

Global Drug Development: Asia's Role and Contribution

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Workshop Report (SECTIONS 1&2)

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Institute for Regulatory Science

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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WORKSHOP ON GLOBAL DRUG DEVELOPMENT: ASIA'S ROLE AND CONTRIBUTION

Section 1: Overview

The pharmaceutical market in the Asia-Pacific region (excluding Japan) currently accounts for less than 20% of the global market but it is the fastest growing region of the world with a compound annual growth rate of 11.4% compared with the global rate of 7.9%. It is projected that, by 2015, this Asia-Pacific pharma market will have risen from 41 to 121 billion US\$ and be half as big as the market in Europe¹.

Return to Tokyo

Against this background, the Institute for Regulatory Science returned to Tokyo, in October 2006, for a second Workshop on Global Drug Development (GDD) which looked specifically at *Asia's Role and Contribution*. The first Tokyo meeting, held in May 2004, had addressed GDD from the viewpoint of the ICH-affiliated regions but the second Workshop focused on the way in which the research-based pharmaceutical industry is extending its clinical development programmes into other countries in the Asia-Pacific Region and on the way in which the local regulatory agencies are responding to the challenge.

The workshop attracted a record participation and the Institute waived its normal size limit for such meetings and accepted over 60 participants. This did not, however, inhibit productive and interactive discussions in the four break-out Syndicate groups that met towards the end of the meeting.

Syndicate views and recommendations

The Syndicate Session was moderated by the Chairman of the Institute's Regulations Advisory Board, **Professor Robert Peterson**, *Professor of Paediatrics, University of British Columbia, Canada*, and the Syndicates presented their views in a series of recommendations and discussion points. The two main themes were:

- Integrating the Asia-Pacific region into global clinical development programmes *and*
- Regulatory progress and models that would help make coordinated registration (and reduction in the so-called 'drug-lag') a reality.

The Syndicates recommended:

Streamlining the procedure for obtaining clinical trial approvals by agreeing a process whereby, once the basic data for a clinical trial application (CTA) has been reviewed and approved by one major agency the authorisation should be recognised by other participating countries.

This procedure would be dependent on the related recommendation on harmonising CTA Requirements:

Harmonisation of CTA requirements as a priority: *In order to share assessment reports and approvals for clinical trial applications there needs to be agreement on a standard format for CTAs, the requirements for supporting data and on a common review template. Ideally there should be similar timings for review so that global and/or multi-country clinical trials can be synchronised.*

On the question of whether involvement in GDD was of benefit to non-ICH countries it was agreed that agencies should: **Support the movement of clinical programmes to Asia Pacific.** *This brings major benefits in investment, improved clinical infrastructure and patient welfare and regulatory agencies should balance their public health obligations with a willingness to cooperate.*

On the part of industry it was felt that: **There is a need for a major change of attitude within some companies** in order to accept the organisational and strategic change needed to work successfully in the region, to establish a local presence and to obtain an understanding of the needs and practices of the region.

Asked about regulatory models that would reduce the lag time between first registration of new drugs in the West and local registration in the region, the Syndicates made two recommendations:

A network rather than an agency: *The concept of an 'Asian Medicines Agency' is not a practical short-term goal for the region. First, a defined Network of participating Asia-Pacific agencies should be formed with a view to establishing a system of Mutual Recognition of authorisations for new medicines.*

A Pilot scheme for coordinated parallel reviews: *There should be one or more designated Reference Agencies in the AP Region with the specific remit of assessing CTAs and NMEs in parallel with the review by EMEA and US FDA Other agencies would agree to recognise this authorisation and to allow simultaneous marketing of new therapies*

It was also observed, however, that: **'Drug lag' may be a strategic choice** for some companies which may delay registering medicines outside the 'ICH regions' as a matter of strategic choice based on marketing and commercial considerations.

The Syndicates discussed harmonisation issues and agreed that in: **Harmonisation through ICH** there should be better representation of the Asia-Pacific region and the opportunity for active participation on ICH Working groups that have a major impact on regulatory procedures in the region.

Examples include, stability guidelines for all climatic zones and the need to address differences between the ICH Common Technical Document (CTD) and regional variations (ASEAN CTD)

Discussions on harmonisation encompassed the ICH E5 guideline on *Ethnic factors in the acceptability of foreign data* which is pivotal to determining the need for bridging studies as part of global registration. It was agreed that an organisation such as the CMR International Institute should carry out a:

Survey on ethnic differences that have had a regulatory impact: *An evidence-based study on real and perceived differences in ethnicity that have led to bridging studies and on the relevance of the outcome.*

It was also observed, however, that the need for bridging studies can be obviated by: **Integrating medical, scientific and cultural differences into clinical development** and *designing global research protocols integrating the Asia-Pacific region, that can incorporate the differences.*

This led to the conclusion that, in practice, the move to carry out clinical trials in the Asia Pacific region, irrespective of the underlying reasons, is a driving force to rationalise questions of ethnic factors. Companies should recognise this and not miss the opportunity.

Presentations to the Workshop

The Syndicate discussions followed two working Sessions in which both regulators and company experts shared their views.

Regulatory participants

The opening session of the Workshop was chaired by **Dr Murray Lumpkin**, Deputy Commissioner, International and Special Programs for the US FDA and a keynote presentation on integrating Japan into GDD programmes was given by **Akira Miyajima**, Chief Executive, Pharmaceuticals and Medical Devices Agency (PMDA). **Melinda Plaisier**, US FDA discussed the challenges of sharing information and scientific advice between agencies and **Dr Tomas Salmonson**, Medical Products Agency, Sweden

The Workshop was rounded off by an overview from the EU, given by **Thomas Lönngren**, Executive Director of the European Medicines Agency (EMA).

Non-ICH Asia was also well represented by regulatory speakers who looked, from a country and regional point of view, at the challenges and opportunities presented by integration into the global development of new medicines.

A viewpoint from Taiwan was presented by **Dr Heng-Der Chern**, Executive Director, Centre for Drug Evaluation, Taiwan, from South Korea by **Dr Jung-Yun Chang**, a team Deputy Director in the Department of Drug Evaluation, Korea Food and Drug Administration and from Singapore by **Dr John Lim**, Chief Executive Officer, Health Sciences Authority.

The global industry

Scientific, practical and commercial drivers all have a role in the movement within the research-based pharmaceutical industry to extend clinical development programmes into key countries in the Asia-Pacific region. Whilst some companies aim at fully integrated development, others are content, for the present, with parallel programmes conducted in the West and the East.

Speakers from the headquarters and local affiliates of multinational companies presented their views and data to the Workshop. **Dr Tadao Suzuki**, Senior Managing Director and Head of R&D, Daiichi Pharmaceutical Co., Ltd., gave the opening presentation on strategies and options for GDD and **Dr Bruce Schneider**, Executive Vice President and Chief of Operations, Wyeth Research, USA gave an industry perspective on integrating Japan into global programmes.

Dr Paul Huckle, Senior Vice President, US Regulatory Affairs, GSK, USA, chaired Session 2 on the challenges and opportunities for global clinical development. In which industry perspectives were presented by **Dr Gabriele Disselhoff**, Merck KGaA, Germany, **Dr Edmund Tsuei**, Roche, Australia, **Dr Hiroshi Matsumori**, Pfizer, Japan on behalf of **Dr Ed Harrigan**, Pfizer Inc., USA and **Dr Zili Li**, Merck Research Laboratories, China

Institute study

In preparation for the Workshop, a survey had been carried out among companies on *Asia's contribution to the Global Development of New Medicines*. The results of the study were presented by **Dr Neil McAuslane**, Institute for Regulatory Science and the findings also provided valuable 'prompts' for the discussions in the Syndicates.

¹Data presented to the Workshop by Dr Edmund Tsuei, Roche Australia

Workshop Organisation

Workshop organised by: Dr Neil McAuslane, CMR International, Institute for Regulatory Science and by Dr Mayu Hirako (formerly with the Institute)

Report prepared by Margaret Cone, Institute for Regulatory Science



**WORKSHOP GLOBAL DRUG DEVELOPMENT:
ASIA’S ROLE AND CONTRIBUTION**

Section 2: Outcome

Syndicate Discussions

Session 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 four Syndicate groups and were provided with briefing documents that included extracts from the Institute for Regulatory Science survey on *Asia’s contribution to the Global Development of New Medicines: An Industry Perspective*¹. The Syndicates were asked to discuss the issues of developing and registering new medicines in the Asia-Pacific region from two main aspects:

- **Fully integrated clinical development programmes**
- **Regulatory models that could make coordinated registration a reality**

The Chairpersons and Rapporteurs for the four groups were:

Syndicate 1	<i>Chair:</i>	Dr Paul Huckle , <i>Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline, UK</i>
	<i>Rapporteur:</i>	Dr Leonie Hunt , <i>Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia</i>
Syndicate 2	<i>Chair:</i>	Professor Sir Alasdair Breckenridge , <i>Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK</i>
	<i>Rapporteur:</i>	Dr Stewart Geary , <i>Vice President, Global Safety Officer, Eisai R&D Management Co., Ltd</i>
Syndicate 3	<i>Chair:</i>	Omer Boudreau , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
	<i>Rapporteur:</i>	Dr Brian White-Guay , <i>Vice President, Head MRL Transformation Task Force, Merck & Company, USA</i>
Syndicate 4	<i>Chair:</i>	Dr John Lim , <i>Chief Executive Officer, Health Sciences Authority, Singapore</i>
	<i>Rapporteur:</i>	Dr Simon Larkin , <i>Director, Drug Development – Europe, Kyowa Hakko UK Ltd</i>

The programme for the Workshop is set out in *Annex 1* and *Part 3* of the report gives highlights and extracts from the presentations at the Workshop which relate to the recommendations and discussion points summarised below.

SUMMARY OF THE SYNDICATE RECOMMENDATIONS

In considering the two Syndicate topics, the groups were asked to consider the current hurdles for integrating the key Asia-Pacific countries into global clinical development programmes and indicate the ones that need to be addressed as a priority, by industry and by regulatory agencies. They were also asked whether there are lessons from established initiatives in the West (for example, the EMEA Centralised Procedure, ICH harmonised technical requirements, mutual recognition agreements) that might make simultaneous filing and registration a reality between Asia and the West and reduce the so-called ‘drug lag’.

¹ Results of the survey presented to the Workshop by Dr Neil McAuslane, Institute for Regulatory Science

The following ten main recommendations and observations were made by the Syndicates and these are discussed in more detail below.

1. Fully integrated clinical development programmes

1.1 Obtaining clinical trial approvals for a global development programme

A Streamlining the procedure for obtaining clinical trial approvals

When a company embarks on an integrated programme of multinational trials there should be a procedure whereby, once the basic data for a CTA has been reviewed and approved by one major agency (within or outside the region), the authorisation should be recognised by other countries in the programme and lead to an abridged clinical trial review process.

(See also the related recommendation G)

B Supporting the movement of clinical programmes to Asia Pacific

Being integrated into the global clinical development programmes of multinational companies brings major benefits to a country in terms of investment, improved clinical infrastructure and patient welfare. Regulatory agencies should balance their public health obligations with a willingness to cooperate with other agencies and willingness to be flexible as a priority for future development.

1.2 Addressing the barriers to clinical development in Asia-Pacific

C Changing company infrastructure and attitudes

There is a need for a major change of attitude within some companies in order to accept the magnitude of organisational and strategic change needed to work successfully in the region, to establish a local presence of appropriately qualified personnel and to obtain an understanding of the needs and practices in the region.

2. Regulatory models that could make coordinated registration a reality

2.1 Addressing the 'lag time' between registration in the Western and the Asia-Pacific Regions

D. A network rather than an agency

The concept of an 'Asian Medicines Agency' (with responsibilities for new drug assessments similar to those of the EU EMEA) is not a practical short-term goal for the region. First, a defined Network² of participating Asia-Pacific agencies should be formed with a view to establishing a system of Mutual Recognition of authorisations for new medicines.

E Pilot scheme for coordinated parallel reviews

There should be one or more designated Reference Agencies in the AP Region with the specific remit of assessing CTAs and NMEs in parallel with the review by EMEA and US FDA Participating Agencies would agree to recognise this authorisation and to allow simultaneous marketing of new therapies

F. 'Drug lag' as a strategic choice

Reducing the lag time in global registration of new medicines should not be viewed only as an issue to be addressed by regulatory agencies. Company policy may mean that the delay in registering medicines outside the 'ICH regions' is a matter of strategic choice based on marketing and commercial considerations as well as perceived practical barriers.

² Chisolm 1998: 'A Network is a set of autonomous organizations that come together to reach goals that none of them can reach separately'

2.2 Harmonisation of Technical requirements

G. Harmonisation of CTA requirements as a priority

In order to share assessment reports and approvals for clinical trial applications there needs to be agreement on a standard format for CTAs and on the requirements for the supporting data. The development of these must involve both regulators and companies. Agreement is also needed on the aims and essential features of the review process, including a common review template. Ideally there should be similar timings for review so that global and/or multi-country clinical trials can be synchronised.

H. Harmonisation through ICH

There should be better representation of the Asia-Pacific region and the opportunity for active participation on ICH Working groups that have a major impact on regulatory procedures in the region, in particular, stability guidelines appropriate to all climatic zones and the need to address difference between the ICH Common Technical Document (CTD) and regional variations (ASEAN CTD)

2.3 The impact on global drug development of ethnic and cultural differences

I. Survey on ethnic differences that have had a regulatory impact

The ICH E5 guideline on 'Ethnic factors'³ is still an active issue in determining the need for bridging studies as part of global registration strategies. An evidence-based initiative is needed with the ultimate goal of facilitating an update of the guideline. It would therefore be timely to carry out a survey, among companies and regulatory agencies on practical experiences of implementation of the guideline, on real and perceived differences in ethnicity that have led to bridging studies and on the relevance of the outcome.

J. Integrating medical, scientific and cultural differences into clinical development

As alternative to bridging studies, companies should take time to learn about the essential medical, cultural and genetic differences relating to a new medicine and design a research protocol, integrating the Asia-Pacific region, that can incorporate the differences.

In practice, the move to carry out clinical trials in the Asia Pacific region, irrespective of the underlying reasons, is a driving force to rationalise questions of ethnic factors and companies should not miss this opportunity.

DISCUSSION POINTS FROM THE SYNDICATE REPORTS

1. Fully integrated clinical development programmes

1.1 Obtaining clinical trial approvals for a global development programme

A Streamlining the procedure for obtaining clinical trial approvals

When a company embarks on an integrated programme of multinational trials there should be a procedure whereby, once the basic data for a CTA has been reviewed and approved by one major agency (within or outside the region), the authorisation should be recognised by other countries in the programme and lead to an abridged clinical trial review process.

B Supporting the movement of clinical programmes to Asia Pacific

Being integrated into the global clinical development programmes of multinational companies brings major benefits to a country in terms of investment, improved clinical infrastructure and patient welfare. Regulatory agencies should balance their public health obligations with a willingness to cooperate with other agencies and willingness to be flexible as a priority for future development.

³ ICH E5 Tripartite harmonised guideline, Revision 1 'Ethnic Factors in the Acceptability of Foreign Clinical Data available from www.ich.org

Whilst there are very real and motivating opportunities to integrate Asia-Pacific countries into global clinical trial programmes, success will depend on good will and cooperation. For those countries and companies willing and prepared to work collaboratively, however, this is an incomparable opportunity to develop greater confidence and experience and to leverage expertise. The following discussion points were raised in this context:

Regulatory attitude

It was felt that agencies should balance their public health obligations with a willingness to cooperate in providing a supportive environment to facilitate global drug development. To this end regulators need to:

- Understand the potential benefits to them, their industry, economy and, above all, patients, from global clinical trial involvement
- Have trust and confidence in each others' processes in order to facilitate sharing and acceptance of reports. This takes time and requires confidence-building processes
- Agree on the aims of a clinical trial review and on the format of evaluation reports (Recommendation G)
- Be prepared to talk with companies on scientific issues
- Be prepared to talk with each other

Industry's state of readiness

- Companies need to plan their global development strategically, including allowing reasonable time for necessary processes, such as translations.
- They are responsible for being aware of local regulatory requirements and should focus on essential issues
 - Time is better spent on addressing substantive scientific matters rather than arguing about details of requirements.
- Companies need to be prepared to talk with regulators and to base their discussions on scientific rationale
- They need to facilitate discussions amongst regulators by recognising the constraints of confidentiality and giving permission, when required, for the exchange of assessment information

1.2 Addressing the barriers to clinical development in Asia-Pacific

C Changing company infrastructure and attitudes

There is a need for a major change of attitude within some companies in order to accept the magnitude of organisational and strategic change needed to work successfully in the region, to establish a local presence of appropriately qualified personnel and to obtain an understanding of the needs and practices in the region.

There was discussion of the barriers that companies might face in developing clinical programmes in the Asia Pacific region and the importance of being prepared for Asia's sometimes unique requirements, in order to avoid surprises. It is also important to accept that, while some things are negotiable, others are not.

The perceived hurdles that companies must overcome include:

- **Barriers of distance and lack of experience**

It is extremely difficult to start to work with, for example, China from an EU or US office without having a capable local presence and experience in the country. Companies need a local presence with regulatory staff and physician contacts, etc. in order to operate effectively.

- **Operational barriers**

- The export of biological samples from patients can be difficult (e.g. genomic samples);
- Local safety reporting requirements for clinical trials may not be harmonised with the ICH E Guidelines⁴. Differences may exist in requirements for reporting to regulators and reporting to investigators
- The level of scientific expertise and capacity of the local regulatory authority may be an issue with applications for innovative 'high tech' medicines

- **Local Regulatory Barriers**

- The long review times for clinical trial approvals in China are a significant barrier to its timely integration into global clinical development programmes
- Chemistry Manufacturing and Control (CMC/Quality) requirements for clinical trials in China are well in excess of the accepted norm in the EU, US and other agencies in the region:
 - There is little or no differentiation between the CMC requirements for an IND and a full NDA
- There is a reluctance in some countries to have 'first in man' studies conducted before the source country, which precludes parallel development of early clinical stages

- **Language as a barrier**

- The inability to collect data from clinical trials in English may form a significant operational barrier in an integrated clinical programme
- The translation of informed consent documents and obtaining consent from trial subjects is not a problem when a single language – e.g., Japanese – is involved but becomes a major issue in a country such as India with 20 or more languages
- There may be problems when assessment scales (e.g., for psychiatric studies in depression) need to be validated in the local language.

2. Regulatory models that could make coordinated registration a reality

2.1 Reducing the 'lag time' between registration in the Western and the Asia-Pacific Regions

The estimated lag in the introduction of innovative pharmaceuticals in Asia-Pacific vs. the Western region ranges from 2-4 years and it has been estimated that 30% of world's top selling medicines were not available to Japanese patients in 2004. Strategies for reducing the lag must take into account that:

- The Asia-Pacific region has heterogeneous models of regulatory resources, market conditions and political expectations to satisfy.
- Agencies and governments in the region acknowledge the benefits of increased R&D efforts in the region and that these offer a new opportunity to participate in Global development programs
- In the longer term, models for collaboration will need to take account of a situation where new medicines *originating from Asia-Pacific* need to be registered by the Western agencies.

⁴ ICH *Clinical Data Safety Management* guidelines E2A-E2E available from www.ich.org

D. A network rather than an agency

The concept of an 'Asian Medicines Agency' (with responsibilities for new drug assessments similar to those of the EU EMEA) is not a practical short-term goal for the region. First, a defined Network of participating Asia-Pacific agencies should be formed with a view to establishing a system of Mutual Recognition of authorisations for new medicines.

- There is an increasing willingness to explore new models of collaboration between Agencies in Asia Pacific but, in setting priorities, the wide and variable remit of the Agencies in each national setting must be balanced against efforts to allow earlier access to new innovative therapies
- The EU model is not entirely realistic for the Asia-Pacific region as there is a political union underlying and driving the collaboration through the EMEA. There are, however, other models being developed in the absence of specific political ties, including the Gulf Co-Operation Council's (GCC's) Central Committee for Drug Registration and the Trans-Tasman agreement.
- There would be value in building from existing informal/formal cooperation mechanisms available in the Asia-Pacific region and establishing an initial list of priorities for reducing barriers to early registration
 - There was recognition of the extensive bilateral arrangements already in place, particularly between the Japanese MHLW/PDMA and, for example, Taiwan, South Korea and Singapore.
- Networking would be facilitated by pairing between agencies and the establishment of a forum that include industry and agencies from the Western world as invited contributors

Mutual recognition

The difficulties of true 'Mutual' recognition (as opposed to one-way recognition, as in the proposed pilot scheme) should not be underestimated and there are lessons to be learned from the EU, where the system does not always work as intended, despite extensive legislation and years of experience.

E Pilot scheme for coordinated parallel reviews

There should be one or more designated Reference Agencies in the AP Region with the specific remit of assessing CTAs and NMEs in parallel with the review by EMEA and US FDA Participating Agencies would agree to recognise this authorisation and to allow simultaneous marketing of new therapies

This would be a challenging undertaking that would depend upon building mutual trust and confidence among agencies:

- It would be necessary to identify an initial group of agencies willing to act as reference reviewers for the Asia-Pacific region and Japan, Singapore, South Korea and Taiwan were given as possible examples
- Other countries not yet ready to join the formal pilot scheme could have observer status in any joint discussions and coordination activities
- Specific targets for reducing the 'lag time' would need to be established for an initial phase-in period of 3-5 years and there would need to be specific enabling requirements in order to realise these goals

Although the goal is to synchronise authorisations in the region it must be recognised that the final licensing conditions may not fully be harmonised in all cases due to national considerations

Enabling factors within the Asia-Pacific Region

The following were proposed as factors that would facilitate the pilot study and the establishment of an Asia-Pacific regulatory network

- The establishment of more formal cooperation agreements in the form of Memoranda of Understanding (MoUs) between national agencies in the region and, particularly, with the 'pilot scheme' countries
- A transparent assessment of Agency staffing models, scientific review procedures and overall project management activities to ensure sharing of best practices and effective cooperation⁵
- A focus on confidence-building exercises to overcome possible 'discomfort' in exchanging review information
- The establishment of effective cooperation in PMS information exchange and consideration of a 'rapid alert' model for emerging problems as part of life-cycle management
- Promotion of a greater recognition of the disciplines of, and training in, clinical pharmacology and clinical research in the Asia-Pacific region

Enabling factors from outside the Asia-Pacific region

An expansion of open collaboration with selected benchmarking Agencies (e.g., FDA, EMEA, TGA) was proposed including:

- Improved 'real time' access to key documentation such as meeting protocols and assessment reports for targeted new applications selected for parallel review
- Sponsorship of joint training programs and the sharing of best practices in review management
- The need to detect and rectify serious misunderstanding about standard practices and requirements in the EU/US that might have an impact on local regulatory practices and act as a barrier to global development

F. 'Drug lag' as a strategic choice

Reducing the lag time in global registration of new medicines should not be viewed only as an issue to be addressed by regulatory agencies. Company policy may mean that the delay in registering medicines outside the 'ICH regions' is a matter of strategic choice based on marketing and commercial considerations as well as perceived practical barriers.

It is not always practical for a company to undertake a major new drug launch all over the world, within a short time-frame and there are, as discussed, clinical, regulatory, commercial supply and, in some cases, IP barriers that may influence strategies for global development.

2.2 Harmonisation of Technical requirements

G. Harmonisation of CTA requirements as a priority

In order to share assessment reports and approvals for clinical trial applications there needs to be agreement on a standard format for CTAs and on the requirements for the supporting data. The development of these must involve both regulators and companies. Agreement is also needed on the aims and essential features of the review process, including a common review template. Ideally there should be similar timings for review so that global and/or multi-country clinical trials can be synchronised.

⁵ The CMR International Institute Study on regulatory procedures in emerging markets is covering this, for selected countries in the region, in the current (2006-2007) third Phase of the project. This could provide a model for a more comprehensive study in the region

Harmonisation of the technical requirements for a CTA application and on a review template is essential for the success of *Recommendation A*, on streamlining clinical trial procedures. Reference was made to the success, in the EU, of adapting the CTD format for use with CTA applications.

Additional tools to facilitate information sharing include an Asian Clinical Trial Database and other electronic support for reviewers

As starting point for developing harmonised CTA requirements a survey should be carried out of current requirements across the Asia-Pacific Region⁶:

- This should include data from industry on both real and perceived requirements, according to their experience
- Information should be collected leading to recommendations on a common time-line for the review of CTAs in the region
- There should be an exchange of information with EU and US agencies on 'best practices' in their countries and regional workshops in Asia-Pacific at which these could be discussed with the 'benchmark' agencies

H. Harmonisation through ICH

There should be better representation of the Asia-Pacific region and the opportunity for active participation on ICH Working groups that have a major impact on regulatory procedures in the region, in particular, stability guidelines appropriate to all climatic zones and the need to address difference between the ICH Common Technical Document (CTD) and regional variations (ASEAN CTD)

It was further suggested that the ICH Global Cooperation Group (GCG), on which Asia Pacific is represented through APEC and ASEAN, should have, on its agenda, the initiatives arising from the EU Roadmap to 2010 and the US Critical Path. The agencies should consider active involvement, on relevant issues, particularly the CP 'Opportunities' list.

2.3 The impact on global drug development of ethnic and cultural differences

There was a general observation that (leaving aside the specific issues addressed in Recommendation G) there is the need for better regulatory guidance on incorporating foreign data into regulatory dossiers. It was noted that FDA launched an initiative to modernise its CT regulations in June, 2006 and that the FDA Critical Path list of 'opportunities' includes 12 specific research projects for streamlining clinical trials.

I. Survey on ethnic differences that have had a regulatory impact

The ICH E5 guideline on 'Ethnic factors' is still an active issue in determining the need for bridging studies as part of global registration strategies. An evidence-based initiative is needed with the ultimate goal of facilitating an update of the guideline. It would therefore be timely to carry out a survey, among companies and regulatory agencies on practical experiences of implementation of the guideline, on real and perceived differences in ethnicity that have led to bridging studies and on the relevance of the outcome.

The CMR International Institute for Regulatory Science would be the organisation of choice to carry out such a survey.

- The study would involve local regulatory agencies, through the proposed Asia-Pacific Network (Recommendation E) and the views of the pharma industry from both headquarters and local affiliates, as appropriate

⁶ Phase 3 of the Institute Study on the emerging markets (see footnote 5) includes data on clinical trial procedures but, again, the number of countries in the Asia-Pacific region is limited

- The survey should explore reasons for carrying out bridging studies and an analysis of findings and outcomes in order to identify pointers for increased harmonisation and efficiency

J. Integrating medical, scientific and cultural differences into clinical development

As alternative to bridging studies, companies should take time to learn about the essential medical, cultural and genetic differences relating to a new medicine and design a research protocol, incorporating the Asia-Pacific region, that can incorporate the differences.

In practice, the move to carry out clinical trials in the Asia Pacific region, irrespective of the underlying reasons, is a driving force to rationalise questions of ethnic factors and companies should not miss this opportunity.

There is increasing volume of data from 'non-core' countries in Western submissions which provides an opportunity for developing a truly global dataset, but this is wasted if ethnic differences are left unaccounted and are not measured and rationalised when presented for review.

It was noted, however, that differences in the practice of medicine and/or definition of disease states may make it difficult for data generated in the Asia-Pacific region to be accepted in by regulators in the EU and US. If so, this removes an important driver for moving more clinical development to Asia. It also has future implications, looking towards a time when new medicines are developed in Asia-Pacific for marketing in the west.

The following were among the factors identified as potential barriers to integrated global drug development:

'Practice of Medicine' Barriers

- **Differences in medical treatment**

Diseases may be treated differently in an Asia-Pacific country compared, for example, with the US but it is important to recognise there are also major differences in medical practice within Europe and within the United States. When planning studies in other regions, however, some considerations are:

- The need to 'reality test' the protocol to see if it is appropriate for the country and involve local key opinion leaders in the development
- The selection of comparator product for controlled trials: The target comparator may not be available on the local market
- There may be problems when looking for 2nd line or 3rd line oncology therapy in countries that do not use the expected 1st line therapy
- Herbal therapies are prevalent in Asia and may lead to unfamiliar drug-drug interactions and/or they may not be recognised as concomitant medication

- **Patient-physician relationships**

- The relationship between patient and physicians is different in Asia and may, perhaps, lead to a higher placebo effect
- Trials designed to meet Western agencies' requirements might not be acceptable in an Asian environment, for example, acceptance of placebo-controlled trials rather than using an active control
- The availability of patients' charts for source data verification can be an issue in China, for example, where patients carry their charts with them

Scientific Barriers (real or suspected)

- **Intrinsic physiologic differences in the Asian population**

Scientific work involving clinical pharmacologists and other key opinion leaders is needed to investigate whether differences in PK/PD and response rates are such that they limit the applicability of the results to other populations

- **Difference in disease states**

Further work is needed to confirm or refute the perception that there are tangible differences in some diseases (for example diabetes in Japan vs. the US and Europe) or whether this is a matter of medical culture.

2.4 Industry representation in the region

There was discussion of the need for the industry to become organised on a regional basis in order to be better aligned on the specific issues for Asia-Pacific. Reference was made to the European Federation of Pharmaceutical Industries and Associations, EFPIA as a model.

The meeting was informed an association, APRIA⁷, has recently been formed among industry associations. This is a regional association representing the common regulatory interests of the research-based pharmaceutical companies in ASEAN.

⁷ ASEAN Pharmaceutical Research Industry Association. APRIA members include the Industry associations from Indonesia (IPMG), Malaysia (PhAMA), Philippines (PHAP), Singapore (SAPI), Thailand, (PReMA) and Vietnam

WORKSHOP PROGRAMME

SESSION 1: THE CURRENT DRUG DEVELOPMENT ENVIRONMENT – REGULATORY AND SCIENTIFIC PERSPECTIVES	
Chairman	Dr Murray Lumpkin <i>Deputy Commissioner - International and Special Programs, Food and Drug Administration (FDA), USA</i>
Current strategies for global drug development – What are the options?	Dr Tadao Suzuki <i>Senior Managing Director, Head of R&D, Daiichi Pharmaceutical Co.,Ltd., DaiichiSankyo Group</i>
Early integration of Japan in Global Drug Development	
Agency perspective	Mr Akira Miyajima <i>Chief Executive, Pharmaceuticals and Medical Devices Agency (PMDA), Japan</i>
Industry perspective	Dr Bruce Schneider <i>Executive Vice President and Chief of Operations, Wyeth Research, USA</i>
Sharing information and scientific advice between agencies: What is the potential impact on improved global development?	
Agency perspective	Ms Melinda Plaisier <i>Assistant Commissioner for International Programs, Food and Drug Administration (FDA), USA</i>
Industry perspective	Dr Gabriele Disselhoff <i>Vice President, Global Regulatory Affairs & Clinical QA, Merck KGaA, Germany</i>
The impact of new markets in Asia on global development strategies	Dr Edmund Tsuei <i>Head, Pharma Development Operations, Asia-Africa/Deputy Head, Pharma Development Operations, Asia-Pacific-Africa, Roche, Australia</i>
Integrating Asia into clinical development strategies: Progress and perceived obstacles	Dr Neil McAuslane, <i>Director, Institute for Regulatory Science</i>
SESSION 2: GLOBAL CLINICAL DEVELOPMENT: THE CHALLENGES AND OPPORTUNITIES OF INTEGRATING JAPAN AND OTHER ASIAN COUNTRIES	
Chairman	Dr Paul Huckle <i>Senior VP, US Regulatory Affairs, GlaxoSmithKline, USA</i>
Acceptability of foreign clinical data between Asian countries	Dr Heng-Der Chern <i>Executive Director, Centre for Drug Evaluation, Taiwan</i>
The justification for bridging studies in South Korea	Dr Jung-Yun Chang <i>Deputy Director, Gastrointestinal, Urinary and Metabolic Drug team, Dept of Drug Evaluation, Korea Food and Drug Administration</i>

SESSION 2: GLOBAL CLINICAL DEVELOPMENT (continued)

Panel discussion on the challenges and opportunities when integrating Asian countries into global clinical development

Industry viewpoint - issues of acceptability of data

*Presentation prepared by **Dr Ed Harrigan**
Senior VP, Worldwide Regulatory Affairs and
Quality Assurance, Pfizer Inc., USA
presented by **Dr Hiroshi Matsumori**, Pfizer,
Japan*

Regulatory viewpoint – acceptance of foreign data by Western authorities

Dr Tomas Salmonson
*Acting Director. of Operations, Medical Products
Agency, Sweden*

Challenges and opportunities for integrating China into clinical development

Dr Zili Li
*Director, Clinical Research Operations-Asia
Pacific, Merck Research Laboratories, China*

Regulatory restructuring in the Asian region

Dr John Lim
*Chief Executive Officer, Health Sciences
Authority, Singapore*

SESSION 3: SYNDICATE DISCUSSIONS -

Chairman

Professor Robert Peterson, *Professor of
Paediatrics, University of British Columbia, Canada*

Syndicate discussions and reports

See report Part 2

Europe's role in facilitating global drug development

Mr Thomas Lönngren
*Executive Director, European Medicines Agency
(EMA)*

SECTION 3

EXTRACTS FROM THE WORKSHOP PRESENTATIONS

This Section will provide extracts and 'snapshots' from the information and views provided by the speakers at the Workshop as they relate to the discussion points raised in the Syndicate reports, Section 2

The section is not currently attached to this consultation draft as it is subject to clearance by the named speakers.