R&D Briefing No 37

CMR International

Adoption of the ICH E5 Guideline in Asia Pacific (excluding Japan)

Key Messages

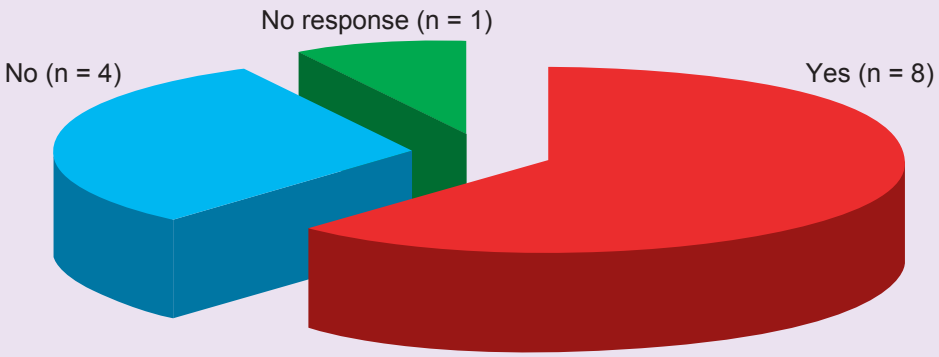
In 2001, CMR International conducted a study among pharmaceutical companies to evaluate their experience with regulatory authorities in Asia Pacific regarding the acceptance of foreign clinical data and adoption of the International Conference on Harmonisation (ICH) E5 guideline.

Two-thirds of the survey respondents are currently conducting or planning to conduct bridging studies as defined by ICH E5, some of which have been actively requested. The expected hurdles of using E5 in this region include resource constraints, misinterpretation, lack of Good Clinical Practice (GCP) compliance and lack of authorities' experience.

Anticipated benefits of using E5 include minimum duplication of studies, faster approvals, better-defined, planned and efficient clinical development, and authority assurance that drug response is similar in local populations.

Most companies are in favour of Asia Pacific authorities implementing the ICH E5 guideline to facilitate the acceptance of foreign clinical data, providing there is scientific justification, replacing local clinical trials.

Figure 1. Is your company routinely conducting clinical trials in Asia Pacific



Source: CMR International

Reference to Asia Pacific throughout this briefing excludes Japan and predominantly refers to the following markets: China, India, Korea, Malaysia, Singapore, Taiwan and Thailand

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References

1. International conference on harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised Tripartite Guideline (February 1998). "Ethnic Factors in the Acceptability of Foreign Clinical Data". Available at: http://www.ich.org/pdfICH/e5.pdf

2. Anderson C & McAuslane JAN (April 2002). "Utilisation, Strategies and Regulatory Acceptance of the E5 Guideline in non-ICH Asian Markets" CMR02-178R. Available at: http://www.cmr.org/institute/utilisation.html

3. Anderson C & McAuslane JAN (April 2002). "Utilisation, Strategies and Regulatory Acceptance of the E5 Guideline in ICH Regions" CMR02-177R. Available at: http://www.cmr.org/institute/utilisation.html

4. Anderson C, McAuslane JAN & Walker SR (October 2002). "The impact of the ICH E5 Guideline on global drug development" R&D Briefing No 36. Available at: http://www.cmr.org/institute/utilisation.html

Background

The ICH E5 Guideline was introduced in February 1998 and subsequently implemented by the regulatory authorities of the USA, EU and Japan. The purpose of this guideline is to facilitate medicine registration among the ICH regions by recommending a framework for evaluating the impact of ethnic factors on a drug's safety and efficacy while minimising clinical trial duplication.

Recent trends in the globalisation of new drug development have encouraged the need for greater harmonisation of procedures and requirements in Asia Pacific. As a result, some regulatory authorities in this region have adopted, among other ICH initiatives, the ICH E5 guideline (Table 1).

However, there have been concerns that there has been partial and conservative interpretation in the implementation of this guideline in Asia Pacific markets, which is clearly an important issue to address.

Table 1. Summary of guidance on the Ethnic Factors in the Acceptability of Foreign Clinical Data[1]

This guidance describes how a sponsor developing a medicine for a new region can deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Results from the foreign clinical trials could comprise most, or in some cases, all of the clinical data package for approval in the new region, so long as they are carried out according to the requirements of the new region. Acceptance in the new region of such foreign clinical data may be achieved by generating "bridging" data in order to extrapolate the safety and efficacy data from the population in the foreign region(s) to the population in the new region.

CMR International developed a 13-page questionnaire comprised of 21 questions in four sections based on background research with input from experts. The questionnaires were sent to 45 international companies of which 13 (including 8 of the top 12 companies by R&D expenditure in 2000) provided data (Table 2). The data has been analysed qualitatively and quantitatively and a report of the study[2] is available. This briefing outlines the key results from the study. A parallel study was conducted to examine the impact of E5 in the ICH regions. A report[3] and briefing[4] of the key findings from this study are also available.

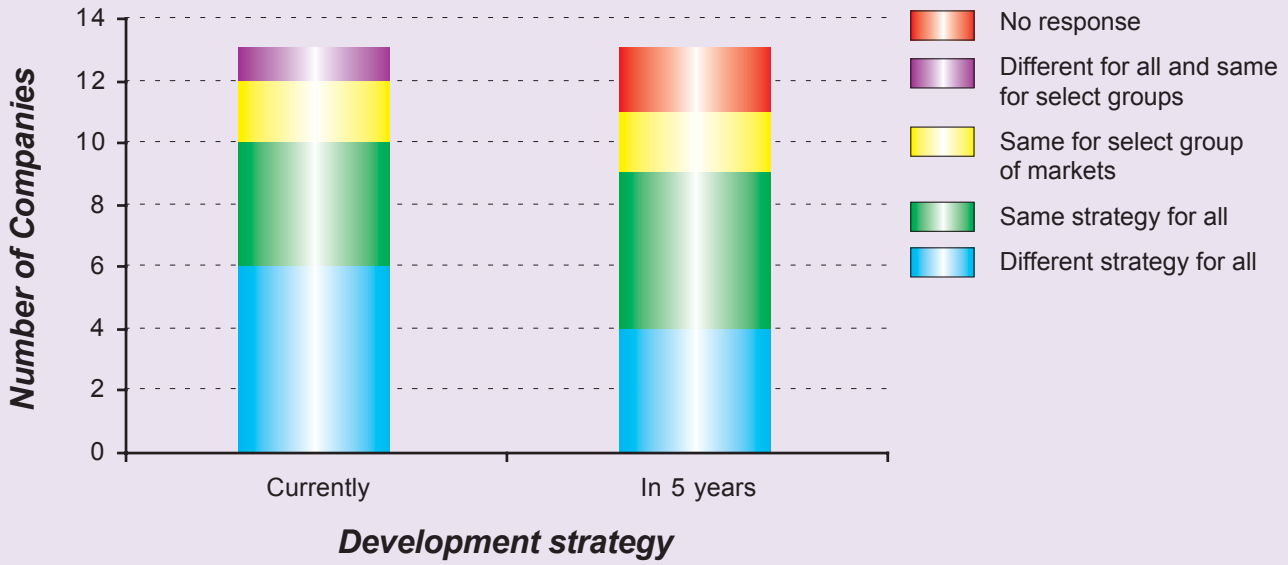
Table 2. Company participants

AstraZeneca Pharmaceuticals	*Lundbeck*
Boehringer Ingelheim Gmbh	*Novartis*
Bristol Myers Squibb	*NV Organon*
Eli Lilly & Company Ltd	*Pfizer*
Genzyme	*Pharmacia Corporation*
GlaxoSmithKline	*Wyeth*
Kyowa Hakko Kogyo Co Ltd	

New drug development in Asia Pacific

Companies' development strategy for Asia Pacific vary. However, over the next five years, more companies expect to have the same development strategy for each market in the region for speed, economy and in order to minimise duplicate development (Figure 2).

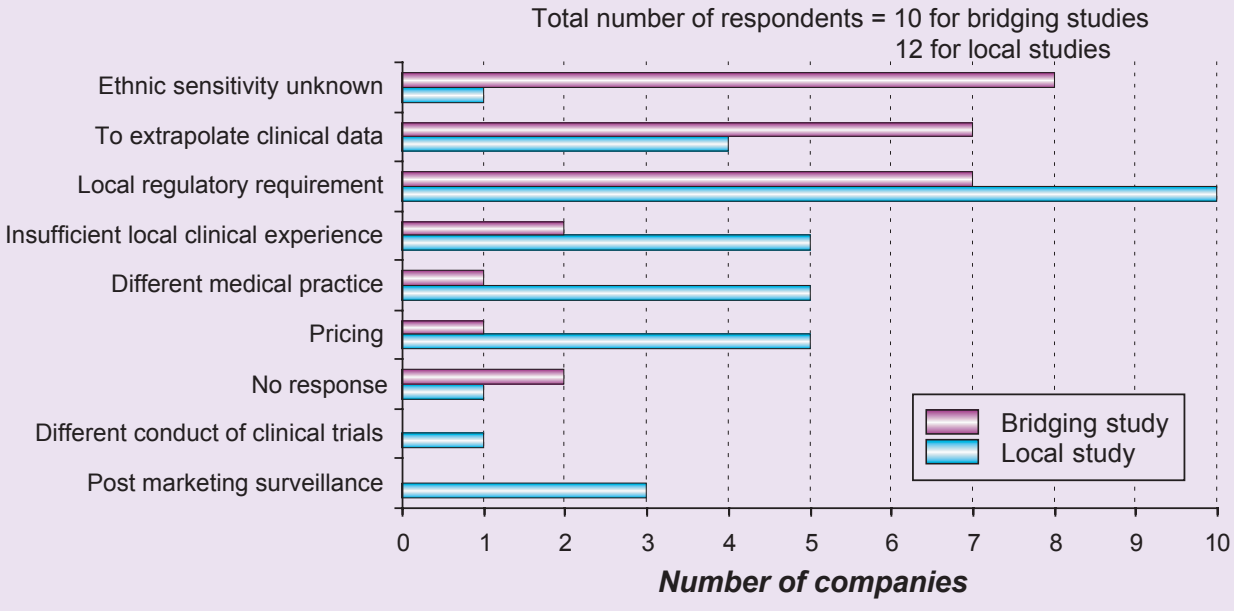
Figure 2. Companies' development strategy for Asia Pacific



Source: CMR International

Clinical trials are currently conducted by companies in Asia Pacific either during or after global phase III (6 companies) or after submission or approval in an ICH market (5 companies). However, over the next five years, companies believe they will begin development in this region earlier, involve more countries and may possibly incorporate some countries into their global development programmes.

Figure 3. Main reasons for conducting studies in Asia Pacific



Source: CMR International

The purpose for companies conducting studies in Asia Pacific are shown in Figure 3. The most common reason for conducting a bridging study is when the ethnic sensitivity is unknown. In contrast, the reasons common to conducting a local study are to meet local regulatory requirements, for pricing purposes, and when there is insufficient local clinical experience or different medical practice.

Clinical development routinely conducted by companies in Asia Pacific (Figure 1) include:

i) local studies for submission to the authority in which the study was conducted (8 companies);

ii) pivotal studies for submission to the authority in which the study was conducted (3 companies);

iii) pivotal studies to support submissions to the ICH regions (2 companies).

Foreign clinical data and bridging studies in Asia Pacific

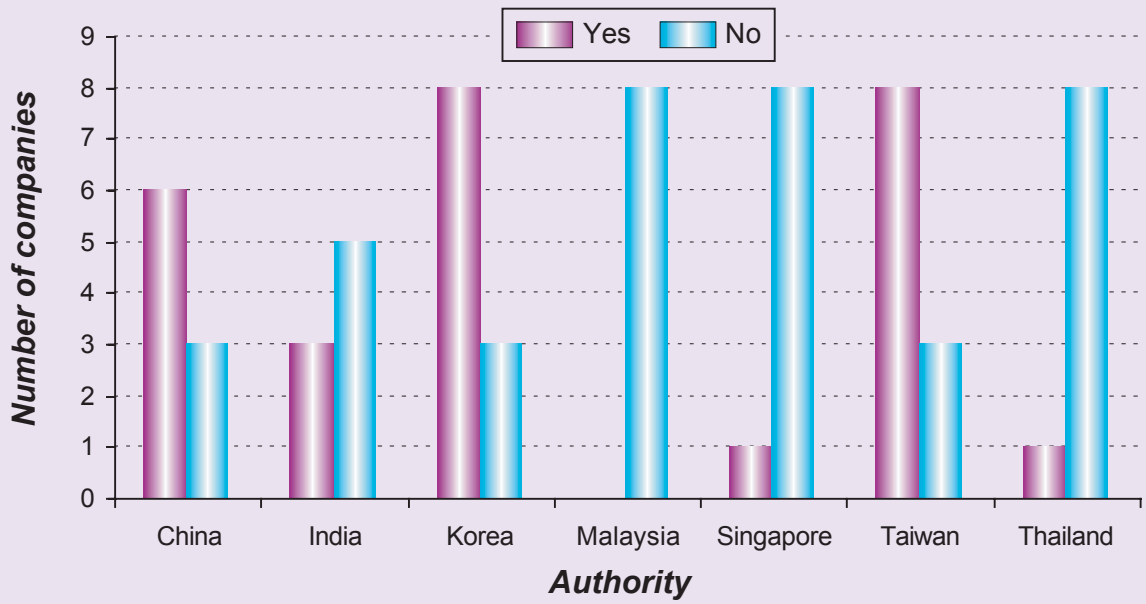
Six companies have been requested to conduct bridging studies during development by Asian authorities as defined by the ICH E5 guideline, the authorities in Taiwan and Korea being most frequently sited. Eight companies have examples of products for which they are planning to conduct or have already conducted a bridging study in Asia Pacific.

Most companies believe Asia Pacific authorities, particularly China and Korea, continue to request duplicate clinical development that is not scientifically justified.

Company consultation with Asian Pacific authorities

Companies most actively seek advice during drug development from the regulatory authorities in Korea, Taiwan and China (see Figure 4).

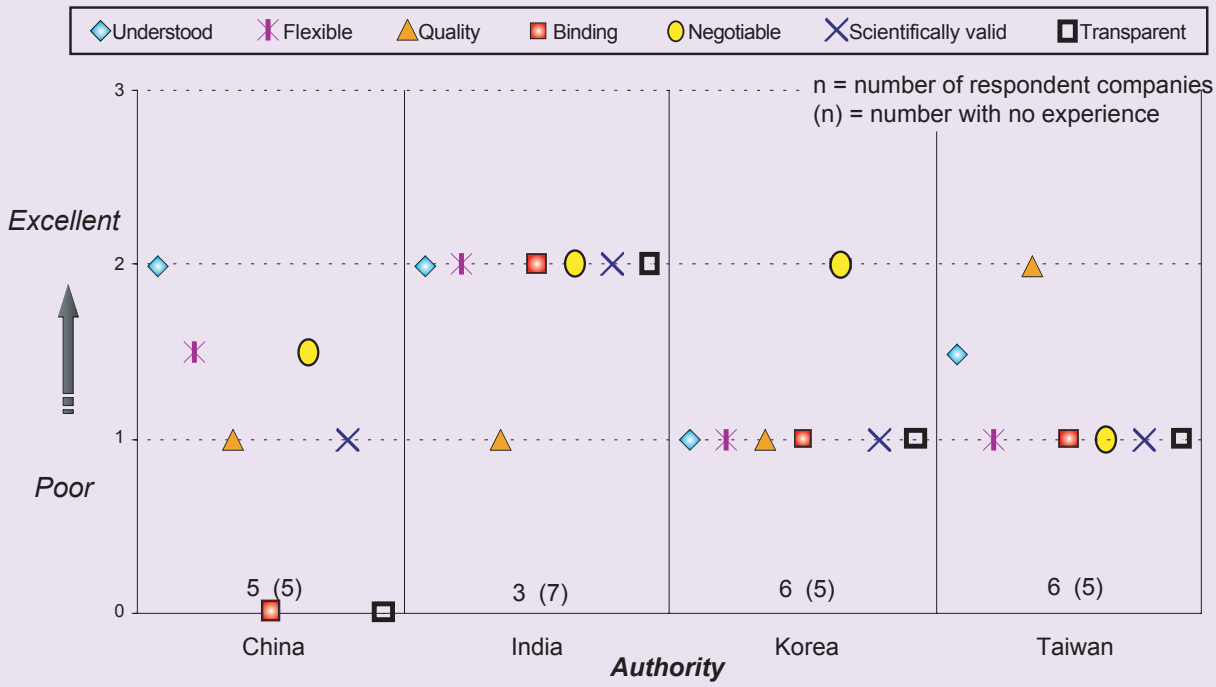
Figure 4. Consultation with authorities



Source: CMR International

Companies' experience of advice from the Korean and Taiwanese authorities has been fairly poor overall (Figure 5). However, advice from Korea has been negotiable and advice from Taiwan has been of good quality and reasonably well understood. Advice from China is considered to have been well understood, reasonably flexible and negotiable but has not been binding or transparent.

Figure 5. Companies' rating of advice from Asia Pacific authorities



Source: CMR International

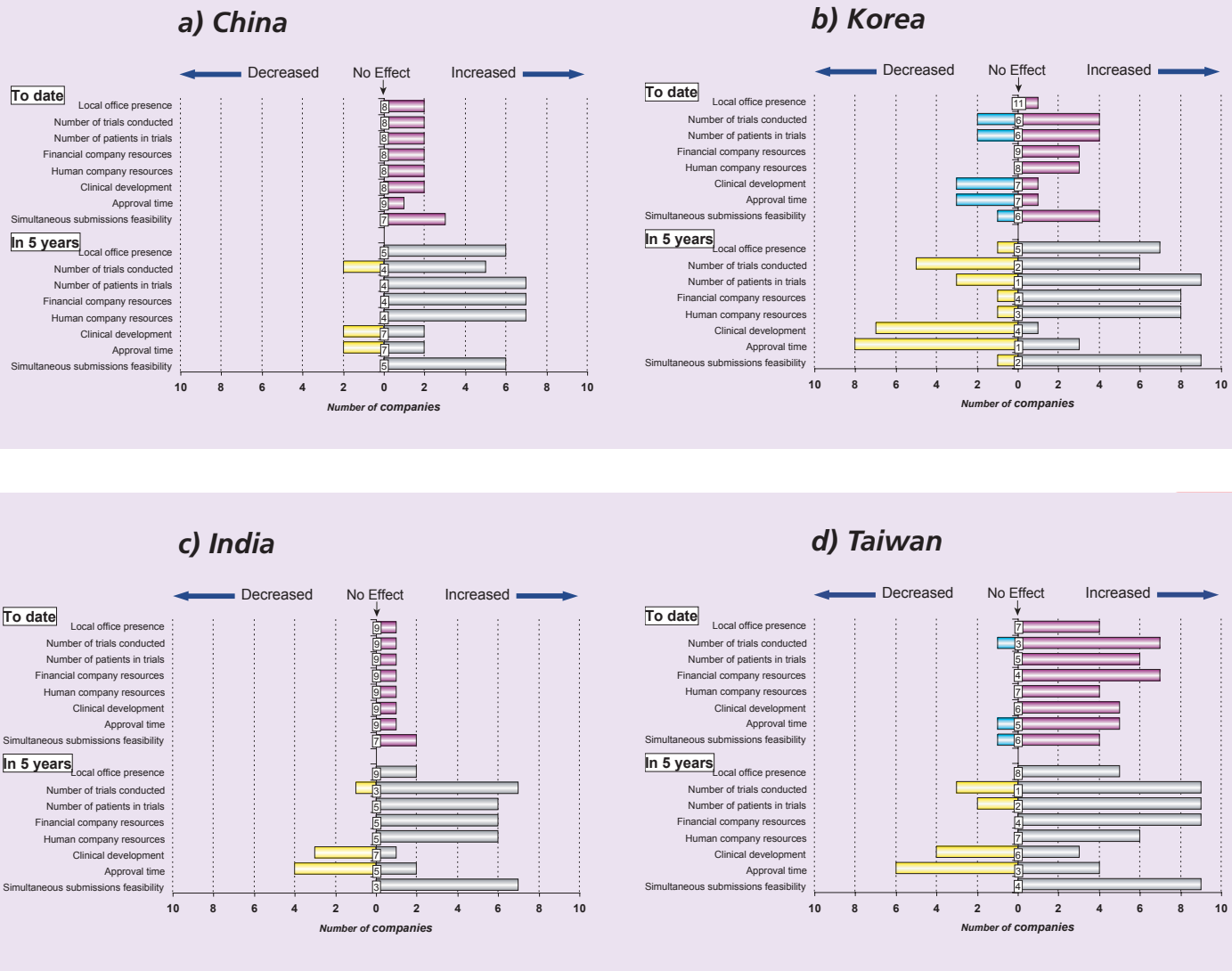
Should Asia Pacific implement ICH E5?

Most companies believe Asia Pacific authorities should implement the E5 guideline with scientific justification, perhaps replacing the current requirement for local trials. They also believe that E5 could truly facilitate the acceptance of foreign clinical data in this region, thereby reducing study duplication where there is no scientific basis.

The impact of E5 implementation in the ICH regions on companies & drug development in Asia Pacific?

Since the introduction of E5 in the ICH regions, there have been minor increases in the size and number of trials conducted by companies and in their human and financial resources in Korea (Figure 6b). In Taiwan (Figure 6d), there has been an even greater increase in these characteristics to date. In five years time more companies are expected to see the same impact not only in Korea and Taiwan but also in China and India (Figures 6a and 6c). These data reflect the situation as it was in 2001.

Figure 6. Impact of E5 in the following markets:



The benefits & hurdles of implementing E5 in Asia Pacific?

The anticipated hurdles of using E5 in Asia Pacific include resource constraints, misinterpretation, GCP compliance, lack of authorities' understanding, experience and knowledge and increased costs, development and approval times.

To favour the implementation of E5 in the region, the hurdles must be outweighed by the expected benefits, which are believed to include the following:

- Minimum duplication of studies - particularly of small local trials;
- Enabling Asia Pacific markets to be included in global development;
- Faster approvals;
- Authority transparency;
- Better defined, planned and efficient clinical development;
- Authority assurance that drug response is similar in local population.

Industry recommendations based on the study results

As follow-up to conducting this survey, CMR International held an industry discussion meeting in February 2002 to achieve the following objectives:

- Present the results of the study;
- Learn from companies experiences;
- Facilitate discussion on the recommendations for the future of E5.

At this meeting, attended by representatives from pharmaceutical companies who participated in the study, a number of key recommendations were made which are outlined below in Table 3.

Table 3. Industry recommendations for the way forward

Asia Pacific countries should be grouped according to their implementation and use of the ICH E5 guideline to date, i.e. i) those that have adopted the guideline; ii) those that have not; iii) those that have adapted the guideline
Need for agreement among all Asia Pacific authorities on a common guideline, its definitions and interpretation
If implemented, E5 should eliminate requests for local studies that are not scientifically justified
Consider establishing an accreditation system whereby hospitals, clinics and countries are certified based on agreed global standards, practices and processes - countries of excellence
Work more closely with local Asia Pacific authorities during development in order to better understand the issues
Industry should consider investing finance in educating and training reviewers in Asia Pacific authorities to improve understanding and implementation of the guideline
Begin collecting data on IND (Investigational New Drug) submissions (application, approval and marketing dates as well as dossier information) in order to monitor the impact of changes to the environment, including the implementation of the E5 guideline

Conclusion

Although Asia Pacific authorities have not officially implemented the ICH E5 guideline to date, some are requesting companies to conduct bridging studies as defined by E5. To enable utilisation of the guideline there is a need for education and understanding of the local issues through dialogue with the local authorities. Companies are in favour of these authorities implementing the guideline to facilitate the acceptance of foreign clinical data providing there is scientific justification as well as adoption as opposed to adaptation of the guideline.

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Bristol-Myers Squibb	Kyowa Hakko	Pharmacia	TEVA
British Biotech	Lilly	Procter & Gamble	Wyeth
Celltech	Lundbeck	Roche	

Recent Publications

Anderson C, McAuslane JAN & Walker SR (2002). Risk Management: the role of regulatory strategies in the development of new medicines; CMR International. For further information visit http://www.cmr.org/institute/risk.html

Hynes C, McAuslane JAN & Walker SR (2001). Fulfilling the potential of electronic interactions between the pharmaceutical industry and regulatory authorities: issues and initiatives; CMR International. For further information visit http://www.cmr.org/institute/characterising.html

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