institute held a Workshop in Tokyo in October 2006 to address similar questions in relation to *Global Drug Development: Asia's role and contribution*.

Innovative new medicines have 'traditionally' been developed and tested in the so-called 'core' countries of the ICH affiliated regions. Increasingly, however, pharmaceutical companies have been seeking new territories outside the ICH regions into which they can extend their clinical research activities.

Highlights from the discussions

Participants at the Workshop received reports on the regulation of clinical trials in both core and non-core countries.

Thomas Lönnqvist, *Executive Director, European Medicines Agency (EMEA)*, Chairman of Session 1, reviewed the implementation of the EU Clinical Trials Directive and discussed the conditions for accepting data from third country trials when marketing applications are made to the EU regulatory system.

Dr Murray Lumpkin, *Deputy Commissioner, FDA* described the Investigational New Drug (IND) process in the US, under which proposals for clinical trials are reviewed within 30 days. He also focused on the interaction between companies and FDA aimed at maximising the efficiency and scientific robustness of drug development programmes.

Dr Leonie Hunt, *Office of Prescription Medicines, TGA, Australia*, described the Clinical Trials Notification (CTN) scheme in Australia, which is based on approval by a responsible and closely controlled Institutional Ethics Committee, followed by a notification to TGA that regulatory requirements have been met.

Japan: CT regulation in Japan was presented by industry speaker **Birgitta Hedin**, *Asian Regulatory Strategy, AstraZeneca, Japan*, who explained how PMDA operates its CT notification system with short timelines. PMDA is very aware of the need to reduce the drug lag in Japan and promote involvement in Global Drug Development, from an early stage.

Institute study: In preparation for the Workshop the Institute had carried out a study of CT regulation in non-core countries ('Emerging Markets').

Dr Neil McAuslane, *Director, CMR International Institute* and **Lawrence Liberti**, *Vice President, CMR International Institute* reported, on the data from pharmaceutical companies and from regulatory agencies that had been provided on CT review models and on perceptions of the key factors in those impact strategies for Global Clinical Development.

Whilst the Institute study reported on key countries in Latin America, Africa and the Middle East, and the Asia Pacific region, the speakers describing CT regulation in 'non-core' countries were all from the Asian region.

Dr Yi Feng, *Center for Drug Evaluation (CDE), SFDA, China* described the evolution CT regulation and government moves address the long timelines for the approval system.

Prof Sang Goo Shin, *KoNECT, Korea National Enterprise for Clinical Trials, South Korea* described ways in which the CT approval system has been streamlined and how it encourages participation in Global Development Programmes.

Yang-Tong Foo, *Clinical Trials Branch, HSA, Singapore* discussed and the Biomedical Sciences Initiatives in relation to building Singapore as a focus for innovative medicines research and clinical development.

Lucky Slamet, *National Agency of Drug and Food Control (NADFC), Indonesia*, described the way in which the agency is able to deliver a fast (10-day) CT approval and the challenges this involves.

Noorizam Ibrahim, *National Pharmaceutical Control Bureau, Malaysia* focused on Malaysia's competitive strength as a country for incorporation in Global Development strategies.

Li-Ling Liu, *Bureau of Pharmaceutical Affairs (BPA), Chinese Taipei* looked specifically at the way in which BPA is building quality into the clinical trial infrastructure in Chinese Taipei.

Industry perspectives were provided by two speakers:

Dr Jorge Puente, *Medical & Regulatory Affairs – Japan/Asia, Pfizer Inc, USA* gave the **Keynote Presentation** at the start of the Workshop and discussed the drivers (demographic economic and medical) that are influencing the migration of clinical trials from core to non-core countries.

Jerry Stewart, *Global Regulatory Affairs, Wyeth Pharmaceuticals, USA* discussed the clinical expectations of companies when planning Simultaneous Global Development and the benefits and barriers that they face.

This provided a valuable introduction to the subsequent discussions in the Syndicate Session.

SYNDICATE DISCUSSIONS

In the third Session of the Workshop, chaired by **Prof Robert Peterson, Professor of Paediatrics, University of British Columbia, Canada** participants divided into three Syndicates which looked at regulatory changes, in the short and longer term, that would help the incorporation of non-core countries into Global Clinical Development plans, and at the key criteria that make countries attractive to companies that are seeking wider Global Development.

Short-term regulatory approaches

Fast Track Review: A 'Fast Track' review system for clinical trial (CT) applications, e.g., notifications or other abridged review process is welcomed by industry but the **transparency** and **predictability** of the process are more important to companies trying to the plan global programmes.

Pre-application dialogue: A structured pre-application dialogue with the agency is considered essential.

Ethical Committee Review: There appear to be advantages in a parallel review by the Regulatory Authority and Ethics Committee but a sequential review is acceptable if the overall timescales are short. Developments in **Brazil** should be studied when it switches from sequential to parallel ethics and regulatory assessments.

Roles and responsibilities of Ethics Committees and Health Authorities need further clarification and. **It was recommended** that the Institute should carry out a Study of existing systems and/or convene a Workshop on best practices.

Clinical Trial Data requirements should be standardised and the components for a CTA must align with, and be appropriate to, the stage of development of the medicine and the proposed type of study. This will require consultation, education and training between Industry and Agencies.

International Guidelines on content and format: **It was recommended** that the ICH Global Clinical Group (GCG) should be asked to initiate and stimulate dialogue between agencies and industry.

Including non-core countries in Global Clinical Development

The Syndicates drew up a 'checklist' of the key criteria that companies might take into account when expanding into new territories.

Socio-Political and Business Environment: Companies will take account of their experience in the country and their ability to make the drug available after the clinical trial has finished. The choice of country will be influenced by a stable political environment with a favourable scientific climate that provides protection of intellectual property.

Ethical practices for clinical research in the country must meet international standards.

Clinical Practice and Operations: Clinical trials sites must have the appropriate capability, be GCP-compliant and provide sufficient incentive for investigators. The country must have a sufficiently developed infrastructure and operations should not be impeded by difficulties in importing and exporting test product and samples.

Resources: The company must assign adequate local resources to support regulatory activities in the country and the agency itself must support the review of clinical trial applications.

Regulatory Process and Requirements: Good access to agency staff, transparency and facilities for dialogue are important as well as a Regulatory Authority infrastructure that applies timelines and follows Good Regulatory Practice.

The Regulatory Landscape in 2015

Ethnic Factors: The ICH E5 guideline on *Ethnic Factors* should be followed up and revisited.

It was recommended that a study should be carried out by the Institute in cooperation with authorities and companies.

Recognition of CT Application decisions: The establishment of a Global Authority for CT approvals may not be realistic but two or three agencies could take on the role of **Reference Authorities** for the scientific review of multi-national clinical trial (MNCTs) applications. National agencies could then deal with local issues of ethics and patient safety.

International policy issues

Safety: Better methodology is expected by 2015, including better use of disease and population registries.

Benefit-risk assessment should be formalised and built into the early stages of drug development and clinical trial design, possibly leading to early *Conditional Approvals* of products.

Global regulatory harmonisation of procedures would facilitate Global Clinical Development.

Health Technology Assessment (HTA) will have an increasing role in the design of clinical trials and will be incorporated into early developmental trials. A key issue will be the development of risk-sharing between government and sponsors.

Introduction of new technologies: The use and development of **genetic markers** will be a major factor in speeding up the early development of valuable new medicines. **Adaptive Clinical Trial Design** will also streamline the design of Phase II studies, particularly in relation to achieving a better dose-response curve.

Geriatric studies: With an ageing population, clinical studies in the elderly will assume the same importance in 2015 that paediatric studies are gaining today.

WORKSHOP ON CLINICAL DEVELOPMENT IN ASIA, AFRICA AND LATIN AMERICA:
Streamlining the procedure for obtaining Global Clinical Trial approvals

Section 2: Outcome

Syndicate Discussions

Sessions 3 of the Workshop, during which the Syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*.

The Workshop participants formed three Syndicate groups. The Chairpersons and Rapporteurs were:

Syndicate 1	<i>Chair:</i> Dr Petra Dörr , Head of Management Services and Networking, Swismmedic <i>Rapporteur:</i> Bill Griffiths , Vice President, Global Regulatory Operations, CMC & Technical Services, Solvay Pharmaceuticals, Germany
Syndicate 2	<i>Chair:</i> Dr Supriya Sharma , Director General, Therapeutic Products Directorate, Health Canada <i>Rapporteur:</i> Estelle Michael , Senior Manager, Regulatory Policy, GlaxoSmithKline Biologicals, Belgium
Syndicate 3	<i>Chair:</i> Dr Heng-Der Chern , Executive Director, Center for Drug Evaluation, Chinese Taipei <i>Rapporteur:</i> Dr Owe Luhr , Regional Medical Director, S.E Asia, Celgene Pte Ltd, Singapore

SUMMARY OF THE OUTCOME

Within the overall objectives of the workshop, the Syndicates were asked to look at ways in which regulatory changes could make it easier to incorporate non-core countries into Global Clinical Development plans, in the short and longer term, and to look at the features which would make a country attractive to companies that are seeking a wider global basis for development.

To this end the Syndicates reported on:

- **Regulatory approaches** to streamlining clinical approvals (Syndicate 1):
 - The changes that could be made to national regulatory requirements and procedures in the short to medium term that would encourage the integration of 'non-core' countries into Global Clinical Development programmes
- **The Key criteria** that might influence companies' decisions to include non-core countries in a clinical development programmes (Syndicate 2):
 - The factors that influence senior management when selecting the global scope of clinical testing programmes for new medicines
- **The regulatory landscape in 2015** and changes that might be expected (Syndicate 3)
 - The main changes in philosophy and practice among companies, regulatory agencies and policy makers that would support the sustainability of clinical research and the efficiency of Global Development for new medicines

1 RECOMMENDATIONS AND OBSERVATIONS

A. REGULATORY APPROACHES TO STREAMLINING CLINICAL APPROVALS

Different review tracks for different types of CTA

A1. Fast Track Review: Regulatory systems that allow a 'Fast Track' review (e.g., notifications, abridged review processes) for applications that are part of multi-country clinical trials (MNCTs) are welcomed but **transparency** and **predictability** of the process are more important to industry. Companies are seeking regulatory systems that allow access and dialogue and that deliver decisions within a timeframe that can be relied upon in planning a Global Programme.

A science based, data-driven, risk-based approach should be used to distinguish between applications eligible for Fast Track assessment and those requiring a full review by the local authority ('Pre-Approval' review)

A2 Pre-application dialogue: Whether an application is handled through a Fast Track or Pre-Approval procedure, the facility for companies to have a structured pre-application dialogue with the agency is considered essential.

Ethical Committee Review

A3. Parallel vs. Sequential processes: There appear to be advantages in a parallel review by the Regulatory Authority and Ethics Committee but a sequential review is acceptable if the overall timescales are short (e.g. < 60 days):

Brazil could be studied as a test case since the government is proposing a switch from sequential to parallel ethics and regulatory assessments. Of interest is the impact on efficiency and the question of whether more international clinical trials take place in the country as a result,

A4 Further study of procedures: A clearer understanding is needed of the respective roles and responsibilities of Ethics Committees and Health Authorities.

It was recommended that this should be addressed by the Institute through a Study of existing systems and/or a Workshop on Best Practices.

Better documentation and information on the way in which Ethics Committees operate in different countries and the guidelines that they follow could lead to improved systems that avoid duplication and overlap, leading to better efficiency

Standardisation of Clinical Trial Data

A5 The data components required for a CT Application must align with, and be appropriate to the stage of development of the medicine and the proposed type of study (e.g., a two-week study does not require long-term stability data).

Consultation, education and training between Industry and Agencies are required to build confidence and ensure that agencies are aware of the rationale for the type of data that companies can provide, in relation to the stages of product development.

A6 It was recommended that the ICH Global Clinical Group (GCG) should be requested to initiate and stimulate dialogue between agencies and industry with a view to developing guidance on the format, content and level of detail that is appropriate for CT Applications.

Although ICH would provide an appropriate forum for initial discussion of international guidelines, action could also be sought from WHO. It was noted that the Organization is already working in this area.

B. KEY CRITERIA FOR INCLUDING NON-CORE COUNTRIES IN GLOBAL CLINICAL DEVELOPMENT

This topic was considered in terms of a 'checklist' of the items that a company might consider in selecting countries for inclusion in the Global Clinical Development of a new medicine. The checklist shown below divides the criteria into the following:

- **Internal (company) factors:** These matters relate to the way in which a company conducts its business. The company can obviously exert a direct influence on such factors.
- **External (local) factors:** These factors relate to the existing environment in the target country that would make it attractive for inclusion in a Clinical Development Programme.
- **Cross-cutting issues:** These are factors on which the company may be able to work alongside the regulatory agency to make the environment more attractive

CHECKLIST OF FACTORS THAT WOULD ENCOURAGE THE INCLUSION OF A COUNTRY IN GLOBAL CLINICAL TRIALS	
B1 Socio-Political Business Environment	
<i>Internal factors</i>	
<ul style="list-style-type: none">• The company's experience in the country• The ability to make the drug available after the clinical trial has finished (e.g., the probability of obtaining a marketing authorisation and/or reimbursement)	
<i>External factors</i>	
<ul style="list-style-type: none">• A stable political and business environment• The 'political will' to support research into the prevention/treatment of a specific disease• A scientific climate that provides incentives for, and encourages innovative research (e.g., Singapore)• The implementation of Intellectual Property Rights (IPR) and data protection• A favourable public perception of clinical trials, which will influence the willingness of patients to participate in trials• Clinical research vs. medical practice: The need for clinicians to be concerned about individual patient results rather than their own overall research goals	
<i>Cross-cutting issues</i>	
Ethics: The country's ethical practices must meet international norms and it is up to the company to have competent local staff working with investigators and CROs to ensure that such standards are understood and applied.	
B2 Clinical Practice and Operations	
<i>Internal factors</i>	
<ul style="list-style-type: none">• Research in the country must contribute to true global development• Key opinion leaders in the country must be consulted and fully engaged in the process	

B2 Clinical Practice and Operations cont.

External factors

- Local practices must be in accordance with global medical practice, e.g. in terms of site capability and compliance with international GCP norms
- There must be sufficient incentives for investigators to engage in clinical research and focus on the project
- The country must have a sufficiently developed Infrastructure to support the project, e.g. adequate IT systems
- Requirements for local sample testing must not impede the study
- Requirements for the import of test products and the export of biological samples must not create a barrier to conducting trials

Cross-cutting issues

Resources: The company must assign adequate local resources to support regulatory activities in the country and the agency itself must assign sufficient priority and resource to the review of clinical trial applications

B3 Regulatory Process and Requirements

Internal factors

- 'Education' of colleagues within the company may be needed in order that they understand and accept the need to work within the regulatory and clinical environment of a new country
- A realistic approach is needed to whether the country has a role in meeting the company's Global Regulatory Strategy or whether the driver for carrying out local trials is to facilitate a subsequent marketing application
- The company must be sufficiently informed of local regulatory procedures to ensure that it meets dossier requirements and produces submissions of a consistent standard

External factors

- Access to the Regulatory Authority is vital, with the facility for continuous dialogue, particularly for innovative products
- The Regulatory Authority infrastructure is important, in particular the application of Good Regulatory Practices and a control process that ensures that all reviewers apply same review standard
- The transparency of the review process and the availability of guidance on regulatory requirements are key factors
- The agency itself must adhere to its stated regulatory requirements and review practices, especially in relation to review timelines

Cross-cutting issues

Feedback: There should be a mechanism that allows feedback between the Regulatory Authority and the Sponsor/CRO in order to improve working practices.

Acceptability of data: The company will need to work with the Regulatory Agency in order to understand requirements and to ensure that the data generated will be acceptable in other regions. Issues might include the acceptance of the comparator used in the trials.

B4 Other factors

Factors that might have a bearing on the choice of a country but are outside the company's or the agency's sphere of influence are:

- Language
- Cultural differences
- Time differences, travel and accessibility
- Religious needs

C. THE REGULATORY LANDSCAPE IN 2015

It is envisaged that key factors to shape the future regulatory environment will be:

- Regulatory life cycle management of drug development;
- Partnership in harmonisation with good regulatory silence

The following were identified as steps towards achieving these goals:

Ethnic Factors

C1 The ICH E5 guideline on *Ethnic Factors*¹ should be followed up and revisited. This could involve a study to evaluate the results of the bridging studies that have been carried out under the guidelines.

It was recommended that such a study should be carried out by the Institute in cooperation with authorities and companies to look at the number and types of study and examine, for example, the impact on labelling.

Recognition of CT Application decisions

C2 Whilst the establishment of a Global Authority for CT approvals is probably not realistic, there may be two or three agencies that are evolving which could take on the role of reference authorities for the scientific review of MNCTs. The local agencies could then recognise the scientific basis for the CT application and deal only with local issues of ethics and patient safety.

International policy issues

C3 Safety: it is anticipated that there will be better methodology to address safety by 2015 and that this will include better use of registries, both electronic registries for clinical trial data but also disease registries based on population data.

C4 Less regulation: Regulatory processes could be simplified by handing back certain tasks to pharmaceutical companies, for example, documenting and validating variations and changes to protocols and product formulations.

C5 Benefit-risk assessment: A more formal basis for benefit-risk assessment could be built into the early stages of drug development and clinical trial design and could lead to an early *Conditional Approval* of products coupled with mandatory post-marketing surveillance.

C6 Global regulatory structure: A Global Programme for greater harmonisation of regulatory procedures would enhance Global Clinical Development.

C7 Health Technology Assessment (HTA): This will have an increasing role in the design of clinical trials and it can be envisaged that HTA will be incorporated into early developmental trials in order to make an earlier assessment of whether a project should be taken forward. A key issue will be the development of risk-sharing between government and sponsors.

Introduction of new technologies

C8 Genetic markers: The use and development of genetic markers will be a major factor in speeding up the early development of valuable new medicines.

C9 Adaptive Clinical Trial Design: Streamlining the design of Phase II studies, particularly in relation to achieving a better dose-response curve, will result from the increased adoption and acceptance of adaptive clinical design.

Aging populations

C10 Medicines for Geriatrics: Special testing protocols for the use of medicines in the elderly will be the routine rather than the exception by 2015. There may need to be special Regulatory provisions (e.g. a 'Geriatrics Rule' similar special requirements and incentives for paediatric testing).

2. POINTS FROM THE DISCUSSIONS

A. REGULATORY APPROACHES TO STREAMLINING CLINICAL APPROVALS

Different review tracks for different types of CTA

The Syndicate considered a differentiation between procedures that entail a full scientific review of a CT application (hereafter referred to as a 'Pre-approval' review) and an abbreviated regulatory review, which may be a simple notification process (hereafter referred to as a 'Fast Track' review).

An understanding of the true nature of current regulatory approval processes that are referred to as 'notifications' is important to avoid misconceptions. For example:

- **The US FDA** Investigational New Drug (IND) application is, technically, a notification process in that there is no formal approval letter or CT certificate. If the FDA does not raise objections within 30 days of the application date, the clinical trial may proceed. In those 30 days, however, a detailed technical review of the data and CT proposal is carried out by the agency staff. An IND review is *not* therefore an abridged or abbreviated process but it is carried out within a short, defined time limit².
- **The Australian TGA** CT notification process (CTN) is an abbreviated procedure but is only available once the clinical trial protocol and technical data has received a thorough review by a closely regulated Ethics Committee with access to scientific advice³.

Fast Track vs. Pre-approval

A Fast Track approval system cannot stand alone but must depend on either the recognition of an approval by an agency in a reference country or on a robust infrastructure of agency and ethics committees working together (as in the Australian model).

Approval in a reference country has the advantage of reducing duplication and the need for scientific data to be assessed repeatedly. In the absence of a fully functional Global CT database, however, there is the problem of obtaining evidence of approval in the reference country and of ensuring that there is full disclosure and that the information is kept up-to-date.

Justification for a fast track approach: A reliably short approval time means that trials in the country can be incorporated into 'simultaneous' Global Clinical Development but there is also a strong case for an abbreviated procedure to deal with:

- Subsequent related protocols after the first CTA approval;
- Amendments to the CT protocol;
- Bioequivalence tests in humans e.g. for generic products.

Note: The benefits of a Fast Track system are lost if there are other significant start-up delays for MNCTs, for example lengthy import/export procedures for test materials and national QC requirements e.g. for biologics.

Risk stratification: A Fast Track procedure would need to be accompanied by risk stratification criteria in order to distinguish between high-tech procedures (e.g. stem cell therapy) that would require a full pre-approval review and routine Phase III clinical trials (e.g. on a new antibiotic) that would be appropriate for Fast Track approval.

Pre-application consultation

A prerequisite for a successful CT application procedure is the ability for companies to discuss the project, in advance, with the regulatory agency. A structured pre-application meeting is an opportunity to consider and predict the life-cycle changes of the product during clinical development.

Conclusions

These discussions led to the Recommendations and Observations noted in Section 1 above:

- A1** That industry welcomes the adoption of a fast track review procedures but that **transparency** and **predictability** of the review process is of greater importance in planning a global clinical development programme.
- A2** That the ability to have a meaningful pre-application dialogue with the regulatory agency is an essential prerequisite for both a Fast Track and Pre-Approval procedure.

Ethical Committee Review

Parallel vs. Sequential models for ethical review

The Institute study on clinical trial application procedure in different countries⁴ had identified two main review models: The *parallel* model in which applications are made at the same time to the Regulatory Authority and the Ethics Review Body and the *sequential* models in which the application for regulatory approval is only made after ethics approval has been received. (China is an exception in that regulatory approval must be obtained *before* and application for ethical clearance is made).

There is a tendency to consider that the **parallel model** must automatically be the most time efficient but, in practice, agencies apply an efficient **sequential model** where the ethics committee has access to scientific resources and expertise, as a way of avoiding duplication and wasted resources. Industry's main concern is that the overall approval time for CT applications should be short, regardless of the model that is used. Indonesia is an example of a country using a sequential model but achieving short approval times.

Brazil is proposing to change from its current sequential model to a parallel system of applications to the Agency and Ethics Boards. The time taken to obtain ethical clearance in parts of Latin America is a cause of concern to industry and Brazil could form a useful case-study to see whether the change results in the country attracting a larger number of clinical trials and being included in more MNCTs.

Conclusion: These discussions led to the observation (**A3**) that a sequential review by ethics and regulatory bodies can be justified if the overall timescales are short and a **recommendation** that Brazil should be studied as a test case of the impact of switching from a sequential to a parallel model.

Roles of Regulatory Agencies vs. Ethics Committees

It was noted that many countries have a 'blurring' of responsibilities between their Ethics Committees and the Health Authority. A better understanding of the roles and working practices among ethical review bodies could lead to a more harmonised approach and could encourage more efficient working methods as regulatory systems evolve.

It was therefore **recommended (A4)** that the Institute should carry out a Study, possibly in conjunction with a further Workshop, with the object of:

- Collecting information on the roles and responsibilities of, and the guidelines followed by different ethics committees;
- Looking at the structure, composition, and level of government support for such bodies;
- Comparing the independence of different ethics committees and their interdependence with the respective regulatory agencies in different systems;
- Studying best practices and the comparative efficiency of systems that have a Central Ethics Committee vs. those with site-based committees.

The workshop would also provide a platform for discussing specific case studies such as that in Brazil.

Standardisation of Clinical Trial Data

The Syndicate referred back to previous recommendations from the Institute Workshop on *Global Drug Development: Asia's Role And Contribution*⁵ at which there was a call for harmonisation of CT application requirements in order to enable the sharing of assessment reports and approvals for clinical trials.

It was noted that the technical data required for clinical trial applications was generally harmonised in the US and EU using the CTD format although the required level of detail was somewhat different. Many agencies outside the core countries were, however, requesting additional data or a greater level of detail than the agencies in the country/region where the new medicines had been developed.

It is difficult to incorporate, into simultaneous global studies, countries that have data requirements outside the norm. The format of data is not the issue but the content and level of detail are of particular concern when data are requested that are not yet available or are not appropriate to the stage of development of the medicine. Requirements for long-term stability data on newly developed formulations are a case in point.

Education and harmonisation

There may be a lack of understanding on the part of regulatory agencies regarding the drug development process. Consultation procedures, education programmes and training opportunities between industry and agencies should be fully utilised in order to increase agency understanding.

Without international agreement on clinical trial data requirements it will be difficult to develop a harmonised Review Template or to share Assessment Reports. Such activities could be essential elements of Fast Track approval systems that are based on reference country approval (see above).

These discussions led to the observations and recommendations on:

- A5** The need for the data components of a CT application to align with, and be appropriate to the stage of development of the medicine.
- A6** The need to stimulate dialogue between agencies and industry with a view to developing internationally accepted guidance on the format content and detail of CT application data. The ICH GCG could initiate such discussions but the ultimate action may rest with WHO.

B. KEY CRITERIA FOR INCLUDING NON-CORE COUNTRIES IN GLOBAL CLINICAL DEVELOPMENT

Discussion of the checklist

The Syndicate that drew up the *Checklist of Key Criteria* set out in Section 1 had originally expected that regulatory factors would be the first priority in selecting a country for inclusion in Global Clinical Development. In fact, the discussions in the group indicated that regulatory factors have less influence on such decisions than the business and socio-economic environment and national clinical practices and operations.

In particular, the regulatory timelines for review and approval of an application, while important, were not the first priority. As in the conclusions from Topic A, (see A1) the soundness and reliability of the regulatory system was felt to be of greater importance than relatively small differences in timelines.

There are however exceptions: Outliers where the timelines are so much longer (e.g., in China) that it is not feasible to include the country in a simultaneous development programme. There are other drivers for including such countries in clinical trial programmes, e.g. the size of the pharmaceutical market.

Financial considerations

The cost of carrying out trials might also have been expected to have higher priority but, in effect, '*time is money*' and a regulatory system which is efficient coupled with a clinical and administrative environment that allows trials to start with a minimum of delay, once authorisation is obtained, represents the most economically viable situation.

C. THE REGULATORY LANDSCAPE IN 2015

Ethnic Factors

Since the ICH E5 Guideline was adopted in the late 1990s, much information has been collected not only from bridging studies but also from other studies carried out in the population. The question of determining the impact of ethnic factors on individual medicines has been a challenge for companies but, in fact, as few as 5-10% of patients may be affected and it is possible that, in practice, too much is being done.

The whole topic needs to be revisited and the Syndicate felt that the Institute should take a lead role in the follow-up.

Ethnic factors survey

This led to recommendation **C1** that the Institute, in cooperation with authorities and companies, should carry out a study on the status and impact of the ICH E5 guideline.

A relatively simple survey might be an easy first approach in order to collect data on the number of bridging studies carried out to date, the number of products and patients, and the impact on labelling and approval conditions. One objective would be to look at the justification for the number of bridging studies currently being undertaken.

Recognition of CT Application decisions

The CT application and approval process could be considerably streamlined by reducing the duplication of assessments of core scientific data. Even by 2015 the establishment of a Global Authority for CT approvals is unlikely to be feasible, but the recognition by agencies of regulatory decisions made by two or three lead reference agencies might be realistic (**C2**).

Designated reference agencies could also be involved in discussions to resolve the CMC problems that were also referenced under A5.

Certain tasks could be delegated to the pharmaceutical industry, to relieve the regulatory burden on agencies. Examples include identifying clinical trials sites that meet international standards for the conduct of clinical trials and for GMP.

International policy issues

Better methodology to address safety (**C3**)

It is envisaged that better safety assessments could lead to earlier approvals in the future. There may be pressure for more safety data and post-marketing surveillance but the latter has its limitations. An option may be to develop and improve electronic registries of patients and populations.

Registries for clinical trials are the responsibility of companies and have limited use but disease registries and population-based databases provide a very valuable source of safety information allowing quick queries and providing answers on safety signals. The development of such databases would, however, need partnership between public and industry.

The use of existing electronic registries might also help in the enrolment of existing patients into clinical trials on new therapies.

Less regulation (**C4**)

Much regulatory time is taken up by relatively menial tasks such as handling the notification and assessment of variations and changes. It is envisaged that pharmaceutical companies can take a greater responsibility for these, providing that changes under the CT authorisation are carried out and validated within agreed guidelines.

Better benefit-risk assessment (**C5**)

The science of benefit-risk (BR) assessment is expected to have advanced and to be more formalised by 2015. Building a formal BR assessment into early drug development could lead to a more standardised regulatory review.

Other possibilities are that the BR assessment would contribute to the decision on whether an application requires a full assessment or is appropriate for a 'fast track' review. It

could also be linked to an early conditional approval (coupled with mandatory post marketing surveillance requirements)

The evolution of better biomarkers might also be expected to result in better assessments of BR and more predictable outcomes, which could lead to earlier access to new medicines.

Harmonised global regulatory structure (C6)

It was recognised that greater harmonisation between the regulatory processes in different countries would have a beneficial impact on the ability to conduct global clinical trials. Japan was seen as an example of a country that has adjusted its national processes as a result of being part of global and regional programmes. There is an obvious role for ICH in improving global harmonisation but the discussions will need to be opened up to a wider range of countries in order to achieve widespread results.

Health Technology Assessment (C7)

There was considerable discussion of the impact of Health Technology Assessment (HTA) in the future and the general belief that this has to be incorporated into clinical testing at an earlier stage. This might result in a greater number of comparative trials but there was the vision of a situation where *Conditional Authorisations* could be granted on the basis of Phase II efficacy trials after which development could move directly into population-based studies (skipping the confirmatory Phase III) in order to address safety and HTA issues.

There is a risk, however, that too great a focus on HTA may prevent some drugs from being approved that might later have been shown to be very efficacious. The examples of Losec (omeprazole) and Gleevec (imatinib mesylate) were given.

A key related issue for the future is some sort of **risk sharing** between governments and industry. This may be achieved in some countries by 2015 but it was felt to be a long-term goal.

Introduction of New Technologies

Genetic markers (C8)

The Syndicate envisaged that the science of genetic markers would have developed by 2015 such that it will be routinely incorporated into drug development. This should lead to faster approval at the clinical trials stage.

Adaptive trial design (C9)

Adaptive clinical trial design should be well accepted by 2015. One major benefit will be in achieving better dose-response curves in the early development stage rather than carrying out many Phase II studies to identify the optimal dose.

It was noted that companies currently try to obtain authorisation of a maximum dose and often need to reduce this in the post approval stage.

Other factors in the 2015 landscape

There will be a very large sub-population of **geriatrics** by 2015 and clinical testing will need to be adapted to incorporate studies in the elderly and particularly interaction studies.

The 'Paediatric rule' may well need to be supplemented by a 'Geriatric rule' in 2015.

¹International Conference on Harmonisation (ICH) guideline E5 *Ethnic Factors in the Acceptability of Foreign Clinical Data* available via www.ich.org

²The IND procedure was described at the Workshop by Dr Murray Lumpkin, Deputy Commissioner, Food and Drug Administration, USA (Section 3, page 20)

³The Australian notification process was described at the Workshop by Dr Leonie Hunt, Assistant Secretary, Office of Prescription Medicines (OPM), TGA, Australia (Section 3, page 29)

⁴The outcome of the CMR International Institute Study was reported to the Workshop by Dr Neil McAuslane and Lawrence Liberti, Section 3, pages 5-14

⁵CMR International Institute Workshop on Global Drug Development: Asia's Role and Contribution was held in Tokyo, October 2006. Report available from the Institute, e-mail: institute@cmr.org

WORKSHOP PROGRAMME

SESSION 1: GLOBAL CLINICAL TRIAL DEVELOPMENT PROGRAMMES: INCENTIVES AND BARRIERS TO INITIATING CLINICAL TRIALS IN ASIA, AFRICA AND LATIN AMERICA

Chairman's Welcome and Introduction	Thomas Lönngren , Executive Director, European Medicines Agency (EMEA)
Keynote Presentation - Why are the new regions becoming so important in global drug development?	Dr Jorge Puente , Vice President, Medical & Regulatory Affairs – Japan/Asia, Pfizer Inc, USA
Panel discussion on Asia's role in global drug development: How are countries encouraging multi-national clinical trials?	
China	Dr Yi Feng , Head of CDE Review Management, SFDA, China
South Korea	Prof Sang Goo Shin , President, KoNECT, Korea National Enterprise for Clinical Trials, South Korea
Japan's role in global drug development	Birgitta Hedin , Global Regulatory Lead & Asian Regulatory Strategy Director AstraZeneca, Japan
Study Report on Streamlining the Review Process for Global Clinical Trials: Company data	Dr Neil McAuslane , Director, CMR International Institute for Regulatory Science

SESSION 2: STREAMLINING THE PROCEDURE FOR OBTAINING CLINICAL TRIAL APPROVALS

Chairman's Introduction	Dr Murray Lumpkin , Deputy Commissioner, International and Special Programs, FDA
Clinical Trial Approval Process in the USA	Dr Murray Lumpkin , Deputy Commissioner, Food and Drug Administration, USA
Study Report on Streamlining the Review Process for Global Clinical Trials: Agency data	Lawrence Liberti , Vice President, CMR International Institute for Regulatory Science
Panel discussion to review competitive advantages and best practises	
Singapore	Yang-Tong Foo , Deputy Director, Clinical Trials Branch, Health Sciences Authority, Singapore
Indonesia	Lucky Slamet , Deputy for Therapeutic Product, Narcotic, Psychotropic and Addictive Substance Control, NADFC, Indonesia
Malaysia	Noorizam Ibrahim , Principle Assistant Director, National Pharmaceutical Control Bureau, Malaysia
Australia	Dr Leonie Hunt , Assistant Secretary, Office of Prescription Medicines (OPM), TGA, Australia

Building quality into the clinical trial infrastructure: What are the requirements?

Regulator's viewpoint	Li-Ling Liu , Deputy Director General Bureau of Pharmaceutical Affairs, BPA, Chinese Taipei
Industry viewpoint	Jerry Stewart , Vice President, Global Regulatory Affairs, Wyeth Pharmaceuticals, USA

SESSION 3: SYNDICATE DISCUSSIONS

Chairman's Introduction	Prof Robert Peterson , Professor of Paediatrics, University of British Columbia, Canada
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**WORKSHOP ON CLINICAL DEVELOPMENT IN ASIA, AFRICA AND LATIN AMERICA:
Streamlining the procedure for obtaining Global Clinical Trial approvals**

Section 3: Summary of Presentations

Section 3 of the report provides synopses of the Speakers' presentations at the Workshop. The Workshop Programme is summarised on Section 2, page 11, but a slightly different sequence has been used in Section 3, for the purpose of the Report.

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Section 3: Chapter 1 KEYNOTE PRESENTATION

**Why are the new regions becoming so important in global drug development?
What are the competitive advantages and limiting factors?**

Dr Jorge Puente

Vice President, Medical & Regulatory Affairs – Japan/Asia, Pfizer Inc, USA

Dr Jorge Puente addressed the changing factors that are making the inclusion of new regions in Global Drug Development both a challenge and an opportunity for the international pharmaceutical industry.

Demographics

The size of the population in the new regions is a major consideration. While there are nine cities in the USA with more than one million people and 35 in all the countries of Europe, there are, in India alone, 35 cities that fall into this category. When China is considered, there are an astounding 211 cities that exceed 1 million inhabitants.

Figure 1



The size of the population automatically means a greater incidence of individual diseases but there are marked differences in the pattern of disease between, for example, Asia and the Western World with consequent differences in the medical needs and priorities. Asia, for example, now accounts for 45% of all cancer deaths worldwide and, as shown in Figure 1, the second and third most common causes of cancer death in Asia (after lung cancer) are stomach and liver cancer, both of which are rare in North America.

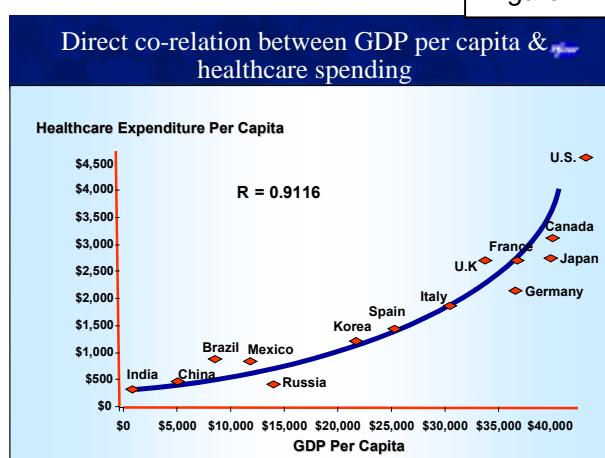
Another example of medical need is stroke, which is much more prevalent than other cardiovascular diseases in Asia. In China alone, there are 800,000 to 1 million deaths per year from stroke and six million stroke survivors. In the infectious disease field, there is the example of Hepatitis B, which affects 2 billion people worldwide and leaves 360 million chronically infected, of which 25% will die of complications.

Prosperity

The increased urban prosperity in Asia can be seen by the transformation of the cities and the changing skylines. An example is the transformation, in the last 20 years, of the city of Chongqing in China which, from the sky, now looks much like Manhattan.

As shown in Figure 2, there is a direct correlation between the GDP per capita in a country and healthcare spending. China, which is the largest population among Asia Pacific countries, is an example of this with the highest healthcare spending growth rate at 17.6 percent.

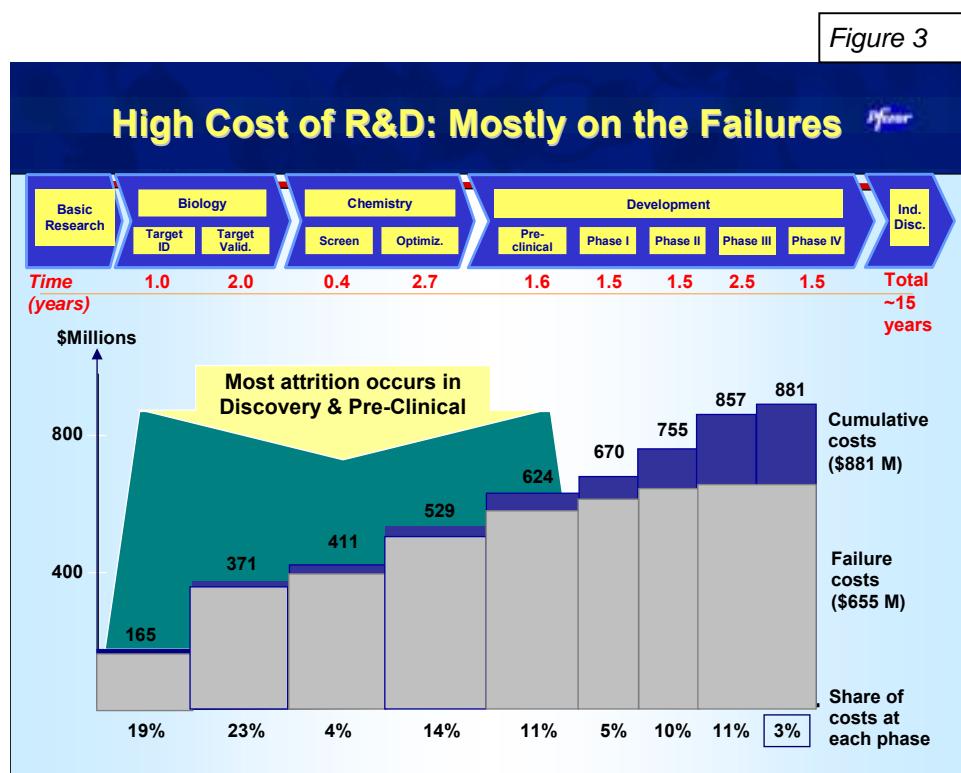
Figure 2



The country has recently seen several significant changes in relation to its healthcare industry many prompted by the "China 2020" vision, under which the China Health Ministry aims to provide basic healthcare for every citizen, including the rural population, by 2020.

The health of the industry

Whilst the pharmaceutical industry seeks new partners and markets in new regions, its own research and development profile is far from healthy. Overall investment in new drug research continues to increase and the cost of R&D is escalating. However, the high failure rate of individual drug development projects continues and it is this failure rate that is driving up the cost of R&D (Figure 3). The overall picture is of an industry that is investing increasing amounts with fewer drugs being approved.



One of the major impacts on industry has been the trend towards consolidation with mergers and takeovers reducing the number of major companies over the last 20 years. For example, PhRMA, the association representing the research-based industry in the US, has seen its membership fall from 42 companies in 1988 to 16 companies in 2005.

Another impact on companies is the trend towards including scientists in senior management, as the future of the industry clearly lies in its capacity to produce successful and innovative medicines. As an example, Pfizer's Executive Team of 12 includes four scientific and technical executives, which would have been unheard of a few years back.

Impact on Clinical Testing

As drug development becomes more complex and more expensive companies must seek competitive advantages in the way they conduct their business. In the clinical area, the number of protocol procedures is increasing and Pfizer's current statistics indicate that the clinical trials conducted by the company between 2005 and 2008 included 11 therapeutic areas, required 990 protocols which involved 137,737 patients in 75 countries, involving a total of 28,414 sites.

One reaction to this demand for clinical resources is to seek clinical trial sites in new regions of the world. The profile of clinical development by Pfizer has changed since the year 2000 when trial sites were concentrated almost entirely the US, Western Europe, Australia and South Africa, with some sites in Israel. By 2008, only 73% of Phase II trials and 59% of Phase III trials were being carried out in these 'developed' regions, with an increasing involvement of sites in Eastern Europe, Asia and South America.

Selecting countries for clinical development

When seeking new countries and regions in which to carry out clinical testing, companies must look for a balance among several factors. The attractiveness of a country as a potential future market is only one factor. More important are the conditions that facilitate the conduct of ethical and appropriate research such as medical need, proper infrastructure, qualified personnel and a matured regulatory environment. One example of an important factor is the time it takes to obtain the regulatory approval for clinical trials as shown in the following table:

Pfizer data on CTA approval times and processes					
Country	PCO Preparation Time	Health Authority Approval Time	Ethics Committee Approval Time	Process for HA & EC Approval	Maximum Total Time from CTA Despatch to CTA Approval (HA & EC)
China	90 days (phase 1 75 days)	7 - 10.5 months (biologic 18 months)	45 days (phase I 60 days)	Serial HA approval first	345 days (Ph II onwards) (biologic 495 days)
Hong Kong	14 days	65 days	70 days	In parallel	84 days
Chinese Taipei	21 days	90 days (phase IV 15 days)	70 days	In parallel	111 days
Korea	30 days	60 days	40 days	In parallel	90 days
India	21 days	90 days	28 days	In parallel	90 days

From the company's experience, there are generally many advantages in including these countries in a Global Clinical Development Programme. Some comments of importance are noted below:

China, whilst an increasingly attractive market, has the obvious disadvantage of long approval times coupled with extensive data requirements for clinical trial applications.

Some of the major issues are that:

- Every protocol requires a separate complete CTA and it is not possible to refer to previously submitted data;
- A rolling submission is not possible under current legislation, and protocol amendments can involve a 3-month delay;
- There are extensive technical data requirements, especially pharmaceutical (CMC) requirements for data not available during early phases of development;
- China studies must be carried out at one or more of the 251 SFDA-accredited clinical sites in China or Hong Kong.

Hong Kong: The Health Authority requires a sample of study medication as part of the CTA application, which can delay the process

India: Currently first in human studies by multinational companies are not permitted in India although it is hoped that this could be changed in the near future

South Korea: The total approval time for CT applications is a favourable 60 days and may be further improved following recommendations in June 2008 for joint IRBs rather than sites-based committees. The Health Authority has also recommended mutual recognition of IRB reviews.

Attractive markets

Whilst the pharmaceutical markets in the West remain hugely attractive on a global scale, the growth rate of markets in Asia-Pacific (12.7% p.a.) and Latin America (14.7%) are outpacing those of North America (7.7%) and Europe (6.1%). This will obviously have a major impact on the way in which pharmaceutical companies plan their future research strategies.

... but in the end...

It is patients' expectations of better and more effective medicines to improve their quality of life that will drive the development of new medicines.

Section 3, Chapter 2

STUDY REPORT

Streamlining the Review Process for Global Clinical Trials

Introduction

As part of its 2008 programme on the Regulation of Medicines in the Emerging Markets, the CMR International Institute for Regulatory Science (the Institute) carried out a study to look at the similarities and differences in the way in which clinical trials are regulated in different regions and markets of the world.

The study focused on the 11 countries in Latin America, Africa, and Asia-Pacific that are shown in *Figure 1*.

Information was collected on the activities and perceptions of the **Regulatory Agencies** in these 11 countries using questionnaires and face-to-face interviews with senior agency personnel.

Fourteen multinational **Pharmaceutical Companies** that are active in all or most of the target countries also participated in the study and provided data from their experiences in the regions.

The focus of the study was on the extension of clinical development to 'non-core' countries and new regions for companies and comes at a time when the industry is looking at these countries as potential venues for their clinical trials. This interest comes in the context of companies being under pressure from increasing R&D costs, increasing timelines for developing new medicines, and facing a decrease in the number of new molecular entities reaching the market (see *Figure 2*).

Figure 1

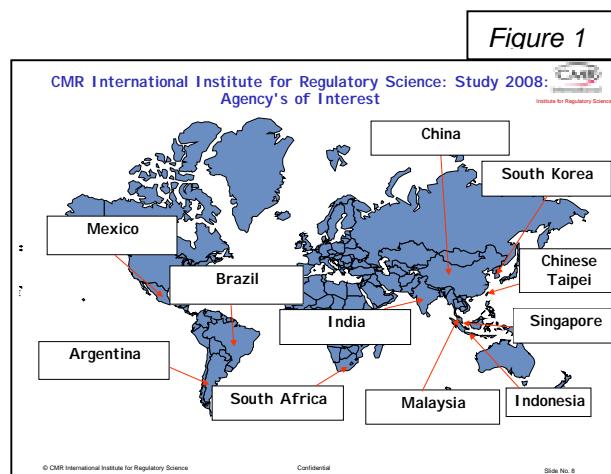
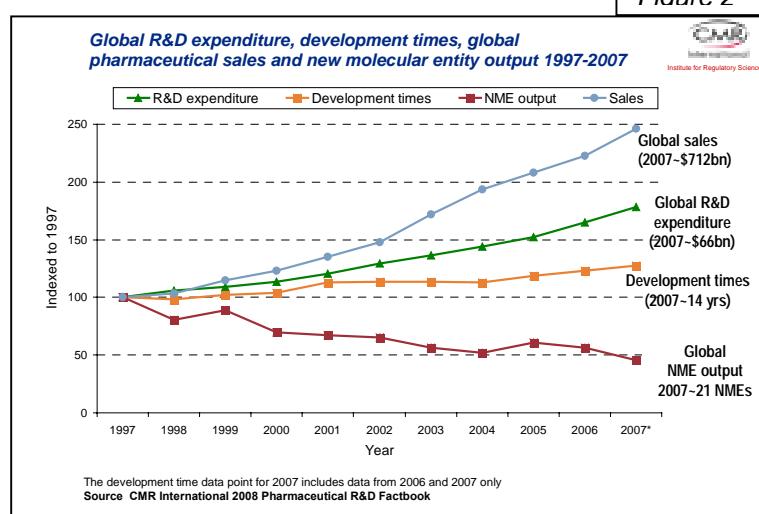


Figure 2



Clinical Statistics

- 2007: Clinical Development spend of **\$24.4bn** accounted for 37% of total R&D spend
- Clinical Development takes about **6.1 years** from first human dose
- 2006: Median Phase III study duration was **726 days** of which Median Phase III Patient enrolment time was **364 days**
- 2002-2006: Phase III Patient enrolment time increased by **22%**

Two presentations on the Institute study were made at the Workshop:

- **Dr Neil McAuslane** gave the background to the Study and summarised the information provided by *Pharmaceutical Companies*
- **Lawrence Liberti** focused on the results from the survey among *Regulatory Agencies*.

The Regulatory Process for Clinical Trial Applications: COMPANY DATA FROM THE INSTITUTE STUDY

Dr Neil McAuslane
Director, CMR International Institute for Regulatory Science

A 'global shift' in clinical development

Data on global patient enrolment in clinical trials conducted by pharmaceutical companies for the years 2000 and 2006 (*Table 1*) show a trend towards fewer trials in the 'traditional core' countries for pharmaceutical development and a move to new regions for clinical research¹.

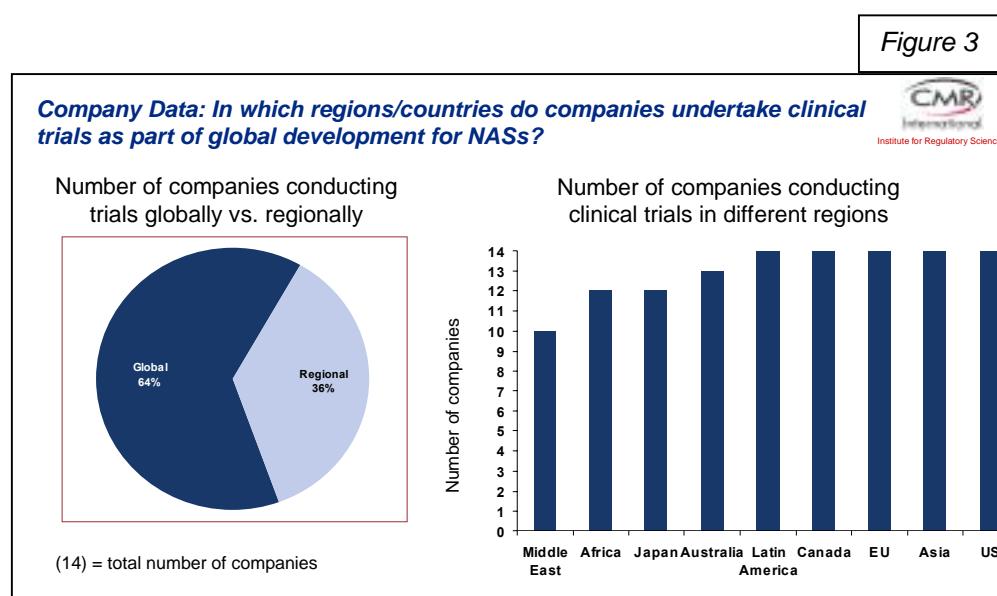
The factors cited by companies as being important when selecting a mix of countries (e.g. compliance with GCP, the regulatory environment, disease prevalence and standards of care, patient availability, enrolment time and costs etc) were integrated into the Institute study.

Table 1 Proportional change in number of enrolled patients		
Region	2000	2006
North America	41%	39%
EU 'Core'	21%	14%
EU 'Non-core'	8%	13%
EU accession	4%	7%
Latin America	3%	7%
Asia-Pacific	2%	7%
ME & Africa	2%	2%

Companies in the Institute Study

The cohort of 14 pharmaceutical companies that participated in the Institute study was made up of 10 'Major' companies (defined as having an annual R&D spend of over 2bn US\$) and 4 medium-size companies.

The participating companies were asked about their current strategies for clinical development and whether programmes were planned on a global scale or confined to specific regions. The results (Figure 3) show that most of the participating companies conduct clinical trials on a global rather than a regional basis and that all are active in the Latin American and Asia-Pacific regions. The companies that confine development to specific regions attributed this to their company's strategy and/or internal constraints.



¹ Based on studies from a consistent cohort of 23 companies where patient enrolment was completed in each year range. Source: 2008 Pharmaceutical R&D Factbook, CMR International a Thomson Reuters Business

Clinical Trial Phases

All 14 companies are currently undertaking **Phase III** clinical trials in the three Latin American countries surveyed and most companies are involved in Phase III trials in South Africa (13/14) and in China, India, South Korea, Singapore, Chinese Taipei (12/14). **Phase II** studies are also relatively frequent in Latin America (Argentina 11/14 companies, Mexico 10/14, Brazil 9/14).

Phase I studies are relatively rare in non-core countries but 3 of the 14 companies reported that they have carried out such trials in Singapore, South Africa, Argentina and Brazil.

Future trends

Companies were asked about the proportion of clinical trials currently carried out in different regions and their predictions for the future. Currently Latin America and Asia-Pacific (excluding Japan) each account for approximately 7% of the total global trials and the greatest growth (100% increase by 2012) is expected to take place in Asia-Pacific.

Barriers and Advantages

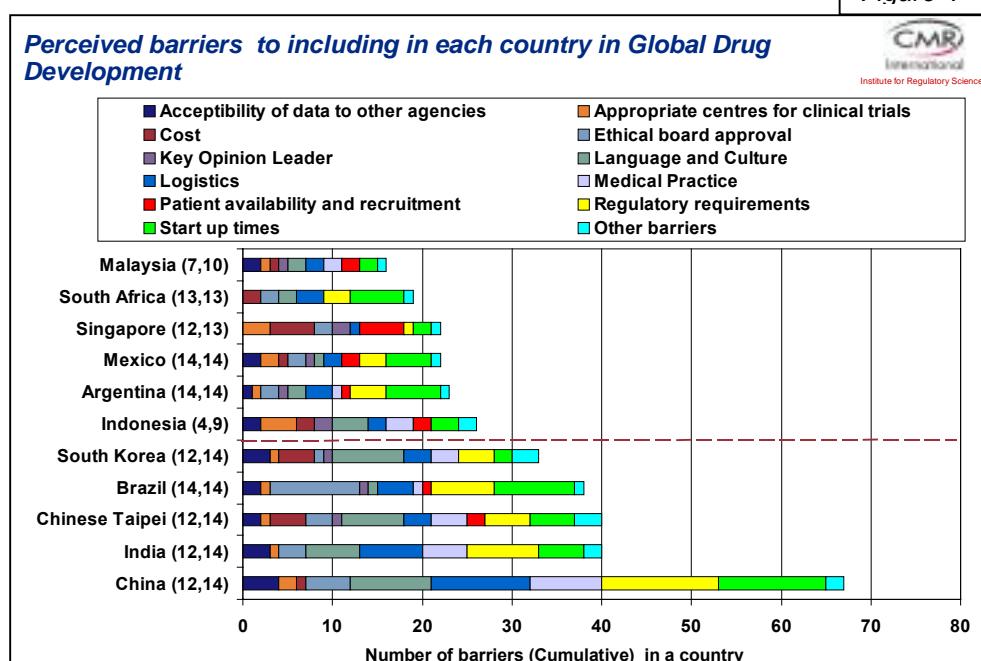
The data collected from pharmaceutical companies in the Institute study (see *Box 1*) included their perceptions of the barriers to, and incentives for, including individual countries in global clinical trial programmes.

Box 1

CMR International Institute Study: Data Collected from Companies

- Current and future *Clinical Trial Strategy*
- Perception of the *CT Approval environment*
 - Key barriers or competitive factors when including each country in global development
- Specific Areas that may make the country *uncompetitive*:
 - Regulatory requirements (data or technical)
 - Ethical requirements
 - Other requirements
- Perception of *Start up Times* and main reasons for delays
- Companies' perception of the country *Benefits* brought by inclusion in global programmes
- The ideal *Regulatory Landscape* for clinical development
- Metrics on the Clinical Trial application processes

Figure 4



(n1,n2) = number of companies conducting clinical trials in a country; number of companies that answered this question

Barriers

Companies were given the list of 12 factors and asked to rate each as either a major, a minor or no barrier to the inclusion of the country in a global programme. A cumulative picture of the responses was built up graphically as shown in *Figure 4*. Whilst many factors relate to the country environment (language, cultural issues etc.) the three which can be attributed to the regulatory environment are *Ethical Board Approval*, *Regulatory Requirements* and *Start-up Times*. All of these were important factors in the five countries (South Korea, Brazil, Chinese Taipei, India and China) which emerged from *Figure 4* as presenting the greatest cumulative set of barriers.

Concerns about regulatory requirements (e.g., in China, India) often cited the quality (CMC) requirements as being inappropriate for the stage of development of the product, for example, stability requirements.

Companies were asked for other factors that caused concern in individual countries and the results highlighted:

- The difficulty in conducting placebo trials in Argentina and Brazil
- The length of approval timelines for CT applications in Brazil, South Africa and China
- Lack of human resources and infrastructure in India, Indonesia, Malaysia and Singapore.

Benefits to the country

Companies were asked for their views on the benefits that countries can derive from being part of global clinical trial programmes, by selecting three from a list of five criteria. The *Companies'* perceptions of benefits are given in *Table 2* and should be compared with the *Agencies'* response to the same question (see *Table 5, page 13*).

Table 2

Potential benefit	Proportion of companies that ranked this in the top three
• Experience of new medicine in the country prior to marketing	85%
• Doctors have access to new treatments early	69%
• Improved clinical infrastructure	62%
• Improved patient welfare	46%
• Country gains economic benefit	23%

Clinical Trial Metrics

Companies were asked to provide the following dates for clinical trial applications submitted in 2006-2007 in the countries of the study:

Date 1: First formal submission in the country (to the Regulatory Agency or Ethics Committee)

Date 2: Submission to the Regulatory Agency

Date 3: Approval by the Regulatory Agency

Date 4: First Patient Enrolment for the study

The following time intervals were studied in the data analysis shown in *Figure 5*:

- **Pre-regulatory submission time:** Date 1 → Date 2, which is Zero for China (ethics approval follows regulatory approval) and can be Zero in countries such as South Africa, South Korea and Malaysia, where ethics and regulatory review are carried out in parallel.
- **Regulatory approval time:** Date 2 → Date 3 (see also *Table 3*)
- **Start-up time:** Date 1 → Date 4
- **Post-approval to Start up:** Date 3 → Date 4

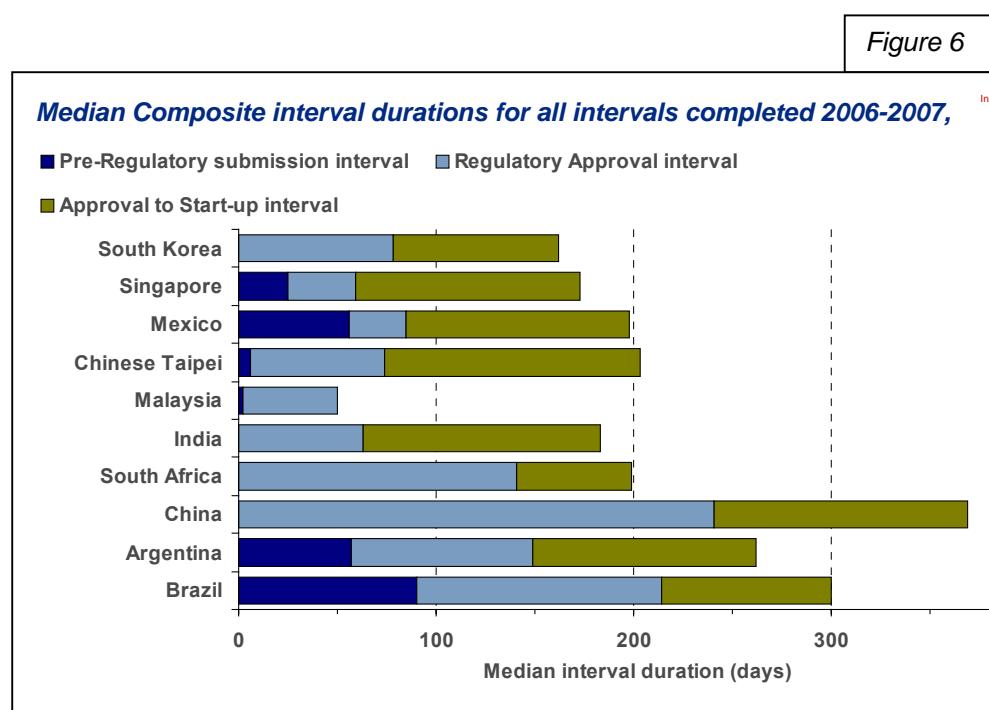
Regulatory approval

Table 3: Median Regulatory Approval Times

Country	No. Applications	No. Companies	Median approval time (days)
Mexico	46	7	29
Singapore	26	7	35
Malaysia	7	3	48
India	33	7	63
Chinese Taipei	33	8	68
South Korea	43	7	78
Argentina	55	9	92
Brazil	52	8	124
South Africa	39	7	141
China	20	6	242

Rollout overview

Figure 5 gives a composite picture of the way in which the three time intervals (Pre-regulatory submission time, Regulatory approval and Post-approval time) contribute to the **overall start-up time** from the first formal submission in a country to enrolment of the first patient in clinical trials.



Notes on Figure 6

Median interval durations are shown for all applications for Phases I, II, III and are shown by country.

Medians are calculated only where data exist for both milestones, therefore different datasets are used for each interval.

There was insufficient data to provide a median *Approval to Start-up* interval for Malaysia

The Regulatory Process for Clinical Trial Applications: AGENCY DATA FROM THE INSTITUTE STUDY

Lawrence Liberti, Vice President
CMR International Institute for Regulatory Science

The CMR International Institute for Regulatory Science (The Institute) collected data from the Regulatory Agencies in the 11 countries shown in Figure 1 in order to study the similarities and differences in the ways in which clinical trial (CT) applications are handled in different countries and regions. The focus was on the way in which Multinational Clinical Trials (MNCTs) that are part of global clinical development programmes are handled by the different agencies. The study covered not only data but also perceptions (see *Box 2*) and was carried out using both questionnaires and face-to-face interviews with agency personnel.

For most countries the data were derived entirely from the agencies but for some (China, India, South Africa) the information was supplemented by public domain data and feedback from industry.

Agency organisation

Agencies were asked about the way in which the review of CT applications fits into the overall activities and responsibilities of the agency. It was found that 8 out of the 11 agencies had dedicated *Clinical Trial Units* responsible for the assessment of CT applications.

There was considerable diversity in number and qualifications of staff assigned to CT review. In some cases a small number of staff work exclusively on CT applications, in others a relatively large number are involved but their duties include a much wider range of activities. Almost every agency has physicians involved in the CT review but the majority of staff are pharmacists and pharmacologists.

Box 2

CMR International Institute Study: Data Collected from Agencies

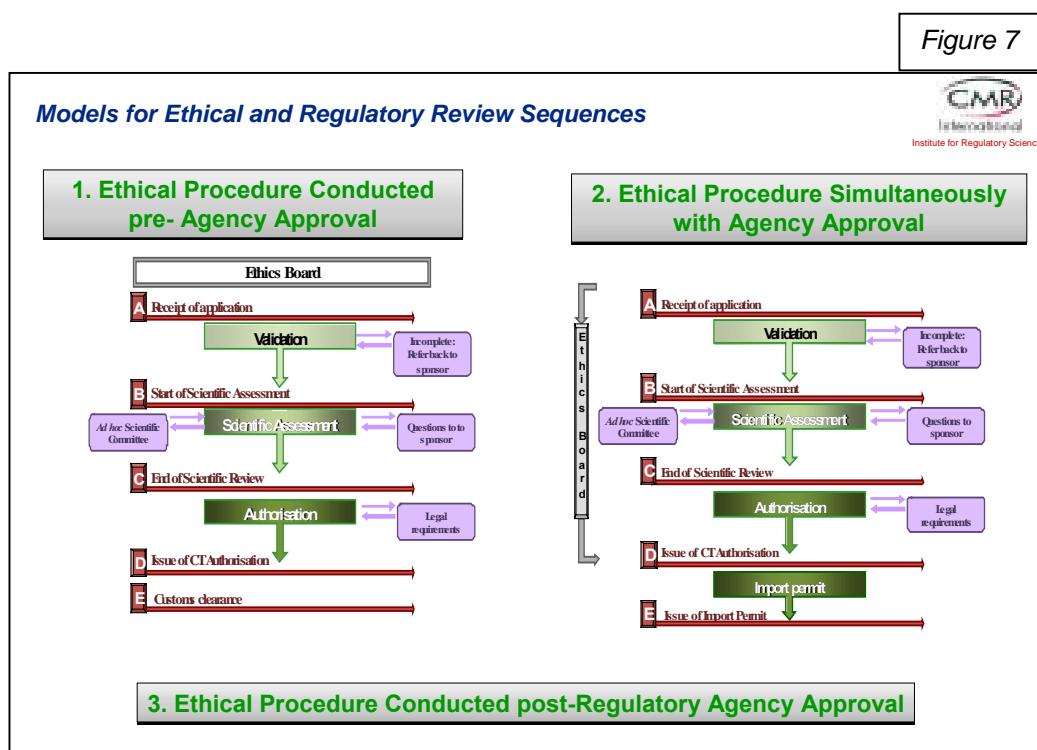
- *Overview of the Agency*
 - Unit and staffing for CT review
- *Regulatory Submission*
 - Administrative requirements
 - Scientific and Technical data
- *The Review Procedure*
 - Steps in the review
 - Priority applications
 - Importation of CT material
- *Good Clinical Practice*
- *Ethical Committees*
- *Clinical Trial Metrics*
- *Perceptions and Reflections*
 - Avoiding delays and rejection
 - Potential barriers to including a country in MNCTs
 - Potential benefits to the country and company
 - Agency advice to sponsors

Considerable diversity was also found when a comparison was made of the fees charged to sponsors for the review and assessment of CT applications. (Fees were converted to US\$ using a common exchange rate). Whereas some countries (China and Brazil) charge several thousand dollars, fees in most other countries are less than \$1000 and no charge is made in Singapore and South Korea.

Review models

For the purpose of the study, the review processes in different countries were compared using a standardised 'Process Map' of the steps in the review. It was found, as shown in Figure 7, that there were two main models: One in which ethics approval has to be obtained before the submission is made to the regulatory authority and a second where submissions for ethical and regulatory approval can be made in parallel. There is a third model (not shown in detail) where the ethical review does not start until the regulatory process is complete.

Overview of Review Procedures



The stages set out in the generalised review models were used in the questionnaire and allowed comparisons to be made between the review and assessment procedures in different countries. Some examples are given below.

Validation and queuing

All the agencies in the survey had a *Validation Process* on receipt of submissions in order to check the completeness of the data elements. In some countries there are backlogs and applications are held in a queue whilst in others the staff pick up the submissions for review as they are received.

Countries with zero waiting time were Argentina, South Africa, South Korea and Chinese Taipei. The waiting time in other countries varied from three days in Singapore to 90 days in Brazil.

Scientific Assessment

All agencies use internal review staff to carry out the scientific assessment with the exception of South Africa, where the agency sends applications to external reviewers for assessment.

In most of the agencies surveyed, questions that arise during the assessment are batched and sent to the sponsor at a single point, often at the end of the review. South Africa is, again, an exception in that questions, although batched, can be sent at any time during the review.

Good Clinical Practice

Standardised *Best Practices* were applied by all agencies in terms of Good Clinical Practice (GCP). The common standards applied are ICH GCP, WHO GCP and PAHO GCP, which are based closely on the WHO model. In some cases there were national codes but these were based on ICH GCP and differences were largely due to incorporation of local requirements. All agencies have a capability for site inspections that are built into their GCP approval process.

Models and Countries

Model 1:
4 Countries:
Argentina, Brazil,
Mexico and
Indonesia

Model 2:
6 Countries:
S. Africa, India,
*Malaysia,
Singapore, S
Korea and Chinese
Taipei

Model 3:
1 Country: China

*Ethics clearance
must be obtained
before regulatory
approval can be
given.

Priority review

A few countries (India, Chinese Taipei and - shortly - South Korea) have a priority CT application review system where the process may be accelerated if the CT protocol has been conducted in another country or under an open IND.

Timelines for Review and approval

Regulatory agencies were asked to provide their *Target Times* for the overall approval of CT applications. These were compared, as shown in *Figure 8*, with the data from companies on their experience of timelines in the different countries.

The results show a greater correlation between target and actual approval times than might have been expected.

The majority of agencies are achieving an approval time of 60 days or less.

Delays and failures

Agencies were asked to give their views on the three main reasons for CT applications being delayed or refused in their country. The results, summarised in *Table 4*, have a common theme of problems related to the quality and completeness of the submission and to the scientific basis of the trial design.

Figure 8

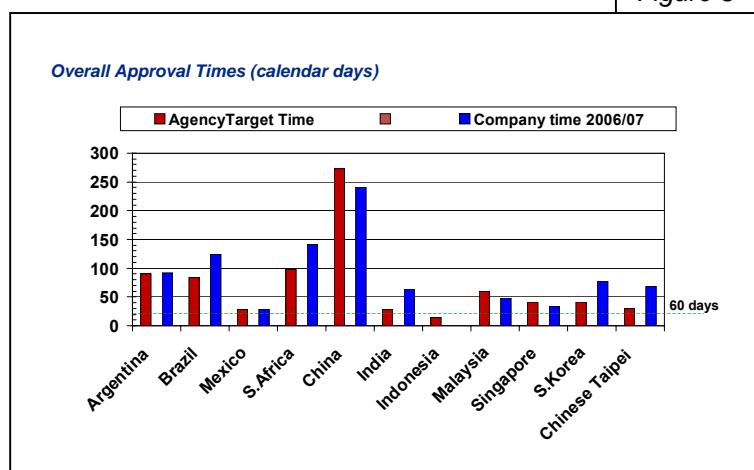


Table 4

Country	Reasons for delays in processing/refusing CT applications		
Argentina	Certain studies with placebo might be considered unethical	FDA demand superiority trials issues with comparator products	Selected investigators do not have appropriate competency
Brazil	Time taken to obtain ethical clearance	Certain placebo controlled trials may be rejected	
Mexico	Misaddressed application forms	Deficiencies in the documentation	
South Africa	Scientific design and incomplete submissions	Increasing demand and limited number of reviewers	
India	Inadequate Staffing	Scientific justification for the study	
Indonesia	Incomplete trial documentation	Risks outweigh the benefits	
Malaysia	Slow response by the company to questions	Incomplete documentation	
Singapore	Inadequate submission dossiers	Agency resource constraints	Benefit risk – unfavourable or not enough information
South Korea	Incomplete company submissions	Shortage of reviewers	Sponsors not following national guidelines
Chinese Taipei	Safety concerns		

The take-home message is obviously that companies could help improve performance by ensuring that their dossiers are complete and in accordance with agency guidelines. There are, however, instances where there are safety concerns over the study design and the agency struggles to understand whether the benefits outweigh the risks such that the trial can be justified in their population.

Barriers and benefits

In the section of the survey on *Perceptions and Reflections*, agencies were asked for their views on the potential barriers that might preclude their country from being included in MNCTs and also the benefits that might accrue from inclusion in the global clinical development of new medicines.

Barriers

When asked for the top three barriers that might deter companies from conducting clinical trials in the country, there was a common theme of acknowledging inadequate staffing at the agency leading to long review and start-up times. Some countries, e.g. Malaysia and Mexico, suggested that potential trial centres were not being adequately promoted. Singapore felt that the small patient pool was a barrier but also cited the relatively high cost of conducting clinical trials in the country.

Benefits

Both the company and agency surveys included the same question on the potential benefits that a country could gain from being included in global clinical trial programmes. The results shown below, from an *agency* viewpoint give a different perspective from the *company* perspective reported earlier (Table 2, page 8). The agency emphasis is on improving the clinical infrastructure and patient welfare rather than the importance of early access to new medicines.

Table 5

Potential benefit	Proportion of Agencies that ranked this in the top three
• Improved clinical infrastructure	70%
• Improved patient welfare	70%
• Country gains economic benefit	60%
• Doctors have access to new treatments early	50%
• Experience of new medicine in the country prior to marketing	40%

The agencies were also asked about the benefits that they thought a company would derive from including their country in a global CT programme. A list of six potential advantages were suggested and agencies were asked to select the top three that applied to their country, with the following results:

Potential Benefit that the country can offer	Proportion of Agencies ranking this in top 3
• The availability of qualified investigators and institutes for the conduct of CTs	90%
• An efficient Regulatory Agency	50%
• Strong government support for clinical development in the country	40%
• An attractive pharmaceutical market	40%
• The application of data requirements within ICH norms	30%
• Good patient availability	30%
• An efficient process for Ethics Review.	10%

Overall Summary from the Institute Study

Company data

- **Clinical trials sites:** The study confirmed an increasing shift away from clinical development in the 'traditional' core countries towards carrying out trials in new regions, especially Latin America and Asia-Pacific.
- **The choice of countries** for global clinical development programmes is influenced by the regulatory process (timelines, data requirements, ethical clearance etc) but factors such as language, culture, medical practice, and logistics can also have a major impact.
- **Approval Times** for CT applications vary widely among the countries studied from 29 days (median time for Mexico) to 240 days (median for China).
- **Start-up Times** also vary widely between countries and the contributing factors include:
 - The timing and timelines for ethical approval
 - Regulatory approval times
 - Logistics, particularly the time taken to negotiate with local clinical trial sites

Agency data

- **Experience of MNCTs:** The majority of agencies in this study have experience in processing CT applications that are part of a global drug development programme and some governments are actively encouraging such participation.
- **The Target Time** set by agencies for reviewing and authorising clinical trial applications is two months or less for most countries.
- **Review Process model:** For more than half the agencies (6/11) the application for ethics clearance is processed at the same time as the regulatory application.
- **Priority Review:** Applications for trials that are part of a multinational development programme are given priority by some agencies.

Overall Observations

Across the regions it is apparent that companies are looking for predictability and efficiency and timeliness in the processes that enable the initiation of clinical trials at a national level.

From a company perspective, MNCT Programmes would be greatly facilitated by: Common global CT data requirements; Standardisation of content and format of CT applications and; A Fast Track procedure if the technical data has already been reviewed by a reference agency.

Agencies' primary concerns are for the safety and well-being of their patient population and it is important that companies demonstrate a positive benefit-risk justification for trials.

Agencies' advice to companies would be to ensure that they understand local requirements and submit complete, conforming submissions.

Section 3: Chapter 3

REGULATION OF CLINICAL TRIALS BY 'REFERENCE' AGENCIES

Comparative demographic data*	Workshop Presentation	Page
European Union (27 Member States) <i>Population: ~491 million</i> <i>Area: 4,324,782 sq km</i> <i>GDP: ~ 18.93 trillion US\$</i> <i>GDP growth rate: ~ 1.5%</i> <i>GDP per capita: ~ 33,800 US\$</i> <i>Life expectancy: 77.32 years</i> <i>Median age: No overall estimate</i> 	Thomas Lönngren, <i>Executive Director,</i> <i>European Medicines</i> <i>Agency (EMEA)</i>	16
United States of America <i>Population: ~ 304 million</i> <i>Area: 9,826,630 sq km</i> <i>GDP: ~ 14.33 trillion US\$</i> <i>GDP growth rate: ~1.4%</i> <i>GDP per capita: ~ 48,000 US\$</i> <i>Life expectancy: 78.14 years</i> <i>Median age: 36.7 years</i> 	Dr Murray Lumpkin, <i>Deputy Commissioner,</i> <i>International and Special</i> <i>Programs, FDA</i>	20
Japan <i>Population: ~ 127 million</i> <i>Area: 377,835 sq km</i> <i>GDP: ~ 4.844 trillion US\$</i> <i>GDP growth rate: ~ 0.7%</i> <i>GDP per capita: ~ 35,300 US\$</i> <i>Life expectancy: 82.07 years</i> <i>Median age: 43.8 years</i> 	Birgitta Hedin, <i>Global Regulatory Lead &</i> <i>Asian Regulatory Strategy</i> <i>Director AstraZeneca,</i> <i>Japan</i>	25
Australia <i>Population: ~ 21 million</i> <i>Area: 7,686,850 sq km</i> <i>GDP: ~ 1.609 trillion US\$</i> <i>GDP growth rate: ~ 2.5%</i> <i>GDP per capita: ~ 39,300 US\$</i> <i>Life expectancy: 81.53 years</i> <i>Median age: 37.1 years</i> 	Dr Leonie Hunt, <i>Assistant Secretary, Office</i> <i>of Prescription Medicines</i> <i>(OPM), TGA, Australia</i>	29

* Data, from the CIA World Factbook, is for comparative purposes only. Information is predominantly based on 2008 figures and actual values (e.g., US\$ equivalents) may be affected by exchange rates.

CHAIRMAN'S INTRODUCTION: EU PERSPECTIVE

Thomas Lönnqvist
Executive Director, European Medicines Agency (EMEA)

Thomas Lönnqvist chaired the first Session of the Workshop and also provided background information on the regulation of clinical trials in the EU, within the context of some of the key issues being addressed at this Workshop:

- The Globalisation of clinical research;
- Reaching a common understanding and framework for ethical and scientific standards;
- Achieving a strong regulatory and ethical framework in all countries where clinical trials are conducted;
- Assistance through sharing of expertise and capacity building; and
- The role of Regulatory Authorities through a global regulatory network

EU procedures relating to clinical trials

The EMEA operates the Centralised Procedure for the approval of marketing authorisations through its Committee on Human Medicinal Products (CHMP) and specialised Committees and Working Parties. The EMEA has also set up databases for the registration of all clinical trials carried out in within the European Union (EudraCT) and the EudraVigilance database which records both clinical trials and post-marketing adverse event data.

At country level, the national competent authorities (NCAs) are responsible for the decentralised and the mutual recognition procedures for marketing authorisation and they also have responsibility for the authorisation of clinical trial applications. The responsibility for national authorisation of clinical trials falls under Directive 2001/20/EC known as the *Clinical Trials Directive*. The primary objective of this Directive is the protection of public health and rights, and the integrity of research participants. It sets out the legal basis of GCP and GMP in clinical trials and it applies to Phases I-IV of clinical research, both for trials sponsored by academia and industry.

When an application for a Marketing Authorisations includes clinical trial reports, the legislation¹ refers back to the CT Directive by stating that: *'it should be verified, at the time of the evaluation of the application for authorisation, that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of that Directive.'*

In the case of trials carried out outside the European Union, the applicant must make a statement that the trials were designed, and implemented in accordance with Good Clinical Practice and Ethical Principles that are equivalent to the provisions of the CT Directive and carried out in accordance with the ethical principles reflected, for example, in the Declaration of Helsinki.

When assessing non-EU clinical trials in Marketing Applications, the EU regulatory authorities will take account of:

- Ethical issues
- Data quality issues
- Applicability to EU populations
- Applicability to EU medical practice

¹ Directive 2001/83/EC as amended and Directive 2003/63/EC
Section 3, page 16

Metrics for the EU

Data on the numbers of clinical trials registered in EudraCT from 1 May 2004 to 1 November 2008 showed:

Clinical trial applications

Total applications	35,571
Total different trials	18,154

Type of sponsor:

Commercial	79.4%
Non-commercial	20.6%

Sites:

Single site	10,158
Multiple site	23,361

Countries

Multiple member state	21,753
Including third country sites	18,410

GCP Inspections

Notes: 52% of EU based trial applications also indicate involvement of sites in third countries;
Between Jan and Nov 2008 EudraCT recorded **576** paediatric trials in third countries

Source of data for pivotal clinical trials

Analyses of the information on pivotal clinical trials submitted to the Centralised Procedure in terms of the location of *Clinical Trials Sites* and *Numbers of Patients* from different countries and regions gave the results shown in the *Figures 1 and 2*.

Figure 1

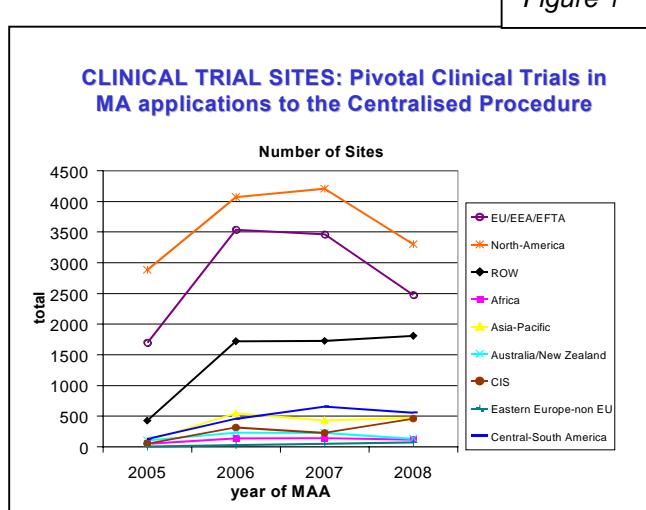
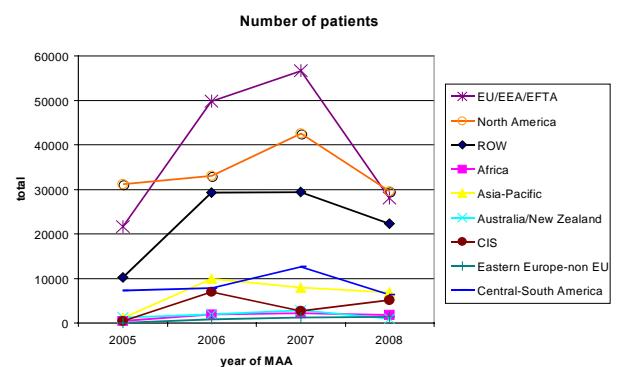


Figure 2

PATIENTS in Pivotal Clinical Trials in MA applications to the Centralised Procedure



Role of EMEA/CHMP

Although the authorisation of clinical trials is the responsibility of NCAs the EMEA, through the CHMP, has a central role in relation to:

- Verification of the need for GCP inspection, especially for vulnerable populations (e.g., children, psychiatric indications);
- Keeping a list of trials conducted in third countries;
- Making routine inspection proposals.

CHMP requested GCP inspections

The numbers of inspections requested for countries outside the EU are given in the following table:

Eastern-Europe-non EU:	2	Asia-Pacific:	16
Croatia	1	China	4
Serbia	1	India	7
CIS:	9	Malaysia	1
Russia	6	Philippines	2
Ukraine	3	Thailand	1
		Turkey	1
North America:	44	Africa	4
Canada	7	Ghana	1
USA	37	Morocco	1
		S. Africa	2
Central-South America	6		
Argentina	1	Colombia	1
Brazil	1	Mexico	1
Chile	1	Peru	1

Current developments

EMEA currently has a strategy paper under development on 'Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications.' This strategy paper has been translated into a detailed work plan for 2008-2010.

Action areas include:

Planning and development:

- Clarify the practical application of ethical standards for clinical trials;
- Consider the issues driving the recruitment of subjects in third countries;
- Review the actions available in response to non-compliance, and establish a policy;
- Ensure links, with other initiatives taken by the EU/Member States in this area, in consultation with the European Commission DG Enterprise and the Heads of Medicines Agencies.

Practical application

- Training and awareness of EMEA, experts and Marketing Authorisation Holders/sponsors;
- Application of the strategy in relation to submission, validation, assessment and inspection;
- Transparency, including improvement of EPAR content and consistency;
- Contribution to capacity-building with developing countries in cooperation with Member States and European Commission initiatives.

EU/EMEA International Cooperation

A cornerstone of international cooperation is the adoption of confidentiality agreements between the EU and USA Canada and Japan. There are also bilateral discussions between the European Commission and China, India and Russia and clinical trial information contacts have been established, for example in India. ICH is also a major factor in international cooperation.

The major objectives of the international policy include agreeing standards and requirements, helping each other, building expertise and systems, developing cooperation between the EU and WHO, reducing duplication of effort and filling the gaps in the Global Network.

In conclusion, it must be recognised that clinical development is 'going global' and there is a need for more regulatory cooperation among countries and regions. Harmonisation and work sharing are essential.

CLINICAL TRIALS IN THE USA

Improving the Efficiency and Maintaining the Quality of Clinical Trials

Dr Murray Lumpkin

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

Dr Murray Lumpkin chaired the second session of the Workshop, which looked at streamlining procedures for obtaining clinical trial approvals in different countries and best practices for the regulatory approval process for clinical trials.

Dr Lumpkin opened the session by providing an overview of the regulation of clinical trial applications by the U.S. Food and Drug Administration (FDA) and that Agency's interactions with companies during the clinical development of pharmaceutical products. He also discussed special perspectives and initiatives for ensuring timely access to new medicines and looked at the way in which foreign clinical data are handled during the review of marketing authorisation applications to the FDA.

The IND process

The regulatory vehicle under which all clinical trials are overseen in the USA is known as the 'IND' (Investigational New Drug) process. An IND application must be submitted before the first clinical study in undertaken the US.

The application includes all animal data, previous clinical data outside the USA (if any), a development plan, and the first protocol with special emphasis on any safety concerns and manufacturing process for clinical trials supplies. It must make the case for proceeding into humans at this point and why the plan for safety monitoring is adequate.

Ethics approval

The application must specify the name of the Institutional Review Board (IRB) (ethics committee) that will have oversight of the proposed trial(s) and it must include an undertaking that trials will not commence until IRB approval has been given. Reference to an IRB can take place *before, during or after* the FDA regulatory review of the IND application.

IND Procedure

After the initial protocol submission under an IND, the company must wait 30 calendar days. If nothing is heard from the FDA during this time, the trial can commence on day 31. There is no formal approval or authorising letter.

Any subsequent protocol submissions to conduct further clinical trials under the same IND are '**notifications**'. Once the notification has been submitted to the IND, the company does not need to wait in order to start the trial.

Screening INDs: An IND is generally substance-specific, but a 'Screening IND' is an exception. Companies apply for a screening IND at a very early ('Phase zero') stage when they have several similar substances and wish to carry out initial pharmacodynamic/kinetic studies in humans in order to identify the candidate drug that will go forward into clinical development. Screening INDs cannot be extended by notification and a full IND application is required for the selected drug.

FDA Review

Although the IND process is described as a 'notification' system this can give a misleading impression about the extent to which the data are reviewed by the FDA. An IND is given a full review within the initial 30-day period and the FDA can place any trial (or part of a trial) on **hold** at any time – either during the initial 30 days or subsequently. A 'Hold' means the trial may not proceed and, if started, that no further patients may be enrolled.

Box 1**Statistics on INDs**

- ~ 450 commercial INDs/year (*products headed for full development*)
- ~ 1500 single investigator INDs/year (*academic or practitioner studies usually on authorised products for off-label research purposes or individual patient treatment, in situations when other products may not be available*)
- ~ 12,000 currently active INDs
- ~ 5,000 FDA reviews/actions on INDs/year

The FDA will put a *Hold* on clinical trials if it finds that the application is not complete or if the FDA believes that:

- It is not reasonably safe to proceed;
- The company is not properly monitoring for potential safety problems;
- That the trial design puts patients at risk for no scientific purpose.

Rationale behind the IND Process

The driver for the FDA to invest resources in the IND process is primarily the promotion and protection of Public Health. Society needs independent oversight of clinical research to provide assurances that subjects are not put at unreasonable risk and not put into trials from which we cannot reasonably expect to learn something scientifically relevant.

The IND process, however, goes beyond this and most companies engage with the FDA during the development of new medicines to an extent that far exceeds the minimum legal requirements. This involves a large number of meetings and interactions between the FDA and companies in order to maximise the efficiency and scientific robustness of the drug development programme.

The target 'label' is the key

The legal and administrative system in the US provides laws and regulations, which are binding on both the company and the FDA, and 'advice' to companies that is given through Guidances, the website, Advisory Committees and direct contact with FDA (phone calls and meetings).

An essential feature of discussions with the FDA is that the company should, even before submitting an IND, have set out its objectives and aspirations in terms of target product labelling or an 'ideal' Summary of Product Characteristics (SPC).

Potential Pitfalls

Close cooperation between a government agency and independent industry is always open to potential criticism. The FDA, in its dealings with companies, must face three critical questions:

- How can the FDA be accessible to companies without being too close and 'cosy'; i.e., how can the FDA maintain its objectivity about the development programme during the review process if it is 'co-opted' in during the development process?
- Is the FDA acting as a taxpayer-funded drug development consulting firm?
- How can a balance be struck between the FDA obligations to review marketing authorisation applications and obligations to engage actively with companies during the development process?

Box 2**Meetings with the FDA: Facts and figures**

Over 2500 formal meetings are held with companies each year (most regarding development plans and issues).

Type A meetings are to discuss stalled development plans

Type B meetings are those to which the company is entitled by Regulation: Pre-IND, End of Phase 2, Pre-NDA

Type C meetings are all others

FDA Performance Goals are to respond to meeting request within 14 days and schedule the meeting within time limits:

Type A 30 days

Type B 60 days

Type C 75 days

The request for a meeting must be in writing (List of attendees, Objectives - desired outcomes, Agenda, Specific questions, etc.)

Official minutes, prepared by FDA, are sent to the company within 4 weeks and the company can suggest modifications

The number of meetings held between the FDA and the sponsor (Box 2) might give the impression that the agency has been co-opted into the development process. The FDA must, therefore, ensure that such involvement does not affect its ability to be objective in the regulatory oversight of the project and in the interpretation of the data submitted before review with the New Drug Application (NDA). The FDA believes it is in the best interest of public health to help assure that product development programmes are well designed and conducted and that they will answer important scientific questions. To enrol patients into development programs that will not provide valid scientific data is not good public health and is, arguably, exploitation of the patients. During the marketing authorisation application review process, the FDA is focused on the evaluation of the data, which are not known until the marketing authorisation application is submitted.

The extent to which the FDA is closely involved in the development of the product will depend upon the nature and degree of novelty of the medicine. If new products and treatments are being developed that are at the 'cutting edge' of science and therapy, appropriate testing standards are a public health concern that justifies the time and resources invested by the FDA. The balance between the time that assessors spend in engaging with companies during the product development phase and on the review of marketing authorisation applications is a management challenge. There is, however, general agreement that Pre-IND and end-of-Phase II meetings should be given priority.

Special Protocols

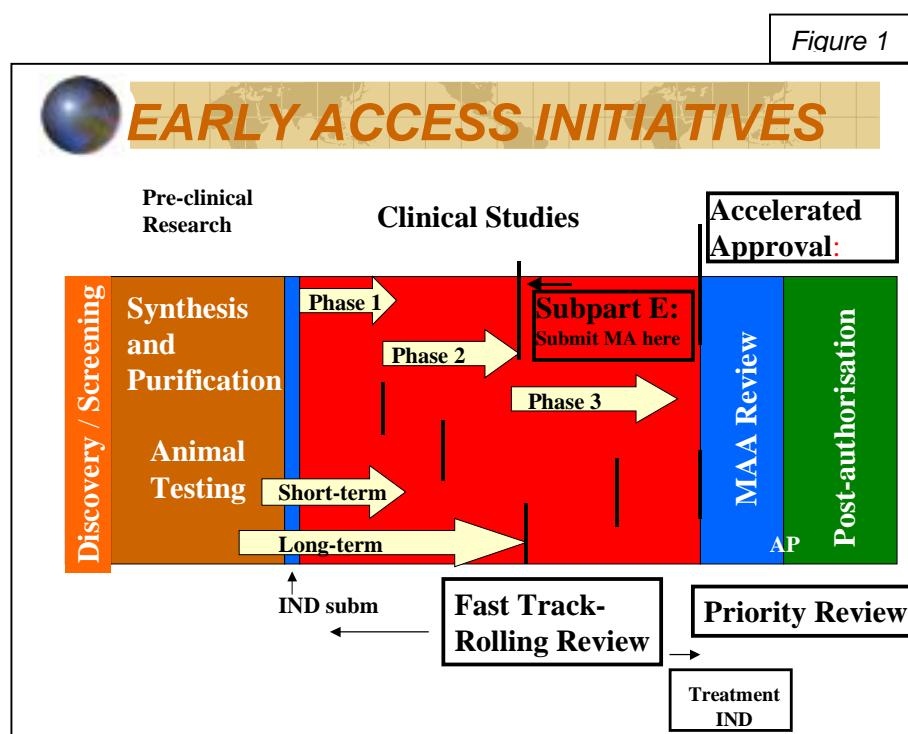
There are three areas where the sponsor can designate testing proposals as Special Protocols:

- Carcinogenicity tests;
- Stability testing protocol;
- Phase III trials to generate primary data for an efficacy and/or safety claim.

The written agreements on the design of these protocols, reached between the FDA and the company during the development stage, are binding on both parties at the NDA submission stage. Exceptions to the binding nature can, however, be made in cases where the science has changed between the product development and marketing authorisation application review stages.

Early Access Initiatives

There are certain initiatives that can be implemented during the INDs stage where early access to the product, on scientific and/or grounds of medical need, is in the interest of patients.



One of the most important is the *Fast Track* or *Rolling Review* (see Figure 1) that allows the marketing application to be submitted 'piecemeal' during the clinical development stage, as data become available, such that most of the data will have been seen by the FDA by the time the final piece of the marketing authorisation application is submitted.

Note: Differences between US and EU nomenclature of can cause confusion:

United States	European Union
Priority Review	Fast track
Accelerated Approval (Subpart H)	Conditional Approval
Subpart E	Approval under special circumstances
Fast Track	No equivalent

Special Initiatives

There are certain *Public Policy* solutions that are designed to improve access to new technologies when the market place itself does not create appropriate incentives. In the United States, these include specific legislative measures that create non-market incentives to encourage the development of *Orphan Drugs*, *Paediatric Medicines* and treatments for *Tropical Diseases*. The special status of research projects in these categories needs to be thoroughly discussed during the IND stage.

The *Critical Path Initiative* (which has similar objectives to the EU *Innovative Medicines Initiative*) has been adopted in order to seek new ways to encourage and develop 'tools' that will be publicly available and will help develop, in a more efficient and more resource-limited manner, the new technologies that are essential for the next-generation of innovative medicinal products.

Globalisation of Clinical Trials

Worldwide clinical development is a growing reality that has many positive aspects, but, like other results of globalisation, has some significant challenges.

From the company perspective the driver may be that *Time is Money* and that recruitment and enrolment of treatment-naïve patients may be quicker in some of the so-called *Emerging Economies* of Eastern Europe, Latin America, and Asia.

Nonetheless, the FDA is still receiving marketing authorisation applications where the majority of patients in the pivotal clinical trials come from non-emerging economies. The Code of Federal Regulation (312.120 and 314.106) has, however, for many years, defined the circumstances under which clinical data can be accepted from trials that are not conducted under a US FDA IND provided that the investigator qualifications are substantiated, the research facility is adequately described, and the study reports and records are accessible for FDA inspection, as they would be for domestic trials.

In addition, ethical standards must be in accordance with ICH GCP and the clinical experience in the trial must be applicable to the US population and US medical practice. (An example is that an application for a new antibiotic must reflect the patterns of microbial resistance in the United States).

Ethical challenges

The globalisation of clinical trials has led to certain important ethical questions being raised with regard to the acceptability of data from such trials. These include questions of exploitation and whether trials are conducted, as per the standard clinical trial social contract, with a view to providing ultimately improved medication for the community in which the trial is conducted. This raises the question of intentions to make the medicine available in the community in which the trial was conducted once trials are completed.

There are issues in defining the accepted 'standard of care' in countries where no alternative to the new therapy is available. This also raises questions about the acceptance of placebo trials or allowing a 'no treatment arm' because standard therapies are not on the local market. The fundamental question raised here is whether the ethical perspective used to judge the 'ethics' of trial conduct: is the local perspective or whether it is that of the country in which the data are being used to make a marketing decision.

Other factors that can have an impact on the acceptance of foreign clinical data include:

- Underlying illnesses that are prevalent in the local population;
- Concomitant therapies and medical culture;
- Cultural issues including diet, dietary supplements, and the use of herbal medicines.

In conclusion

The globalisation of clinical trials is a growing reality and brings with it many apparent benefits including the greater communication between regulatory agencies. It also brings significant challenges from a regulatory perspective. These require open and constructive discussions between regulatory authorities and sponsors as the product is being developed.

The world is getting 'flatter' and, as regulatory agencies become more knowledgeable about each others' systems and practices, they will be better able to make regulatory decisions for their own jurisdictions based on a global clinical trials database.

JAPAN'S ROLE IN GLOBAL DRUG DEVELOPMENT

Birgitta Hedin

Global Regulatory Lead & Asian Regulatory Strategy Director AstraZeneca K.K., Osaka

Birgitta Hedin gave an overview of the Clinical Trial application process in Japan, with a particular focus on the way in which the Government and Regulatory Agency are addressing the 'drug lag' issue in Japan. Although Ms Hedin spoke from an industry perspective, her presentation was based on extensive experience of the regulatory system in Japan and from working closely with both the Ministry of Health Labor and Welfare (MHLW) and the Pharmaceutical and Medical Devices Authority (PMDA).

CT authorisation in Japan

The legal procedure under the Pharmaceutical Affairs Law (PAL) for the conduct of clinical studies in Japan is a *Notification* process. A Clinical Trial Notification (CTN) is made to the PMDA and the study can start after a 30-day review by the Agency unless PMDA raises questions or requires further information.

A Notification and review is required for each clinical trial protocol but, once the initial CTN is approved (30 days), the Notification and review of subsequent protocols takes only two-weeks.

The CTN process applies to both Sponsor Initiated Studies (SIS) and Investigator Initiated Studies (IIS) and is required for both studies on patients and in volunteers. The exception is bioequivalence studies where a CTN is not required but Ethics Approval must be obtained for these types of study.

Although the data are thoroughly reviewed by the PMDA, no formal approval letter is issued at the end of the 30 days.

Data Requirements

The documentation to be attached to a CTN includes:

- **Justification** of the ethical and scientific basis for the study and the rationale for conducting it. The scientific data include up-to-date summaries of preclinical and clinical data;
- **Investigator's Brochure**: An up-to-date IB in Japanese;
- **CT Protocol**: A copy of the latest study protocol;
- **Reporting**: A sample of the case report form (CRF);
- **Patient Consent**: A copy of the Informed consent documentation;
- **Quality data**: Brief CMC information, except in the case of biologics when greater detail is required.

Where the clinical trial is part of a global clinical program, the Japanese IB must include a direct translation of the content of the Western IB, plus appendices. The appendices include summaries of ongoing Western and Japanese clinical studies. Information on formulations or non-clinical study results may be included.

Box 1

Categories of CTN in Japan

- Clinical Trial Plan Notification (initial CTN)
 - For NCEs
 - New administration (dose/formulation) of approved drugs
 - New combinations of approved drugs
- Notification of change to clinical plan
- Notification of discontinuation of study
- Notification of completion of study

The 'Drug Lag' Issue

The 'Drug Lag' or the delay in obtaining Marketing Authorisations for new medicines in Japan compared with the time at which they become available in other countries and regions (e.g., USA and EU) is a major cause for concern not only for the pharmaceutical industry but also for the authorities in Japan.

The stated role of the PMDA in drug development is to promote and protect public health by assuring that safe and effective drugs are available to the public through:

- Ensuring **fast access** to new drugs after thorough review to confirm safety and efficacy;
- Surveillance of drug safety through pharmacovigilance;
- Assurance of Good Manufacturing Practice to ensure product quality.

Industry viewpoint

The drug lag in Japan is also of major concern to the pharmaceutical industry, not least because in the ranking of global pharmaceutical markets by value, Japan (58US\$bn) is second only to the US (252US\$bn).²

The issues were discussed in a paper (No 31) published in 2006 by the Office of Pharmaceutical Industry Research of the Japanese industry association, JPMA. This paper noted that:

- The time needed for new drugs to be launched in multiple countries has been rapidly shortened in the past 20 years, and the access to new drugs has been improved considerably in many countries around the world.
- The time lag for Japan has also been shortened, but the speed of change is slower than for other countries. The relative order of drug launch in Japan has dropped, and Japan is recently being one of the countries where drugs are launched in the last place among 66 countries surveyed.
- A new drug is launched approximately 2.5 years later in Japan compared to the US
- Thirty percent of the world's top selling drugs are not yet launched in Japan. Japan is faced with the worrying situation from the standpoint of access to new drugs.

Government initiatives

The government has taken seriously its obligations to address the delay in access to new medicines in Japan. Internal the PMDA/MHLW initiatives include the recruitment of a large number of additional reviewers and revised working procedures in order to speed the assessment of new medicines. The drug lag, however, is also becoming one of the main drivers for Japan's participation in Global Clinical Trials.

The MHLW paper on Basic Principles of Global Clinical Trials (see *Box 1*) is an important publication which includes the following Key Messages:

- All nations and institutions participating must conduct trials under Good Clinical Practices (GCP) regulations as defined by the International Conference on Harmonisation (ICH).
- All participants must accept onsite GCP inspections by Japan's regulatory authorities.

Box 2

Drug lag in Japan

Ref: *Basic Principles on Global Clinical Trials*, published by MHLW, 28 September 2007:

Drug lag as defined as "*Circumstances where drug approved in EU and US are not approved in Japan and cannot be provided to nations*"

Drug lag in Japan is frequently mentioned as a major issue by the MHLW and PMDA, e.g., at the East Asian Pharmaceutical Regulatory Symposium (EAPRS) 2008 by: Dr Tatsuya Kondo, Dr Tatsuo Kurokawa and Dr Kazuhiko Mori and that the DIA Euro meeting 2008 by Dr Satoshi Toyoshima

² IMS Health Quarterly Data

- Japan should participate in global clinical trials from an early stage of drug development
- Priority status is given to sponsor's request for consultation on global clinical trials
- Important to take the ethnic factors into account
- Important for sponsors and PMDA to discuss the design and data handling
- The study design, protocols, and analytical methods must be acceptable to the PMDA.

The paper also includes an important Q&A section that poses 12 thought-provoking questions. These are shown in *Box 2* with highlights added to the questions that are of particular relevance from an industry viewpoint.

Regional Collaboration

The MHLW paper focuses on global cooperation but Japan is also active in encouraging Asian collaboration. In April 2008, Japan organised the East Asian Pharmaceutical Regulatory Symposium (EAPRS 2008) that brought together industry and regulatory agency participants from the region to discuss clinical trial and Asian development issues.

A Health Ministers' meeting was organised just prior to EAPRS 2008 at which the following actions were agreed and subsequently initiated:

- A Joint study to clarify the impact of ethnic factors on clinical data among East Asia populations
- Annual Pharmaceutical Directors' meetings with representatives from China, Korea and Japan with the aim to exchange information

Impact of Initiatives

The promotion of Japanese participation in global clinical trials is having an effect. The proportion of global clinical trial consultations is increasing³:

2004	6%
2005	8%
2006	14%
2007	23%

Box 3

12 Questions from the Q&A section of the MHLW paper on Global Clinical Trials

1. What are the basic requirements to conduct a global clinical trial?
2. What is an appropriate timing for Japan to participate in global drug development?
3. Is it mandatory to have Phase I trial data or PK information in Japanese population prior to conduct of a global clinical trial for patients?
4. Is a development program acceptable in which Japanese subjects are included only from a confirmatory phase III trial using a dose determined based on results from non-Japanese clinical trials, without conducting any dose –finding study in Japan?
5. What are the basic points to consider in designing a global clinical trial?
6. When conducting an exploratory trial like a dose-finding study or a confirmatory trial as a global clinical trial, how is it appropriate to determine a sample size and a proportion of Japanese subjects?
7. There may be cases where a global trial has to use an evaluation index which has been established overseas but not in Japan. In such a case, can the index be also acceptable in Japan?
8. If a global trial has been performed outside Japan and the identical protocol is used for a smaller clinical study separately performed in Japan, can it be justified to conclude that the efficacy and safety are the same in both Japan and outside Japan based on the results of these studies?
9. Regarding control groups in a Phase III confirmatory global trial
Are placebo controlled studies accepted? What if the control drug is not approved in Japan?
10. In a global trial, it is difficult to define the use of concomitant medications or therapies in a completely identical manner between Japan and other countries. How can these be appropriately defined?

³ Data on CT Notifications is taken from the presentation by Dr Kazuhiko Mori at EAPRS 2008
Section 3, page 27

In 2007 there was a total of 508 CT notifications. Eighteen companies applied to conduct 38 multi-national clinical trials (MNCTs) of which 5 were Japan-based companies (8 protocols) and 13 were Global Pharma (30 protocols).

Most of the MNCTs were Phase III studies and the leading therapeutic area was oncology followed by cardiovascular, CNS, and respiratory indications.

In Conclusion

The CTN process in Japan is very similar to Western CT application with the main difference being that very little CMC information is required. As in the case of the US IND process, no approval issued.

Drug lag is a recognised issue in Japan and MHLW/PMDA is taking this issue seriously and promoting Japan's involvement in Global Development from an early stage.

Asian collaboration is being actively encouraged by MHLW and PMDA.

Japan's involvement in global clinical trials is increasing and the number of consultations on Global Clinical Development Programmes is rising.

Marketing approvals: There are a number of J-NDAs approved based on Global Clinical Trial data.

There are challenges, but sponsors and authorities are looking forward to a good cooperation leading to earlier access for Japanese patients to innovative medicines.

REGULATION OF CLINICAL TRIALS IN AUSTRALIA

Dr Leonie Hunt

Assistant Secretary, *Office of Prescription Medicines (OPM), TGA, Australia*

National Medicines Policy

As background to the discussion of clinical trials in Australia, Dr Leonie Hunt explained the role of the Therapeutic Goods Administration (TGA) within Australia's National Medicines Policy. TGA is part of an infrastructure that is designed to provide the medicines that the Australian population needs.

The components of the National Medicines Policy are:

- **Quality, safety and efficacy:** Covered by TGA
- **Equity of access to medicines,** which is the role of the Pharmaceutical Benefits Scheme
- **A viable industry,** which is being supported by government through the Department of Industry, Science and Resources (DISR) with campaigns to encourage pharmaceutical industry R&D and clinical development in Australia
- **Quality of use of medicines:** Pharmaceutical education programmes to ensure that medicines are being used correctly

There is also the National Health and Medical Research Council (NHMRC) which is responsible for setting standards for research as well as allocating government funds for research projects.

The role of TGA

The role of TGA is similar to that of the majority of regulatory authorities in that it:

- Sets quality standards;
- Maintains a register of Therapeutic Goods (authorised products) which are evaluated on the basis of quality, safety and efficacy;
- Audits and licences manufacturers for products for both domestic use and export;
- Tests samples from complaints and random sampling programmes;
- Conducts a voluntary adverse drug reaction (ADR) and device Incident reporting scheme;
- Monitors and regulates advertising and claims;
- Controls access to medicines and devices that are unregistered (unapproved).

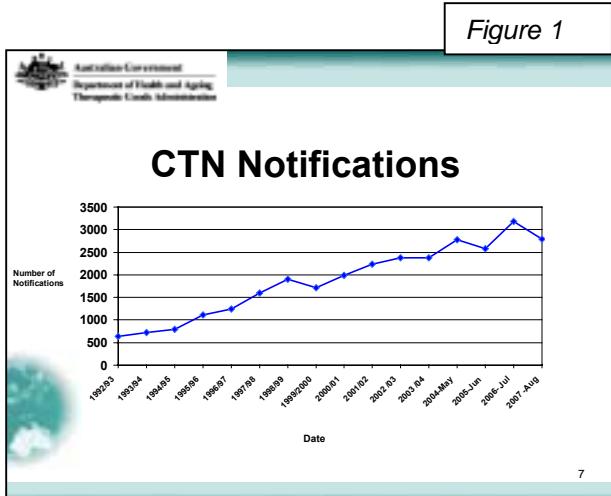
Unapproved medicines

Unapproved medicines are not only new medicines at the clinical trial stage but also medicines that are being used outside their authorised use (e.g., indications and/or dosage). There are Special Access Schemes to allow unapproved medicines to be provided for use by individuals as well as for specialist prescribers. This is in addition to the two types of clinical trial programmes that TGA administers.

Clinical Trials in Australia

Two clinical trial systems are operated by TGA: the **Clinical Trial Notification** scheme (CTN) and the **Clinical Trial Exemption** scheme (CTX). A large majority of trials are carried out under the CTN scheme, which is available for low-risk trials such as the majority of Phase III studies and bioequivalence studies. The CTX scheme applies to higher risk studies involving, for example high-tech biotechnology, gene therapy or cell therapy medicines. Such trials are often carried out by academia. Early Phase and other high-risk trials are rarely carried out by industry, in Australia but would need to be approved under the CTX Scheme.

Figure 1



The cumulative number of CT Notifications made to TGA, since 1992 (measured mid-year to mid-year) is shown in Figure 1. The figure has risen steadily and equates to about 6-700 clinical trials annually, for a population of about 22 million.

By contrast, the numbers of CTX trials is low with not more than six applications being received annually.

CTN

The notification scheme is a simple regulatory notification based on the prior approval by a responsible Institutional Ethics Committee.

The scheme allows medicines to be supplied for purposes of clinical trials provided certain conditions are met. These include compliance with Guidelines for Good Clinical Practice (published by ICH and CHMP) and compliance with the ethical standards set out in the *National Statement on Ethical Conduct in Research Involving Humans*, (equivalent of the Declaration of Helsinki) published by the NHMRC.

The CTN depends upon clearance by Ethics Committees that report to the NHMRC, which has, as one of its principle sub-committees, the Australian Health Ethics Committee (AHEC). Ethics Committees also have access to the general and specific scientific expertise that they need to evaluate CT proposals. A Notification is only accepted with the signature of the Chair of a Committee operating under the AHEC rules and it also requires certification by the Principle Investigator, the head of the Institute at which the trial will take place, and the sponsor company. The certifiers all have to make certain commitments including access, agreement to report and answer any TGA queries and compliance with GCP.

After these agreements are obtained the CTN comes to TGA who routinely speaks to the sponsors and can, at any time, seek further information or conduct an audit.

A notification can cease instantly, in the words of the legislation, '*if, at any time the regulator becomes aware that it would not be in the public interest for the trial to proceed*'.

CTX

In contrast to the Notification Scheme, the Exemption (CTX) Scheme is one where TGA examines and reviews data and gives a specific approval or refusal to the proposal for a clinical trial. As noted, these are trials on relatively high-risk products that are often at the cutting edge of technological development. Not only does TGA review data but there will often be an intensive round of meetings to discuss the project in advance of the CTX being submitted.

TGA has a dedicated Clinical Trial Unit that deals with the administrative and professional oversight of clinical trial applications. In the case of CTX applications the review will also involve scientists and specialists from other TGA units that assess clinical, preclinical and quality data. The necessary expertise is called in, as appropriate, to evaluate CTX data and discuss issues with companies.

Scientific Advice

TGA will, on request from the sponsor, hold pre-submission meetings to discuss clinical trials and advise whether the Notification or Exemption Scheme is appropriate. Whilst the primary motivation is protection of public health, this is also in the interests of promoting good pharmaceutical research. It is better to identify early, rather than at the end of the day, a problem that arises from a lack of appropriate science or a safety issue.

Conclusion

The Notification system has been in place since 1991 and has worked well without any major problems. It illustrates the need for *all* involved parties: Researchers, Companies, Ethics Committees, the Clinical Trial Sites, and the Regulator, to take responsibility for ensuring that the regulatory system works when clinical trials are undertaken.

The CTN scheme has been very successful for Australia in ensuring that patients have early access to new therapies and that trials are conducted within closely defined Ethical and GCP guidelines.

The government is promoting and sponsoring schemes to foster research in Australia in the belief that the country provides a strong infrastructure for clinical research. All parties work together with the objective of supporting the integrity of the science while protecting the patient.

Section 3: Chapter 4

REGULATION OF CLINICAL TRIALS IN EMERGING ECONOMY COUNTRIES



Comparative demographic data*

China

Population: ~ 1,330 million
Area: 9,596,960 sq km
GDP: ~ 4.222 trillion US\$
GDP growth rate: ~ 9.8%
GDP per capita: ~ 6,100 US\$
Life expectancy: 73.18 years
Median age: years



Republic of Korea (South Korea)

Population: ~ 48 million
Area: 98,480 sq km
GDP: ~ 953 billion US\$
GDP growth rate: ~ 4.3%
GDP per capita: ~ 27,100 US\$
Life expectancy: 78.64 years
Median age: years



Singapore

Population: ~ 4.6 million
Area: 692.7 sq km
GDP: ~ 192 billion US\$
GDP growth rate: ~ 3%
GDP per capita: ~ 52,900 US\$
Life expectancy: 81.89 years
Median age: years



Indonesia

Population: ~ 238 million
Area: 1,919,440 sq km
GDP: ~ 496 billion US\$
GDP growth rate: ~ 5.9%
GDP per capita: ~ 3,900 US\$
Life expectancy: 70.46 years
Median age: years



Malaysia

Population: ~ 25 million
Area: 329,750 sq km
GDP: ~ 214 billion US\$
GDP growth rate: ~ 5.5%
GDP per capita: ~ 15,700 US\$
Life expectancy: 73.03 years
Median age: years



Chinese Taipei (Taiwan)

Population: ~ 23 million
Area: 35,980 sq km
GDP: ~ 393 billion US\$
GDP growth rate: ~ 1.7%
GDP per capita: ~ 33,000 US\$
Life expectancy: 77.76 years
Median age: 36 years

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SFDA, China

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Bureau of Pharmaceutical
Affairs, BPA, Chinese Taipei

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* Data, from the CIA World Factbook, is for comparative purposes only. Information is predominantly based on 2008 figures and actual values (e.g., US\$ equivalents) may be affected by exchange rates.

GLOBAL DRUG DEVELOPMENT AND CHINA: A Regulatory Perspective

Dr Yi FENG
Director of Office of Drug Review Management, Center for Drug Evaluation, SFDA

Dr Yi Feng discussed the changes that are taking place within the State Food and Drug Administration (SFDA) with the growing trend towards the inclusion of China in Global Clinical Trials.

The changing market

In a recent study carried out by the CMR International Institute,¹ major pharmaceutical companies were asked to estimate the proportion of clinical trials currently conducted in different countries and regions and to predict the situation in 2012. The results indicated that trials in Latin America and Asia each currently account for 7% of total global clinical trials and that the companies' estimates for 2012 predicted a 100% increase for the Asia region, i.e. 14% of the global total.

An increasing number of international companies are building R&D capacities in China and the major companies that are established in China and becoming involved in global clinical development are given in *Box 1*.

The pharmaceutical market size in China is growing rapidly and a comparison of the size and growth rate is given in *Table 1*.

Box 1

Companies building R&D capacities in China

AstraZeneca	Novartis
GlaxoSmithKline	Otsuka
Lilly	Pfizer
Merck	Roche
Novo Nordisk	Wyeth
Mitsubishi Tanabe Pharma	

Table 1: Pharmaceutical market size: China vs. Global

	2004	2005	2006	2007
CHINA				
Total Sales (Billion)	\$9.5	\$11.7	\$13.4	\$16.8
Growth Rate (%)	28%	20%	12%	26%
GLOBAL				
Total Sales (Billion)	\$550	\$602	\$643	\$712
Growth Rate (%)	7%	7%	7%	6%

Source: IM S. Health

Global drug development

The trend towards global drug development was discussed at the 2008 symposium of the APEC Network on Pharmaceutical Regulatory Science where the following definition was given by PhRMA, (the US Association representing the research-based pharmaceutical industry) for their 'ideal' perception of *simultaneous global development*:

"Simultaneous Global Development (SGD) is the ability to study patients in all regions at the same time under the same protocol resulting in a single database for analysis and review by the relevant regulatory authorities at the same time. (SGD does not mean that separate clinical trials are conducted in a given market at the same time as the global studies nor that all portions of clinical development will contain subjects from each market)".

Discussions about the incorporation of China into Global Clinical Development was continued when a delegation from PhRMA visited China in October 2008 and held meetings with CDE, SFDA and the Ministry of Health. The companies set out a list of their main concerns about China's ability to participate in Global Development. These were:

- The lengthy clinical trial application review times;
- Inability for China to participate in early drug development;
- A lack of adequate communication mechanisms with the agency prior to submission;
- CMC requirements that are inconsistent with the drug development stage;

¹ CMR International Institute study under the Emerging Markets Project, 2008, see Section 3, page 5
Section 3, page 34

- A lack of focus and relevance of the questions from the reviewers to the sponsor. **The Regulatory Review of CT Applications in China**

There has been a significant increase in the number of CT applications made and approved in China between 2002 and 2007 (*Table 2*):

Table 2: Multinational clinical trial approvals in China 2002 to 2007		
Year	Number of applications	Number of approvals
2002	3	
2003	10	
2004	13	3
2005	72	31
2006	74	61
2007	70	53

The upward trend is continuing and 100 applications were approved in 2008.

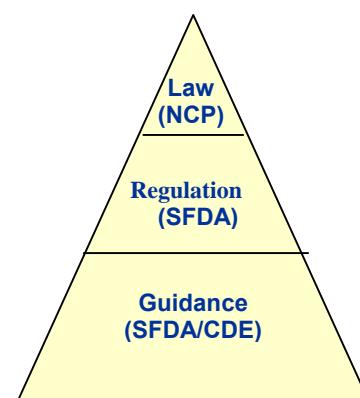
The distribution between different **Phases** for multinational clinical trials is Phase II: 13% and Phase III: 87%.

An analysis of **review times** shows that 59% of applications take 4-7 months, 33% take longer than seven months but 8% are approved within less than 4 months.

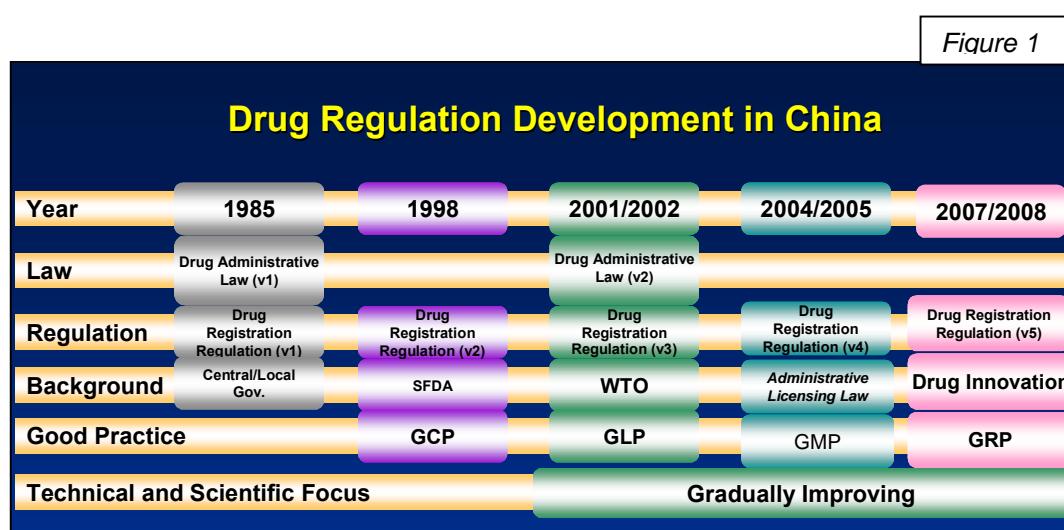
Implementation of legislation

China has a system of Drug Law, Regulation and Guidance that is similar in its structure to that of the more mature markets and can be represented by the triangle show opposite.

The regulation of medicines has different requirements for products that are manufactured within China and those that are imported. Although the Drug Law was first established in 1985, the chapter on Multi-Centre Global Clinical Trials was only added to the Regulations after 2002.



The development of drug regulation in China since the Drug Administrative Law was first implemented in 1985, is shown in the *Figure 1*. As shown, the SFDA was set up in 1998, under Version 2 of the Drug Registration Regulation and the update to Version 3 (2001/2002) included the adoption of Intellectual Property protection for pharmaceuticals in accordance with WTO.



Drug Registration Regulation Version 5

There were important changes to the Regulations when Version 5 was introduced in October 2007. The key guiding principles behind these changes were:

- To promote **drug innovation**;
- To focus on **unmet medical needs**;
- To build a transparent and consistent, **high quality** system.

The main process improvements related to Global Drug Development that were introduced at this time were:

- Plans for a special review procedure;
- A 25% reduction in the CSA review time for new drugs;
- Agreement that the ICH-CTD format is acceptable for applications made in China;
- Simplified sample testing requirements.

CT Application approval process

There are five SFDA units that have a primary role in the review and approval of Clinical Trial Applications (Figure 2).

The scientific review is carried out by the Center for Drug Evaluation (CDE).

The review of CT applications is, however, only one component of CDE's workload as the Center also deals with New Drug Applications from domestic manufacturers, generic products, OTC medicines and imported products. In addition there are Post-Marketing Applications for variations and changes to authorised products as well as applications for the Renewal of Authorisations for both domestic and overseas products.

The review of CT applications carried out by CDE is clinically led and safety focused. The safety review is carried out by reviewers who examine the clinical protocol, pre-clinical safety data and quality (CMC).

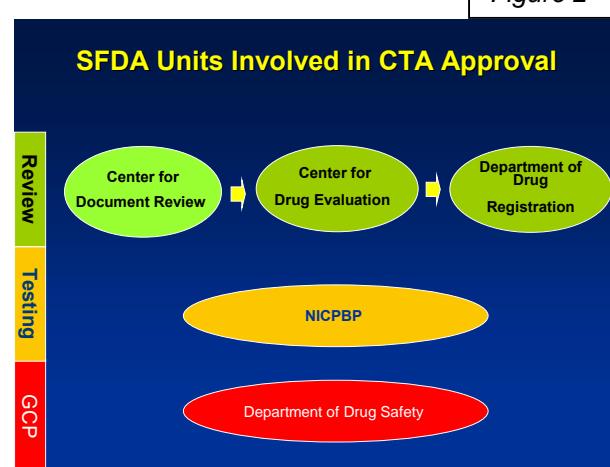
The Review Model

Clinical trial approval has two components: Clearance by the Regulatory Authority and clearance by an appropriate Ethics Committee and in different countries, applications for regulatory and ethical clearance are either made in parallel or sequentially. The process in China is sequential but, unlike most of the other sequential models studied by the CMR International Institute, an application for Ethics Clearance in China is made *after*, rather than before the Regulatory Review Process. In other respects, however, the review model in China is similar to that found elsewhere with the main stages being validation, scientific assessment and a request to the sponsor for any further information that is required before the final evaluation and decision is made.

New proposals

As noted, the 2007/2008 revisions to the Drug Law included a special focus on innovative drug development and this includes special review procedures for CT applications. This is the first time that procedures for innovative medicines have been set up in China and they will apply to both domestic and overseas applications for clinical trials on pharmaceutical and biological products that have never been marketed in any country.

Figure 2



Special features of the proposals include:

- A review time reduction (80 days);
- Sponsor initiated consultation meetings;
- Allowing amendments to be made, in some cases, during the review. **Reducing Review Times.**

Whilst recognising that the review timeline in China is a cause for concern, Dr Feng emphasised that a reduction of approval time is the joint responsibility of both the agency and the industry.

The timeliness of the review would benefit from improvements, on both sides, to:

- Quality (of the submission and of the review);
- Technical competency of local company and Agency staff; and
- Communication skills.

Even with revised targets for the technical and administrative review of CT applications it must be remembered that once questions are asked the review clock stops. The overall review time therefore depends not only on the speed and efficiency of the regulatory review, but also on the speed and efficiency of the company response when asked for further information.



HOW KOREA IS ENCOURAGING MULTI-NATIONAL CLINICAL TRIALS

Professor Sang Goo Shin

President, KoNECT, Korea National Enterprise for Clinical Trials, South Korea

Professor Sang Goo Shin gave a brief history of the way in which the regulation of clinical trials in South Korea has developed from the 1990s to the present and, the role of the Korea National Enterprise for Clinical Trials (KoNECT) in national initiatives to encourage Korea's participation in multi-national clinical trials (MNCTs). Professor Shin also informed the Workshop of impending regulatory changes to streamline the approval of MNCTs.

Regulatory history

The regulation of clinical trials for domestically developed or foreign medicinal products started in 1993 with the review of clinical trial protocols by the Ministry of Health and Welfare (MOHW). At this time, the major university hospitals established institutional review boards (IRBs).

Other milestones in the 1990s were the introduction in 1995, of **Korean Good Clinical Practice** (KGCP) and the establishment, in 1998, of the **Korean Food and Drug Administration** (KFDA).

During 1998-2000 there were extensive discussions among the Agency, industry and academia on regulatory evolution leading to:

- **2000:** Revision of KGCP in line with ICH GCP and clarification of the role of the IRBs;
- **2001:** Adoption of the bridging concept in line with the ICH E5 Guideline;
- **2002:** Separation of CT regulation (IND) from the new drug application (NDA) process.

The separation of IND/NDA regulations permitted Korean institutions and researchers to participate in Multinational Global Studies during new drug development and global pharmaceutical companies, through their local subsidiaries could include Korea in global development strategies.

This was reflected in an increase in the number of clinical trial applications (see *Figure 1*) which, in 2007, reached 134 for domestic or bridging studies and 148 for global trials.

Figure 1

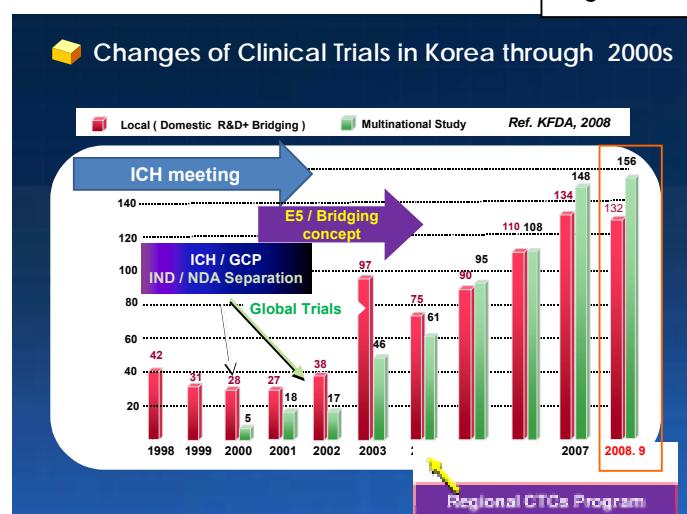
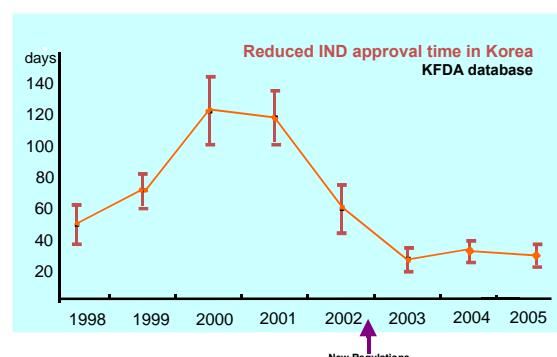


Figure 2

Changes of CTA timeline



The CT Application Review Process

The KFDA regulatory review is carried out in parallel with the IRB process. Facilities are offered for a pre-IND consultation with companies and the CT application data consists of the Trial Protocol, CMC and Pre-clinical data and Investigator's Brochure.

Approval from both KFDA and the IRB is required before finalising the contract with the hospitals and starting the trial.

The regulatory review time for CT applications was reduced to a target of **30 days** from 2003 and this has been reflected in actual review times achieved from submission to approval, as shown in *Figure 2*.

National Technology Roadmap

In 2002, The Korea Ministry of Science and Technology, and MOHW initiated the *National Technology Roadmap Project* which included a long-range strategy for building national capacity.

The importance of improved clinical trial technology in the development of new drugs and biologicals was highlighted and the experts recommended:

- The establishment of Clinical Centres of Excellence (CTCs);
- Training programmes for CT professionals;
- International Accreditation of IRBs; Early regulatory harmonisation with ICH guidelines.

Strengthening the IRBs

In 2002, the **Korean Association of IRBs** (KAIRB) was formed and now has more than 50 University Hospitals in membership. The Association has published general guidelines for the establishment and operation of IRBs and holds an annual Workshop to provide updated education for IRB members.

In 2007, MOHW endorsed the educational activities of KIRB and has provided funds to support short-term fellowship training for IRB members at the Western IRB, Seattle, USA.

Six of the major University Hospitals have attained IRB accreditation from SIDCER/FERCAP² and one from the Association for the Accreditation of Human Research Protection Program (AAHARP).

Support for Regional Clinical Trial Centers

A major initiative to come out of the *National Roadmap Report* has been government support and major funding for Regional Clinical Trial Centers. Twelve Centres have been established and the programme goal is to set up 15 internationally competitive clinical trial centres by 2009.

In January 2008, *Nature Review* published data on 'Country trends in participation in global multinational clinical trials, in which South Korea ranked 25th among the major international players.

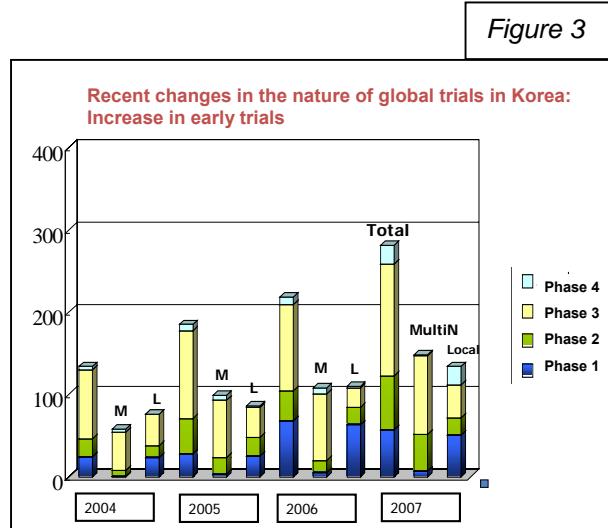
Changing trends in CTs in Korea

Not only has there been a dramatic increase in the number of clinical trials undertaken in Korea, but also the nature of those trials has changed. In the early 2000s, trials were limited to Phase III studies but, in recent years, there has been a marked increased participation in Phase II and also in Phase I studies (Figure 3)

The role of KoNECT

KoNECT, the Korea National Enterprise for Clinical Trials is a non-governmental organisation for the promotion of clinical development that is endorsed by MOHW.

Figure 3



² The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) is a TDR/WHO founded initiative undertaken in partnership with regional fora and health research organisations focused on developing global capacity in ethical review and Good Research Practices. FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region) is one the regional fora of SIDCER.

KoNECT was established in 2007 and integrates three key areas:

- **Regional Trials Centers:** By 2008, 12 regional CT Centres had been set up and the goal for the CTC network, in 2009, is 15 Centres
- **Human Resources Training Academy:** 19 education programmes provide training for CT professionals, including Clinical Investigators, Clinical Pharmacologists, Biostatisticians, CT Pharmacists, Clinical Research Associates and Clinical Research Coordinators.
- **New Technology:** 16 Research Units for new technology developments known as 'Critical Path Technology' and including IT, biomarkers, PK/PD modelling and simulation.

Current and Future Regulatory Changes

During 2008, KFDA has been given the authority to recruit 6 medical reviewers to strengthen the IND review capability. Other changes have included amendments to the Quality assurance requirements in IND dossiers with the inclusion of documentation on the manufacturing site for CT materials, including GMP Certification.

Clinical Trial Notification (CTN)

The most important development in 2009, however, will be the adoption of draft legislation for a formal **30-day Approval Clock** for IND submissions and a partial **Clinical Trial Notification Scheme**.

Under the 30-day Approval Clock:

- The sponsor submits an IND application in accordance with discussions at a pre-IND consultation;
- The KFDA reviews the application within **30 days**;
- If no objections are raised within the 30 day time limit, the trial may commence.

Eligibility for a CTN

The Notification procedure, after IRB approval will be available for:

- **Phase III trials** that have been evaluated and approved by an ICH member (EU, the United States, Japan), that is, trials that are part of a Multinational Development Programme;
- **Phase I Bioequivalence studies** for Pharmaceutical alternatives;
- **Investigator-Sponsored trials** on marketed anticancer products (except biological products)
- **Protocol amendments**, which do not involve a new CT protocol.

THE CLINICAL DEVELOPMENT ENVIRONMENT IN SINGAPORE

Yang-Tong Foo

Deputy Director, Clinical Trials Branch, Health Sciences Authority, Singapore

Yang-Tong Foo presented an overview of the Health Sciences Authority (HSA) and discussed the ways in which the Biomedical Sciences Initiatives are enabling Singapore to be a leader in supporting advanced biomedical research, clinical development and scientific innovation in the Asia-Pacific region.

Health Sciences Authority

HSA is a Statutory Board of the Ministry of Health. It is under the direction of the HSA Board and CEO (Dr John Lim). The vision of HSA is to be the leading innovative authority protecting and advancing national health and safety. There are three professional groups:

Health Products Regulation Group

The Group ensures that drugs, innovative therapeutics, medical devices and health-related products in Singapore are wisely regulated to meet appropriate standards of safety, quality and efficacy. It includes the Therapeutic Products Division, which is responsible for the authorisation of products for marketing and for clinical trials. The Group also includes the Complementary Health Products Division, Manufacturing & Quality Audit Division, Pharmacovigilance & Compliance Division, and the Enforcement Division.

Blood Services Group

This serves as the nation's transfusion medicines resources, securing the nation's blood supply to ensure safe and adequate supply of blood and blood products.

Applied Sciences Group

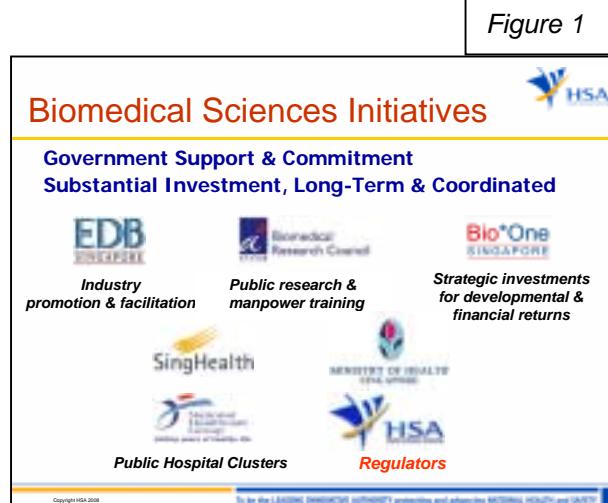
The Group applies forensic medical, scientific, investigative and analytical expertise to serve the administration of justice and to safeguard public health. Divisions include forensic medicine and forensic science, illicit drugs and toxicology, and food safety.

Biomedical Sciences Initiatives

The Biomedical Sciences (BMS) Initiative was launched in 2000 to develop the core infrastructure and scientific capabilities for basic biomedical research. Over the years Singapore has invested heavily in this initiative.

Spearheading the BMS Initiatives are three groups: the Economic Development Board (**EDB**) that oversees industry promotion and facilitation; the Biomedical Research Council of the Agency for Science, Technology and Research (**A*STAR**), which oversees and coordinates public sector biomedical research and development activities; and **Bio*One** which is the investment arm of EDB.

Figure 1



Working closely with these three groups (Figure 1) are government departments, the Regulatory Agency and public hospitals.

The Biopolis

The centre for biomedical sciences R&D, 'The Biopolis', in Singapore, has been developed as a hub for biomedical research and houses seven public research and technology institutes and provides facilities for private companies within the same complex. Close to the Centre are the public sector hospitals.

Box 1

Biomedical Sciences Initiatives

- One of the key strategic initiatives in Singapore's drive towards a knowledge-based, innovation-driven economy
- Strengthening basic research capabilities to support clinical research with necessary capabilities, talent and infrastructure
- Emphasis on Early Phase and 'Proof of Concept' studies - key in enabling MNCs to set up dedicated Phase I centres to promote global drug development
- MNCs partnership with Singapore Institutions in joint pre-clinical and clinical development in oncology

Developing 'human capital' in R&D has attracted world-renowned scientists to Singapore, bringing expertise and leadership to help overcome capability gaps. At the same time Singapore is investing in its own talent and sponsoring bright, young Singaporeans to gain higher qualifications from local and overseas research institutions.

Phase 2 of the BMS Initiative launched in 2006 focuses on strengthening Singapore's capability and capacity for translational and clinical research including developing research programmes in strategic areas of:

- Cancer;
- Neurosciences;
- Cardiovascular/Metabolic disorders;
- Infectious diseases;
- Eye diseases.

Clinical Trials Regulatory Framework

Under the CT application process in Singapore, parallel submissions can be made for Regulatory Authorisation by HSA and Ethical Clearance by the IRBs.

Electronic submission of CT applications can be made to HSA and there is a target review timeline of **4-6 weeks**. Regulatory approval is in the form of a Clinical Trial Certificate (CTC) which is specific for the protocol, principal investigator (PI) and site.

There has been a considerable rise in the number of clinical trial applications in recent years (see *Figure 2*). The increase is particularly noticeable in relation to Phase I trials (see *Figure 3*) which are facilitated by the BMS initiative.

Figure 2

No. of CT Applications & CTCs issued

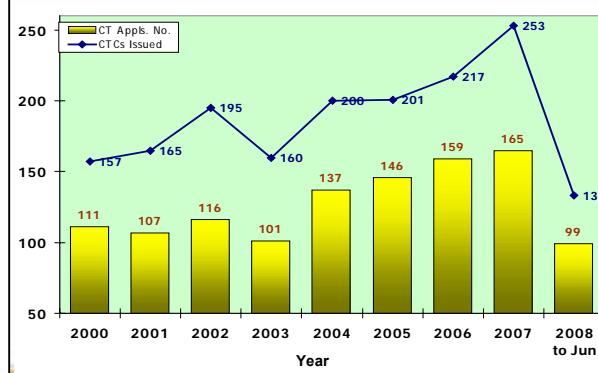
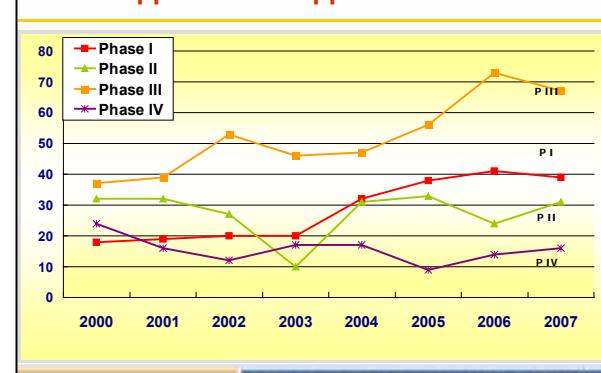


Figure 3

No. of Approved CT Applications



Clinical Trial Trends

CT statistics show that:

- **70-80%** of applications are for commercial studies, multinational or global trials sponsored by pharmaceutical companies or CROs;
- **50-60%** of Multinational or Global Trials (Phase II-III) are used to support NDAs to major regulatory agencies;
- **30-35%** of studies (see *Box 2*) are for Oncology research, especially in molecular targeted therapies. This reflects advances in genomics and support from the cancer research centres as well as collaboration with the US National Cancer Institute;
- **20-25%** are in the growing area of Phase I Clinical Pharmacology studies:

The BMS Programme has been key in establishing Phase 1 units in Singapore and there are four such facilities (two run by companies) that provide a full spectrum of scientific and technological expertise for early phase drug development.

Regulatory Perspective and Practices

HSA is a relatively small agency but is committed to be an enabling regulator. It applies innovative approaches in carrying out these duties enabling timely access of innovative new drugs to patients in a safe and conducive research environment facilitating global drug development in the country

Components of the Agency's regulatory strategy include:

- **Technical Standards:** Compliance to International Regulatory Standards, particularly the ICH Guidelines;
- **IPR:** A rigorous intellectual property framework that was enhanced by 2004 amendments to the Drug Law;
- **GCP:** Active promotion of Good Clinical Practice to meet international (ICH) requirements;
- **New technologies:** Continually enhanced capabilities to manage emerging technologies and therapies;
- **Dialogue with sponsors:** Providing opportunities for regulatory meetings with companies and encouraging early consultation for planned applications on novel compounds;
- **Expert Advice:** Access to scientific experts not only on HSA's advisory committees but also external scientists and clinicians when particular issues arise.

The agency operates a system of ***Applications Triaging*** at the initial validation stage using a risk-based classification system depending on the novelty of the drug's mode of action and available clinical experience.

The Agency response to the increasing numbers of CT applications has been to assign additional resources with staff increases, in 2007-8, and attention to training and knowledge management in order to keep abreast of scientific advances.

Box 2

CT Therapeutic Areas (2007)

Oncology	34%
Clinical pharmacology	18%
Cardiology	11%
Neurology	9%
Gastroenterology	5%
Urology	5%
Infectious diseases	3%
Immunology	3%
Endocrinology	3%
Others	9%

N=153 clinical trials approved

CLINICAL TRIALS IN INDONESIA: An Overview

Lucky S. Slamet

National Agency of Drug and Food Control (NADFC), Indonesia

Demographics

Indonesia is the largest archipelago in the world, stretching for more than 5,000 kms across the equator, with an estimated 17,508 islands, about 6,000 of which are inhabited. The estimated population is approximately 238 million with an annual population growth rate of 1.4%. The GDP is US\$ 935 billion and the GDP per capita is US\$ 3,800. The total pharmaceutical market value is about US\$ 2.6 billion.

The healthcare infrastructure includes 85 Health Research Institutes and provides >1215 Hospitals (0.6 bed/1000 population) with a Health Research Budget of US\$ 5 million.

The regulatory framework

The conduct of clinical trials on substances not yet registered in Indonesia involves the regulatory agency, NADFC, in interactions with many parties: the sponsor/CRO; the investigators; the clinical testing site or laboratory; the Ethics Committees (IEC) and the Scientific Committee (SC).

The main objective of the Regulatory Framework for clinical trials is to ensure that trials are carried out in accordance with GCP in order to enable the sound assessment of Benefit and Risk. In pursuing this objective the agency seeks to:

- Protect CT subjects, particularly in relation to safety issues;
- Safeguard the merits of scientific research;
- Ensure consistency in the CT application assessment;
- Maintain the credibility of data from the trials for subsequent regulatory submission;
- Engender sponsor, stakeholder and public trust.

The regulatory basis for the Framework is set out in Laws and Decrees has shown in *Box 1* but the pivotal document is the Indonesian **Guideline on GCP**. This covers:

- **The type** of clinical trial (Art. 2)
- **Institutions** which may conduct trials (Art. 4)
- **Applications** for the conduct of CT (Art. 7-9)
- **CT Authorisation:** Regulatory approval for the conduct of a CT (Art. 11-12)
- **Reporting** and reports (Art. 13-15)
- **Termination** of trials (Art. 16 & 17)
- **Inspection** for GCP compliance (Art. 18 a)
- **Procurement** of drugs and products for clinical trials (Art. 20 & 21)

Box 1

Laws, Guidelines, Decrees

- Health Law, 1992
- Consumer Protection Law 1999
- Indonesian Guideline on GCP (2001)
- NADFC Decree on Procedures for Clinical Trial (CT) Authorization No. 02002/SK/KBPOM, February 2001.
- NADFC Decree on GCP Inspection No. HK.00.05.3.4991, 11 November 2004
- NADFC Decree on Guideline for the Conduct of Bioequivalence Study No. HK.00.05.3.1818, 29 March 2005
- MoH and NADFC Decree on Drug Registration (Guideline and Procedure) 2003, updated in 2008

CT Application Procedure

There are three types of clinical trial procedures:

Pre-marketing clinical trials

These are clinical trials on products not yet registered in Indonesia and are carried out by the Sponsor or a CRO. Clearance must first be obtained from an Ethics Committee, which includes reference to a Scientific Committee. Once this clearance is obtained and the

applications submitted to NADFC, the timeline for obtaining clinical trial approval/certification and an import permit for the study drug (if needed) is **10 working days**. Details of the procedure are given below.

Post-marketing clinical trials

These are trials carried out by the sponsor or a CRO on products that are registered in Indonesia. The application must be submitted to an Ethics Committee and NADFC. If there is no response within 10 working days, the trial may commence.

Clinical trials for educational purposes

These are trials carried out by individual investigators or academic institutions. Ethics Committee clearance is required but the trial only needs to be *notified* to NAFDC without a formal application process.

The process

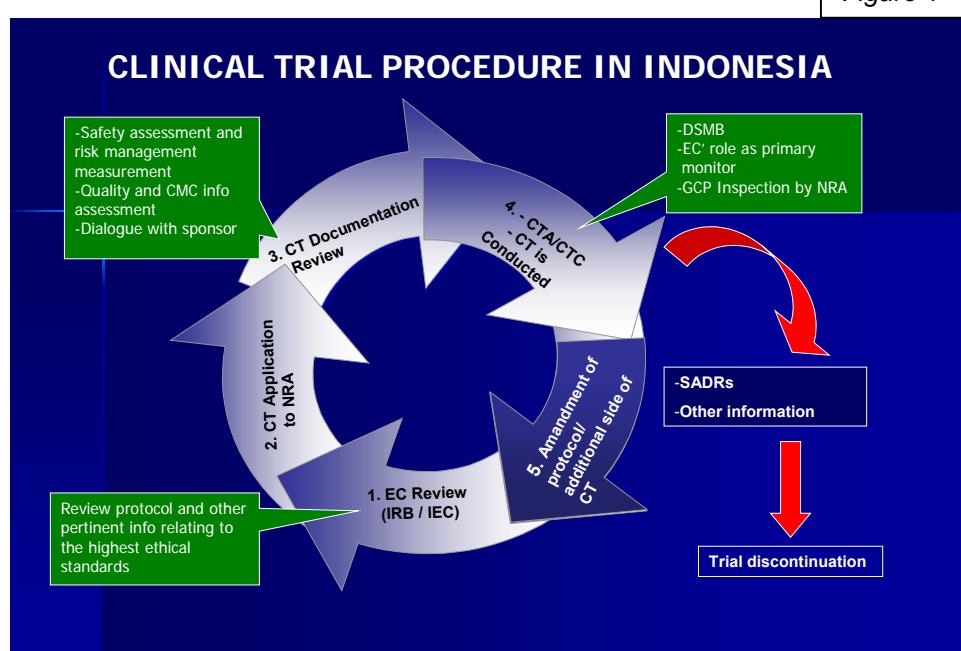
The main steps in the clinical trial approval procedure for pre-marketing trials are set out in *Figure 1*

Step 1. Documentation on the trial is submitted to the Ethics Committee for review and approval.

Step 2. The clinical trial application is made to the regulatory authority. This consists of:

- The Protocol and its amendments
- Informed consent and its amendments

Figure 1



- Investigator's brochure and its amendments
- Clinical trial drug documentation
- Ethics Committee's approval (related to the trial)
- A Letter of authorisation (if any)

Step 3. The review of documentation focuses on the safety assessment, risk management, and benefit risk assessment. Quality and CMC information is assessed and there may be dialogue with the sponsor over questions, clarifications or missing information.

The regulatory assessment target is 10 working days from the receipt of complete documentation but the time will be extended if the application is not complete or is delayed by queries.

Step 4. Authorisation is given for each protocol, PI and site. Once this is granted and the trial has commenced the Ethics Committee will be the primary monitor but GCP inspections are carried out by the Regulatory Authority. It is the responsibility of the sponsor to report serious adverse drug reactions (SADRs) and other information that is relevant to the conduct of the trial. Safety issues can lead to the trial being discontinued.

Step 5. Amendments to the clinical trial protocol and the inclusion of additional trial sites require further submission under the same procedure, starting at Step 1.

Metrics

The increasing rate of receipt and approval of CT applications, particularly for phase 3 trials by multinational companies, is shown in *Figure 2*.

The number of trials does not include bioequivalence studies (*) and the most recent total of 81 applications in the last column is up to September 2008 (**).

When the total number of trials (2002 to Sept. 2008) is analysed the most frequent therapeutic categories are:

- **Malignant disease** and immunosuppression (18%)
- **Infections** (17%)
- **Cardiovascular** system (12%)
- **CNS - Central Nervous System** (12%).



Perception of limitations

An analysis, by the agency, of problems encountered in the implementation of CT regulatory requirements showed the following:

Problem	Frequency	Notes
Informed consent	40%	Problems involved: subject rights, lack of information on drugs, treatment, or investigator: information omitted from the application.
Product data	40%	Inadequate product and all quality information
No CT authorisation	5%	Trials on unapproved products
Serious adverse events reports not sent to the regulatory authority	30%	Non-compliance with GCP found on inspection
Protocols amended without approval	10%	Changes not notified to Ethics Committees and/or the Regulatory Authority

Companies were also asked for their views on difficulties in implementing the clinical trial requirements:

Problem	Frequency	Notes
Preparation of CT protocol	4/10	Problems with the development of CT design, sample size, product or comparator standards
Investigator recruitment	5/10	Investigator qualifications, lack of understanding of GCP, limited time of investigators
Lack of research facilities	3/10	Scarcity of qualified contact research organisations (CROs)
Development of informed consent	4/10	Difficulties with the local language and inappropriate informed consent

Current challenges

The agency has recognised the challenges that it faces in terms of the country's preparedness to participate in multinational clinical trials (MNCTs). These are summarised below:

Patient pool:	There is a large, diverse patient population with the possibility of numbers of therapy-naïve individuals, but there are no comprehensive data on the incidence of acute or chronic diseases.
Cost efficiency:	No comprehensive data are available
Regulatory conditions:	The Government encourages the inclusion of Indonesia in MNCTs and the basic regulation is in place but more comprehensive Regulation and Guidelines are needed for the CT application process. The gap between functions of the Regulatory Agency and Ethics Committees needs to be bridged.
Relevant expertise:	There are many medical scientists but still a lack of the special expertise needed for clinical trial investigations.
Infrastructure and environment:	Teaching and private hospitals are ready to be involved in clinical trials but the number of CT sites with adequate facilities is limited.

The way the forward

The Agency believes that the way to move forward is through the establishment of an IND-like process for the regulation of clinical trials.

Improvement in the current system would include:

- Better links between the Agency and Ethics Committees through structured communication and harmonisation of the review processes, including timelines;
- Sharing responsibilities for the implementation of GCP principles between the Ethics Committee, Investigator, Sponsor/CRO and the Regulatory Agency;
- A more robust review and evaluation process for clinical trial proposals;
- Training for clinical trial investigators and researchers on GCP principles and also training for GCP site inspections.

Indonesia is at the Centre of International Collaboration through WHO. For example, the country has been proposed as the Global Training Network (GTN) location for training programmes in CT applications and the Clinical Data Evaluation for Vaccines.

REGULATORY ASPECTS OF CLINICAL TRIALS IN MALAYSIA

Noorizam Ibrahim

Principle Assistant Director, National Pharmaceutical Control Bureau, Malaysia

Presented on behalf of Selvaraja Seerangam, Director, NPCB, Ministry of Health, Malaysia

Under Malaysian law it is prohibited to manufacture, sell, supply, or import a medicinal product that has not been registered and granted an appropriate licence by the Regulatory Authority. As unregistered medicinal products, clinical trial materials, whether manufactured locally or imported for the purpose of clinical investigations, require exemption from this legal requirement. The exemptions take the form of:

- A **Clinical Trial Import Licence (CTIL.)** which allows an unregistered product to be imported into Malaysian; or
- A **Clinical Trial Exemption (CTX)** which allows a product to be manufactured locally for the purpose of clinical trials.

Background

The **Drug Control Authority (DCA)** was established in 1985 under the legal framework set out in the *Control of Drugs and Cosmetics Regulations* (see *Box 1*). The DCA is the national body responsible for drug registration and for the licensing of premises. The main objective of DCA is to ensure the safety, efficacy and quality of pharmaceutical, traditional, cosmetic and veterinary products marketed in Malaysia.

The National Pharmaceutical Control Bureau (NPCB) was set up in 1978 and now serves as the Secretariat to DCA.

DCA's Mission

The primary mission of the DCA is to provide public protection by ensuring the safe use of regulated products that are themselves safe and efficacious. Underlying this mission is DCA's decision-making on marketing applications and appropriate product labelling.

This, in turn, is based on complete and accurate information from well-designed, ethically conducted, and well-monitored clinical research.

DCA ensures that Clinical Trials/Research is conducted in compliance with **Good Clinical Practice (GCP)** that meets international ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

The GCP requirements adopted by DCA embrace trial objectives, trial design, study oversight, data collection and quality assurance, study analysis, as well as human subject protection in studies that support product applications.

Independent Ethics Committee (IEC)

A prerequisite for the conduct of clinical trials in Malaysia is approval by an IEC.

- Clinical trials conducted in **Ministry of Health** facilities must get ethical approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia
- **Private hospitals/clinics** which do not have an IEC, may use the MREC for ethical approval
- **University hospitals** have their own IECs.

A Directive had been issued that all IECs that approve drug-related clinical trials requiring a CTIL or CTX must be registered with the DCA. The relevant guidelines for clinical trials are shown in *Box 1*.

Box 1

Laws Regulations and Guidelines
Laws
Control of Drugs and Cosmetics Regulations 1984 (Revised 2006)
The Poison Regulations (Psychotropic Substances) 1989
The Sale of Drugs Act 1952
Guidance related to CTs
Malaysian Guidelines for GCP (Updated 2004) NPCB website
Guidelines for Application of CTIL and CTX in Malaysia (updated, NPCB website).
Guidelines for the Conduct of Bioavailability and Bioequivalence studies, Sept 2000
NIH Guideline for Research Conduct in MOH

Clinical Trial Approval

The legal basis for CTILs and CTXs is contained in the *Control of Drugs and Cosmetics Regulations 1984 (Revised 2006)*, Part III: Registration and Licensing. Regulation 7 prohibits the manufacture, sale, supply, importation, possession and administration of unlicensed products and the *Exemptions* are set out in:

- **Regulation 15(5)** on CTXs: ... 'Any person who wishes to manufacture any products solely for the purpose of producing samples for registration/clinical trials under these Regulations may on application be exempted by the Authority from the provisions of regulation 7(1).'
- **Regulation 12(1)(c)** on CTILs which provides for A Clinical trial import licence in Form 4 in the Schedule, authorising the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product

The procedure

To conduct clinical research in Malaysia, approval must be obtained from a relevant IEC for the trial site. The application for ethics approval can be made in parallel with the regulatory application. The application for a CTIL or CTX for drug-related clinical trials is made to the DCA through the National Pharmaceutical Control Bureau (NPCB), MOH. The application requirements are contrasted in *Box 2*.

In either case the approval by DCA is based on approval from the IRB/IEC complete information on the investigational products.

The applicant for either a CTIL or CTX can be the Principal Investigator (PI) or an authorised person from a locally registered company.

The details required are:

- **Annex A:** Clinical Trial Protocol
- **Annex B:** Pharmaceutical Data
- **Annex C:** Investigator Brochure

The review

The application is made to the NPCB and maybe submitted in parallel with the application to the IEC. After a preliminary review by the Secretariat the application is referred to the Drug Evaluation Committee, which gives its opinion to DCA. The decision on the application is made by the DCA and transmitted to the applicant.

The timeline for the regulatory review is **4-8 weeks**.

Factors affecting the timeline for approval depend upon:

- The completeness of the information submitted;
- How fast the sponsor or PI responds to queries;
- Adherence to established procedures;
- The timing of the ethical approval procedure.

Malaysia's competitive strength

Malaysia can offer many advantages as a country for inclusion in programmes for the Global Clinical Development of new medicines. The Malaysian government has a strong commitment to supporting pharmaceutical development and the contract research industry.

Box 2

CTIL and CTX Application	
CTIL Application	CTX Application
For unregistered products and those used or assembled (formulated or packaged) in a way different from the approved form.	For unregistered products.
Form: BPFK 442.4	Form: BPFK 443.1
Fees: RM 500 for each product	Fees: Free of charge
Licence A required for Poisons (where applicable)	Licence A required for Poisons (where applicable)

Malaysia also offers a favourable **clinical research environment** including:

- Qualified and well-trained medical professionals who are English literate and work in modern medical facilities;
- A large patient population in diseases such as diabetes, cancer, heart diseases and hepatitis who would benefit from participating in clinical trials;
- A varied culture and multi-ethnic population that has the advantage to researchers of providing a diverse gene pool;
- The advantage of a relatively low-cost environment for setting up and conducting clinical trials;
- Efficient logistics for the supply of clinical trial materials and the transport of bio-specimens;
- The availability of competent local contract research organisations (CROs)

The **regulatory environment** adds to Malaysia's competitive strength by providing:

- Enforcement of, and compliance with, GCB that meets international requirements;
- Intellectual Property Rights (IPR) protection;
- Fast timelines for ethics review and regulatory approval.

BUILDING QUALITY INTO THE CLINICAL TRIAL INFRASTRUCTURE IN TAIWAN

Li-Ling Liu

Deputy Director General, Bureau of Pharmaceutical Affairs, Taiwan

Li-Ling Liu discussed the role of the Bureau of Pharmaceutical Affairs (BPA) in regulating the conduct of clinical trials in Taiwan and ensuring, in particular, the implementation of Good Clinical Practice to standards that encourage the inclusion of Taiwan in Global Clinical Development Programmes.

Bureau of Pharmaceutical Affairs

BPA is responsible for the authorisation of medicines for marketing and for clinical trials in Taiwan. Its remit, however, extends beyond the quality, safety and efficacy of products and includes Risk Management and Health Promotion. By ensuring that quality measures are built in to the review and assessment processes BPA also has a role in Globalisation.

The Bureau is part of the Department of Health (DOH), reporting directly to the Minister of Health and is responsible not only for pharmaceuticals but also for medical devices and cosmetics. The Centre for Drug Evaluation (CDE) is a Nongovernmental Organisation (NGO) that supports the Bureau's work by carrying out technical reviews.

Stakeholders in clinical development

There are four parties that have a key role in building a solid infrastructure for clinical trials in Taiwan. These are the DOH (through BPA), Medical Institutions, the Industry (through sponsor companies and CROs) and the Public. In addition to DOH, the government's economic departments also have a role in supporting moves to attract medical research and development to the country.

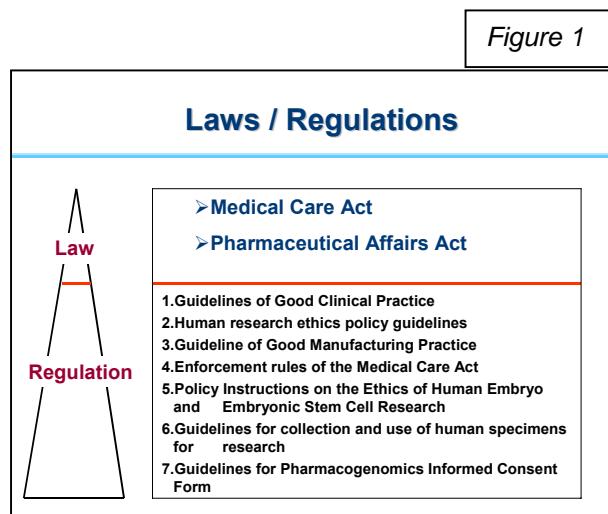
Good Clinical Practice is at the heart of the infrastructure for quality assurance in clinical trials and this is supported by transparent Laws and Regulations, sound personnel training and a good clinical environment.

Implementation of GCP

Taiwan was one of the first few countries in the Asian region to enforce GCP inspection, and other laws and guidelines relevant to clinical testing standards are shown in *Figure 1*. The sequence for implementing the laws and guidelines is shown below.

1996	Good Clinical Practice (GCP)
1997	GCP Inspection
2005	GCP Guidelines revised
	Further hospitals allowed to conduct clinical trials
2006	Development of a clinical trial network in Taiwan
2007	GCP Guidelines for Medical Devices
	Revised Informed Consent form

Figure 1



CT Application and Approval Process

The flow chart for the CT application procedure is shown in *Figure 2*. BPA has taken note of the extent to which the US FDA includes meetings with companies at key stages in clinical development, including preclinical research, end of Phase II, and pre- NDA. The Bureau has therefore implemented procedures to allow consultation with sponsors in the application and review process.

Initially the review process was sequential with application for Ethics (IRB) clearance being made before the regulatory application. In order to speed up the process, this was changed a few years ago, to a parallel process, which allows review by the IRB to be carried out at the same time as the Regulatory Review.

Government support

There are almost 130 teaching hospitals in Taiwan that have the basic requirements as clinical trial institutions but the government has provided funding to establish four *Centres of Excellence* for clinical trials in 4 large hospitals (over 2000 beds) and a further 14 Clinical Research Centres with a high standard of facilities.

Training is provided for clinical trial professionals and seminars are held with industry. Since physicians in Taiwan can earn more from medical practice than from medical research the government also rewards professionals for their involvement in conducting clinical trials.

Ethics Review

The quality of the Ethics Review for clinical trials is pivotal to clinical research and in 2005 the Bureau of Medical Affairs (BMA) announced a project to monitor and certify the status of Institutional Review Boards (IRBs) at medical institutions. Certification is carried out under the SIDCER³ initiative, and the results of certification within APEC region and Taiwan are shown in *Box 1*.

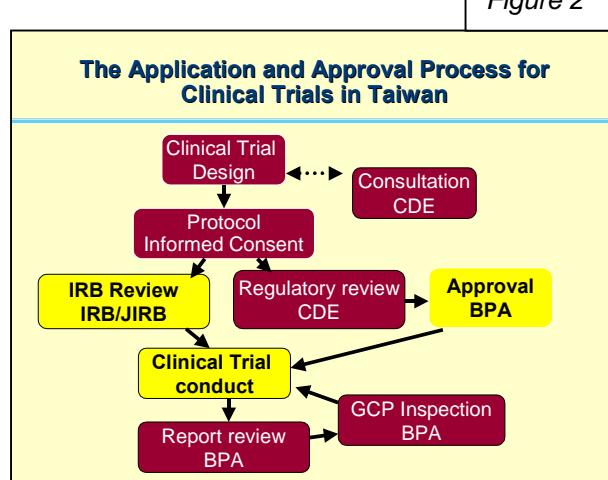
Joint IRB

A Joint IRB (JIRB) has been established and is authorised by 87 hospital IRBs to review clinical protocols on their behalf. The JIRB provides a 'one stop' review for multi-centre trials and has an average review time of 32 calendar days. The Board meets every 2 weeks and approves most multi-centre trials in Taiwan.

Clinical Trial Information Network

Information on clinical trials conducted in Taiwan is published by the Clinical Trial Information Network on the website: www.cde.org.tw/ct_taiwan/index.htm

Figure 2



Box 1

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

³ SIDCER is WHO/TDR initiative undertaken in partnership with regional fora and health research organisations focused on developing global capacity in ethical review and Good Research Practices. See www.sidcer.org and www.who.int/sidcer

CT Application Metrics

There has been a dramatic increase in the number of clinical trials carried out in Taiwan, as shown in *Figure 3*. Some 75% of the trials are part of multinational (MN) programmes. *Figure 4* shows the distribution of trials according to Phase. Whilst most are Phase III trials there are a significant number of the Phase II studies. The predominant therapeutic area is oncology.

An analysis of review performance shows that over 90% of CT applications are approved on

Figure 3

IND by Type (2004 - 2008 11.21)												
	2004		2005		2006		2007		2008.11.21		P	S
	P	S	P	S	P	S	P	S	P	S		
TW single site	32	32	24	24	11	11	21	21	40	40		
TW multiple sites	25	88	10	43	22	74	20	81	13	44		
MN trials	62	196	86	284	100	337	127	479	143	545		
% of MN trials (P)	52.1%		71.7%		75%		75.6%		72.9%			
Total	119	316	120	351	133	422	168	581	196	629		

P: Protocol S: Sites

Figure 4

Distribution of CT Phases												
	2004		2005		2006		2007		2008 (-11.21)		P	S
	P	S	P	S	P	S	P	S	P	S		
Phase I	8	12	14	26	12	20	10	18	15	18		
Phase II	22	57	33	78	32	98	46	158	45	116		
Phase III	85	237	69	242	86	300	106	391	128	487		
Phase IV	4	10	4	5	3	4	6	14	8	8		
Total	119	316	120	351	133	422	168	581	196	629		

P: protocol S: site

the first cycle. The review times have been getting shorter over the years and have decreased from **65 days** in 2005 to **36 days** in the first part of 2008. It should be noted, however, that these are regulatory review times and do *not* include the time taken by companies to respond to queries.

International Cooperation

The government has stipulated that Taiwan's Regulation must be in conformity to International Standards. A mechanism for the Exchange of Letters (EOL) and Mutual Recognition has been established with several countries. In the field of Medical Devices, EOLs have been established with the US FDA, the European Commission and Switzerland.

Membership of international organisations includes participation in:

- **APEC** Industrial Science and Technology Working Group (ISTWG), Network on Pharmaceutical Regulatory Science;
- **APEC** Life Sciences Innovation Forum (LSIF), APEC Regulatory Science Symposium of CPP;
- **ICH** Global Cooperation Group (GCG) Participants.

Future developments

With over 10 years experience of GCP implementation, Taiwan is hoping for further cooperation with other countries in the conduct of clinical trials. It is anticipated that overseas GCP inspections might be carried out, as they have been for GMP over the last five years.

Another vision for the future is that joint reviews and exchange of assessment reports could be carried out with other countries in order to speed up the clinical trial review process. This would benefit both companies and the Regulatory Authority but, most importantly, it would give the populations of the region earlier access to new medicines.

Section 3, Chapter 5

CLINICAL TRIAL INFRASTRUCTURE, REGULATORY AND CLINICAL EXPECTATIONS: AN INDUSTRY PERSPECTIVE

Jerry Stewart

Global Regulatory Affairs, Wyeth Pharmaceuticals, USA

Jerry Stewart, as the final speaker at the Workshop, gave an overview from an industry perspective, of the benefits that can be gained from the Simultaneous Global Development of new medicines and the improvements in the regulatory environment that could not only help companies achieve this goal but also bring benefits to the 'waiting patients' through earlier access to therapeutic advances.

Global Development

The speakers at this Workshop had clearly confirmed that there is a geographical shift in the selection of countries for inclusion in clinical trials and that Clinical Development is truly becoming increasingly 'Global'.

From an industry perspective the drivers for the geographical shift in country selection include access to a wider, and often treatment-naïve patient population as well as reductions in the cost of clinical development. In some cases national registration requirements that require data from local clinical trials may be a factor in the choice of country. Increasingly however, countries outside the traditional 'core countries' for drug development are offering quality sites and good investigators that are attractive to industry.

Simultaneous Global Development

The industry goal is that clinical development should not only be carried out globally but should be essentially *simultaneous*. This has two major objectives in the *Learn & Confirm* paradigm for drug development:

CT Application: Data from early development (the 'Learn' phase) in a wide range of countries and different ethnic populations can be used to develop a single dossier of global data for subsequent CTA applications to support the next critical phase of development (the 'Confirm' stage).

Marketing application: Data from Global Clinical Development can then be used to develop a single NDA dossier to support simultaneous product registration and marketing authorisation in all regions (US, EU, Asia, Latin America, etc).

Benefits of Simultaneous Global Development

Four main benefits were identified:

- **Broader regulatory oversight:** Submission and review by regulatory agencies at the same time allows the benefit of their views and experience to be built in to the Clinical Development Programme;
- **Reduced drug lag:** Successful simultaneous clinical development should result in earlier availability of innovative drug therapies to populations in the new markets and ultimately leads to a reduction in the 'drug lag' from the time of marketing in the core countries, which can be several years;
- **Ethnic factors:** Broader clinical development enables a science-based approach to defining intrinsic and extrinsic ethnic factors and to identifying clinically meaningful ethnic differences in order to discuss the next steps. Also, the registration dossiers for marketing will include a higher percentage of ethnically diverse patients
- **Improved medical infrastructure:** Conducting trials that must meet international standards will advance the knowledge and experience of local investigators and, ultimately the medical community.

Barriers to Simultaneous Global Development

Although not all the barriers listed below apply to all countries, the cumulative effect on companies is that they are faced with an *unpredictable* regulatory environment and this is a major deterrent to Global expansion.

The main barriers are:

- **Lack of harmonisation** of requirements and processes between different countries and unique data requirements that are outside international standards:
 - Quality (CMC) requirements are a predominant issue.
- **Approval and start-up times:** Simultaneous development is undermined when CT application approval times (by Agencies and Ethics Committees) and start-up times are much longer than those in the core countries.
- **Inefficient review processes:** Insufficient resources within the agency, lack of transparency, unpredictable questions and requests and a lack of formal mechanism for agency consultation all contribute to companies' reservations about including new countries;
- **CTA amendments:** Major problems can arise in managing co-ordinated development programmes if agencies are inflexible and cause delays in implementing the protocol changes and minor quality amendments that are almost inevitable in clinical trials;
- **Acceptance of data:** Uncertainty of ICH/WHO GCP enforcement can raise doubts about whether the trial results will be acceptable to other agencies;
- **Intellectual property:** IP concerns can be a barrier to providing, for example, detailed quality information at an early stage.

An ideal CT process and infrastructure

When a company is considering a country for inclusion in Global Clinical Development what are the expectations for a CT process and infrastructure that would make the country attractive?

The paramount criteria are *predictability* and *efficiency*. Requirements must be clear and understandable with timelines that can be relied upon. Ideally the overall approval times should be <60 days.

Data requirements

When aiming at the simultaneous submission of a CT application dossier, there should be commonality in the data requirements. Companies would expect to submit:

- A Summary of nonclinical, clinical and quality data that is commensurate with stage of development of the CT product;
- Proof of GMP certification for the production of CT material;
- The trial protocol and informed consent documents.

Technical requirements should be standardised and harmonised within the ICH framework.

The ultimate objective is a single technical dossier that will satisfy global registration requirements at the marketing stage and avoid costly sequential or duplicative developments

Ideally, an integrated Global Development Programme should provide data that satisfy not only the US and EU requirements but also address ethnic differences and satisfy the requirements of countries such as Japan, China, S Korea, Taiwan, India and Mexico that all have local data requirements for marketing applications.

Regulatory Expectations

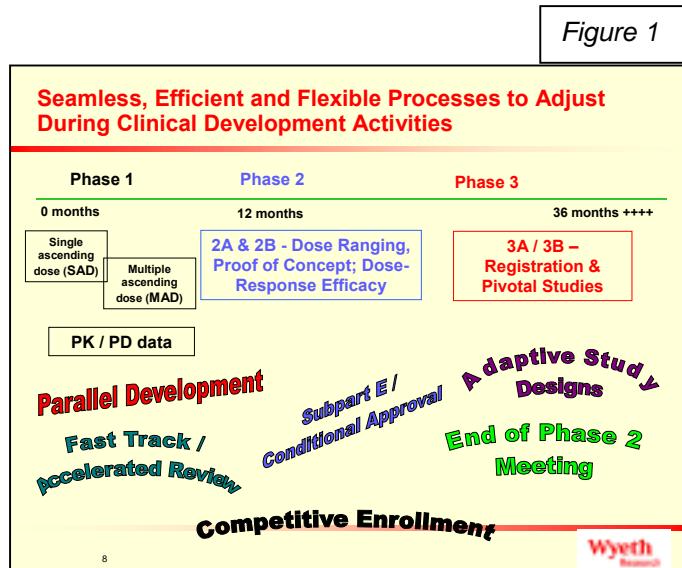
In addition to transparency and reliability there are three particular features that companies are looking for in the regulatory process.

Protocol and quality amendments: Regulatory agencies need to recognise the dynamic nature of clinical trials that are part of Global Clinical Development (see *Figure 1*) and companies' need to make changes to the protocol and quality data. There should ideally be a **notification system** for these with minimal delay to starting the trials. Similarly there should be an **abbreviated pathway** for subsequent trial protocols within the development of the same medicine (e.g. moving from Phase II to Phase III).

Interaction with the agency: Formal agency interactions are needed that are efficient and flexible. There should be facilities for pre-submission meetings particularly to discuss safety mitigation plans. Companies also need the option to hold an end-of-Phase II meeting, if necessary, to discuss issues such as Ethnic Factors that will be important in planning Phase III and the pathway to registration.

GCP reliance: It is important that the clinical data from trials in any country will be acceptable as part of the Global Marketing Dossier. Although companies carry out their own audits and controls for GCP compliance, they also expect Regulatory Agencies to operate inspection schemes.

Figure 1



Clinical Expectations

The quality of the clinical testing sites in a country is pivotal to the decision on incorporating the country in Global Clinical Development. There must be Centres that can offer efficient patient recruitment and monitoring with acceptable standards of care, medical practice, and standard operating procedures (SOPs) for clinical trials. As emphasised, compliance with international GCP standards is paramount.

Of the factors that would affect a company's decision include:

- **Data quality:** The way in which data are captured and consolidated and the standards of narrative writings;
- **Key opinion leaders:** Calibre of local experts who might be consulted by the Regulatory Agency or Ethics Committees particularly in early development projects;
- **Validation:** Whether there are country-specific requirements for validation of the instruments or therapeutics scales that will be used in the trial;
- **Comparators:** Whether the comparator agents selected for the global trials are available and approved in the country at the appropriate dosage;
- **Language:** The advantage of investigators who speak multiple languages and are able to communicate with colleagues involved in the same Development Programme;
- **Patient recruitment:** Whether the centre has a strong network in the community and the extent to which patients are available in the therapeutic area;
- **Ethics Committees:** Whether these have a strong makeup and transparent, efficient working practices;
- **Logistics:** Companies will be seeking short study start-up times (e.g., < 30 days) that are not impeded by issues such as the import of trial materials and laboratory testing requirements for biological products and samples.

Achieving Simultaneous Development

Companies may set out to design a Global Clinical Development Programme but whether this can be truly *simultaneous* depends entirely on the timing, regulatory performance, and start-up times in individual countries.

A company's clinical development plans cannot be 'open-ended' but must have specific performance targets, for example in the total number of patients to be enrolled in the Global Study. (See the reference to 'Competitive Enrolment' in *Figure 1*). If there are delays resulting from long approval times, inflexibility in dealing with protocol updates and amendments, or other delays in starting local trials, a situation can arise where the global patient recruitment target is reached before local trials have commenced or when only a few patients have been enrolled in a particular country.

Under these circumstances the country can no longer benefit from being part of a Global project and the local trials may be terminated. This means that both the company and the regulatory agency will have invested (and wasted) time and resources on a regulatory dossier and scientific review that have not brought the expected benefits to patients.

'The patients are waiting' and Industry needs to work with Regulatory Agencies in all regions to establish a predictable and efficient regulatory framework within which the goals of Simultaneous Global Development can be achieved.
