

The impact of the ICH E5 Guideline on global drug development

Key Messages

The regulatory authorities in Europe, Japan and the USA implemented the ICH E5 guideline in 1998 to facilitate the acceptance of foreign clinical data.

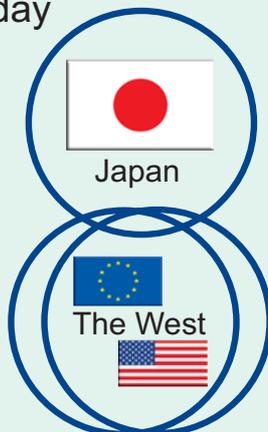
Hopes and expectations of E5 include expedited clinical development in the ICH regions, without significant delays in any one region.

In 2001, CMR International conducted a study among pharmaceutical companies operating in the ICH regions to ascertain the use, experience and implications of implementing the E5 guideline since its introduction.

Most companies are currently using the guideline but experience is limited and has been varied to date.

Despite some difficulties, future aspirations are promising with most companies expecting E5 to facilitate global development in the next five years with better understanding and regulatory acceptance of the guideline as a result of continuous dialogue, cultural change and greater experience over time.

Today



E5



In five years



Source: CMR International

Background

Index

Background	2
Are companies thinking or achieving global development	3
Interactions between companies & authorities on E5	3-4
The effects of E5 today & tomorrow	5
Benefits & hurdles	5-6
Industry recommendations based on the study results	6-7
Conclusion	7

Authors:

Carly Anderson
Neil McAuslane
Stuart Walker

October 2002

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/pdf/ICH/e5.pdf>
2. Thomas K & Walker SR (1997). "The Impact of ICH Efficacy Guidelines on the Clinical Development of New Medicines" CMR02-177R.
3. Anderson C & McAuslane JAN (April 2002). "Utilisation, Strategies and Regulatory Acceptance of the E5 Guideline in the ICH Regions" CMR97-57R.

The ICH E5 Guideline was introduced in February 1998¹ 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.

Since clinical trials are arguably the most complex, costly, time consuming and resource intensive aspect of drug development, this guideline is expected to have a significant impact on the pharmaceutical industry. A survey of companies from the three regions, which was conducted by CMR International in 1997, indicated that this guideline is also expected to have positive effects in terms of reductions in clinical trial patient numbers in Japan, as well as reducing costs and development times².

Companies have expressed concern that there has been conservative interpretation in the implementation of this guideline in Japan - the second largest pharmaceutical market in the world. This is clearly an important issue to address, especially in light of the radical changes in the regulatory and clinical development environments that have taken place in Japan in recent years.

Table 1. Summary of guidance on the Ethnic Factors in the Acceptability of Foreign Clinical Data¹

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.

A 17-page questionnaire was developed comprising of 35 questions in five sections based on background research and input from experts. The questionnaires were sent to 45 international companies (2001) and achieved a 70% response rate (including 9 of the top 12 companies by R&D expenditure in 2000) of which 17 companies (table 2) were able to provide adequate data. The data has been analysed qualitatively and quantitatively and a full report of the study³ was sent to all participant companies. Key survey results are outlined in this briefing.

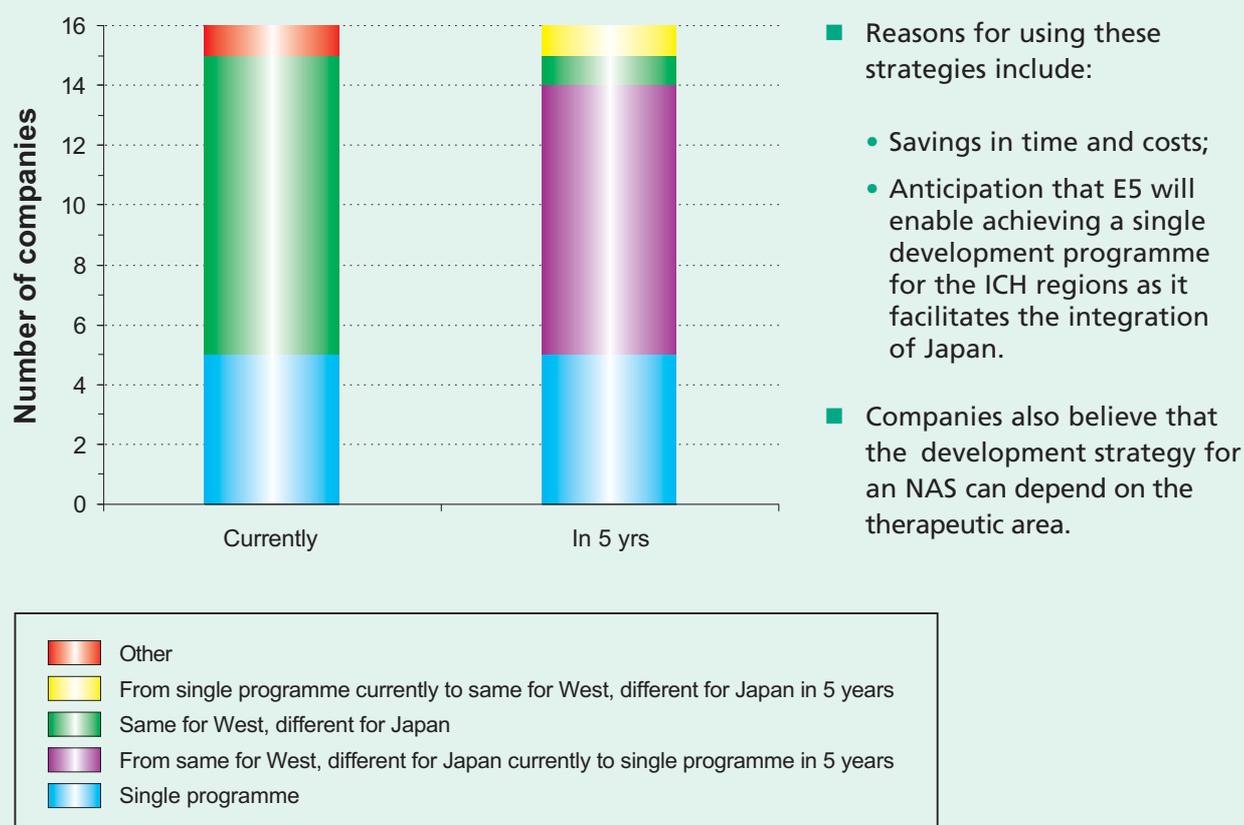
Table 1. Company participants

AstraZeneca Pharmaceuticals	Pfizer	Procter & Gamble
Eli Lilly & Company Ltd	Bayer	Bristol Myers Squibb
NV Organon	Genzyme	Kyowa Hakko Kogyo Co Ltd
Aventis Pharmaceuticals Inc	Pharmacia Corporation	Wyeth
EntreMed	Boehringer Ingelheim GmbH	Daiichi
	GlaxoSmithKline	Novo Nordisk A/S

Are companies thinking or achieving global development?

In practice, most companies' (63%) current strategy for New Active Substance (NAS) development is to have one development programme for the West and a different programme for Japan with data generation and submissions being made sequentially in the ICH regions (figure 1). However, in five years time, companies hope to have one development programme with simultaneous data generation and submissions for all three ICH regions.

Figure 1. NAS development strategies for the ICH regions



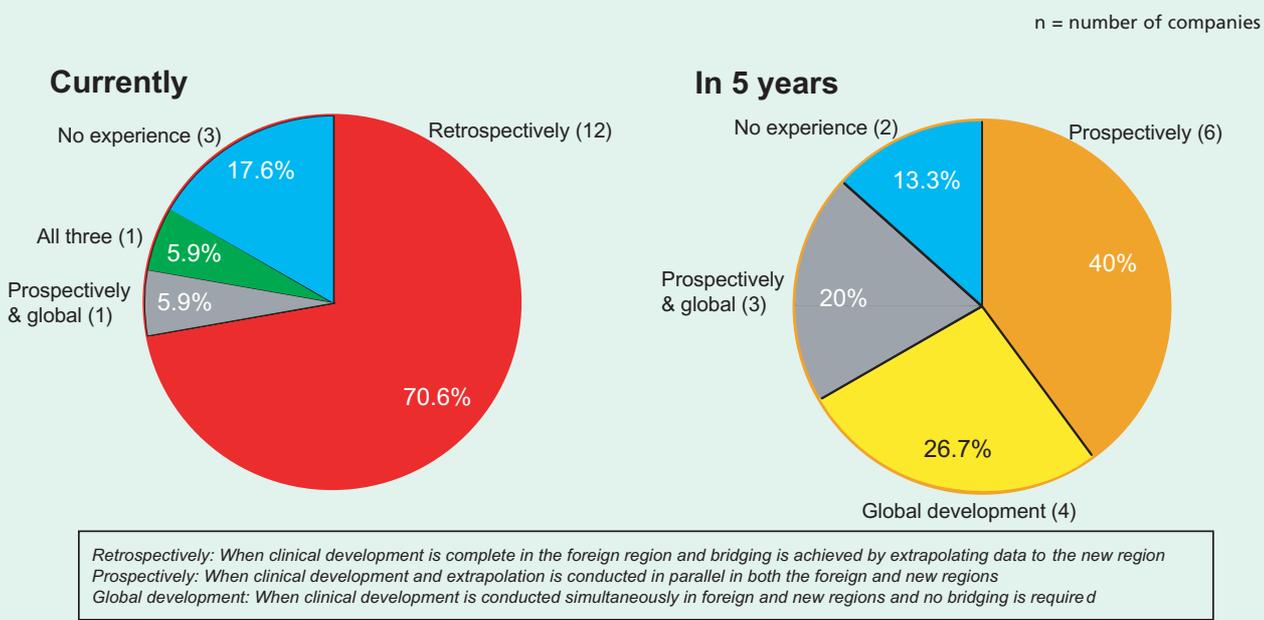
Source: CMR International

Supporting evidence that companies are moving towards global development is the fact that the priority for seeking product registration in Japan has increased for a number of EU and US-based companies (9 out of 15) since the implementation of E5.

Is E5 being used?

Industry's primary driving force for implementing E5 has been to achieve shorter and more efficient development times. The E5 guideline has the potential of enhancing the opportunity of global development with minimal delays. Already a number of companies (14) have used the guideline since its introduction. Those that have not yet used it because they have not had compounds at the relevant stage of development expect to do so in the next five years.

Figure 2. In five years time, companies believe they will no longer bridge data retrospectively

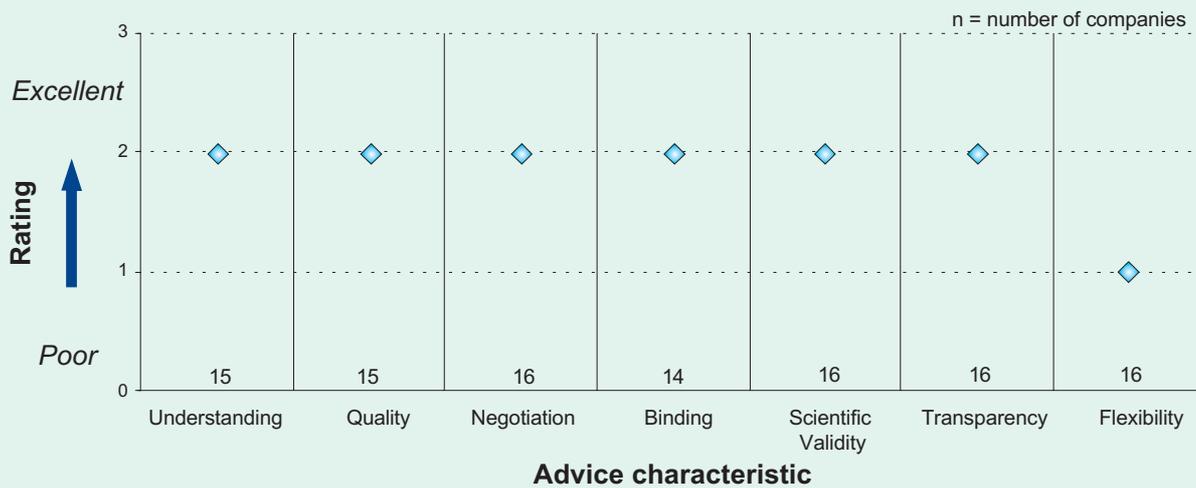


Source: CMR International

E5 is currently being used in most cases to retrospectively bridge data from a foreign to a new region (figure 2). However, in five years time, companies believe that they will be either bridging data prospectively, or will be conducting full global development in all three ICH regions, perhaps removing the need for bridging altogether.

Interactions between companies and authorities on E5

Figure 3. Companies' rating of advice from KIKO



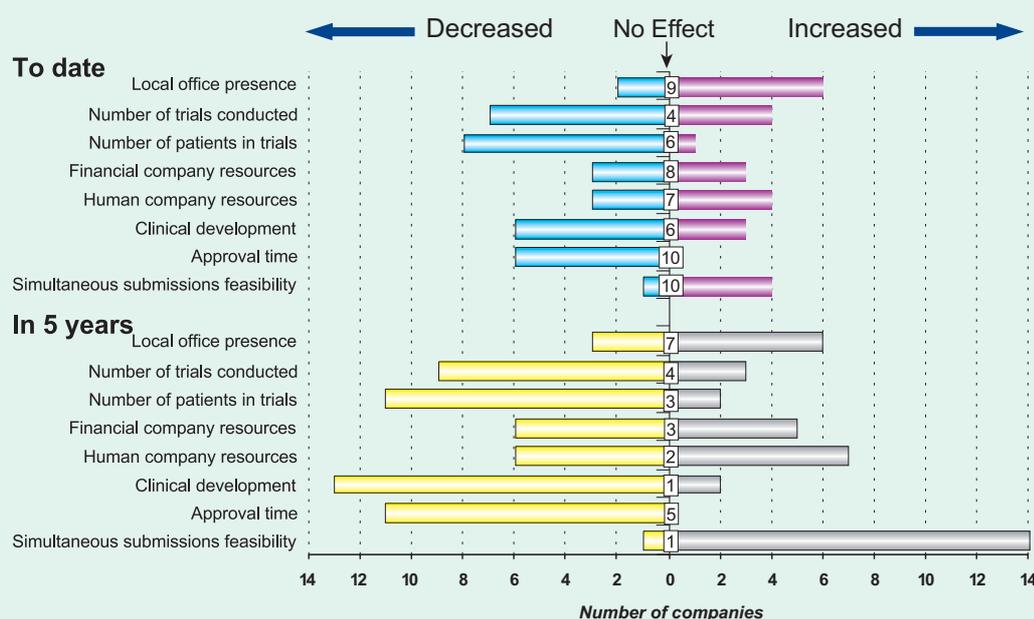
Source: CMR International

The recent restructuring of Japan's Ministry of Health, Labour and Welfare (MHLW) and the creation of Organisation for Pharmaceutical Safety and Research (KIKO) together with the adoption of the E5 guideline has encouraged increased dialogue with companies and improved their experience of advice received. The majority believe that KIKO is currently providing advice that is well understood, of good quality, scientifically valid, negotiable and transparent (figure 3). However, companies believe there is still little flexibility in the advice they receive from KIKO.

The effects of E5 – today and tomorrow...

In general, most companies believe that E5 has had very little effect on the size and number of trials conducted in the EU and US or on companies' presence, resources and development times. These elements are not expected to change in these regions over the next five years. However, companies have seen overall improvements in Japan where the size and number of trials conducted have decreased as have companies' development and approval times (figure 4).

Figure 4. Impact of E5 on companies operating in Japan



Source: CMR International

To ascertain companies' perception as to whether or not E5 is working effectively companies were asked if they believe that the potential of E5 has been realised by their company. Responses were evenly split between yes and no. Clear understanding of the guideline by industry is believed to be true for 66% of companies but they are divided in their perception of regulators' understanding. Furthermore, 57% of companies do not believe that E5 is truly facilitating the acceptance of foreign clinical data.

What is encouraging is that the possibility for simultaneous submissions in all three ICH regions is believed to have increased for some companies since implementation of the guideline and this is expected to be true for many more companies over the next five years.

Benefits & hurdles

Those companies who participated in the study believe that the hurdles of E5 encountered to date include:

- misunderstanding;
- lack of experience;
- conservative views;
- reluctance to accept E5 concepts;
- cultural and clinical practice differences;
- lack of GCP centres in Japan.

Most (80%) companies believe that E5 is not being used to its full potential throughout industry and the majority (73%) believe that Japan continues to request scientifically invalid clinical development; further exploration is needed to ascertain the reasons for these findings.

Despite continued difficulties in the acceptance of foreign clinical data in ICH regions companies do believe there are benefits of using E5. These benefits all of which will save industry time and costs, include:

- elimination of duplicate trials;
- more efficient development and approval;
- ability to create a global plan;
- facilitation of global simultaneous submissions.

Industry recommendations based on the study results

As follow-up to conducting this survey, CMR International held an industry discussion meeting in 2002 to enable companies to share experiences of using the E5 guideline and to produce recommendations for improving companies success with the guideline.

The meeting was attended by representatives from pharmaceutical companies who participated in the study. Table 3 and 4 outline the key recommendations that were made.

Table 3. Industry recommendations for companies

Internally

To better manage and communicate the expectations of E5 within companies, as it is believed a divergence exists between project managers and regulatory staff internally.

To consider the needs for Japan early during development (in parallel to West) to enable simultaneous submissions and to manage the increased resources that may be required.

The need for company-wide agreement on the development and submission strategy for the ICH regions, particularly from project managers to ensure strategies are achieved without concerns that Japan will be the rate limiting step.

Externally

To consider investigator training of Good Clinical Practice standards.

To increase the feedback between companies and regulators on the advice given and received in order to learn from experiences and improve communication, understanding and relationships.

To encourage phase IV study commitments post launch to reduce agency concerns over safety issues during the approval process when limited data is available.

Table 4. Industry recommendations for the way forward

To continually monitor the implementation of E5 by industry & authorities to ensure guidance is being followed. Greater information on the types of study that are included in submissions and whether or not submissions are made simultaneously to any additional regions may also be of value.

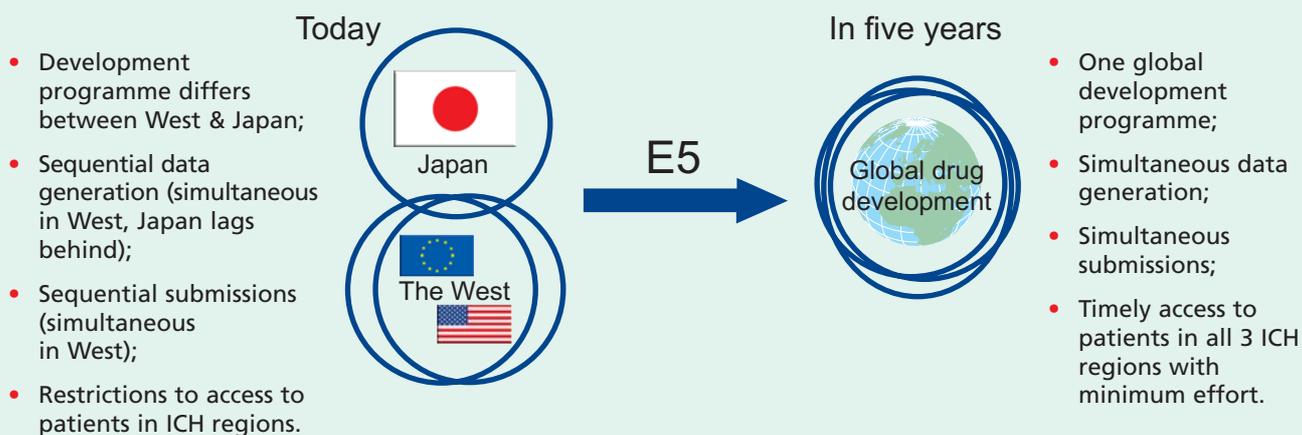
To look at a subset of simultaneous submissions and measure the consistency and predictability of regulatory review decisions by reviewing the questions asked by agencies to companies, which will also help to assess the quality of the review.

To establish a regular forum for debate for a small, targeted and focused group of industry and regulators to enable two-way discussion on the use of E5 in the ICH and non-ICH regions. Addressing the ICH with non-ICH regions would be beneficial, as there will be some correlations that can be made and lessons and experiences that can be transferred.

Conclusion

In conclusion, companies are using E5 but experience is limited and has been varied to date. Despite a number of hurdles that need to be overcome the future looks promising. Most companies are expecting E5 to bridge the gap between today's segregated development and global development in the next five years with better understanding and regulatory acceptance of the guideline as a result of continuous dialogue, cultural change and greater experience over time (figure 5).

Figure 5. Drug Development of the Future



Source: CMR International

If synchronised global development is to become a reality, Japan must be integrated into plans for the West early during development, which can be facilitated by using the ICH E5 guideline.

In addition to the study reported in this briefing, research has been conducted to examine the adoption of the ICH E5 guideline in non-ICH Asian countries. An R&D briefing of this study will be published towards the end of 2002.

"To establish a thought leadership role in the development and implementation of regulatory policy in the field of medicines innovation."

The CMR International Institute for Regulatory Science has been set up as a not-for-profit division of the Centre for Medicines Research International Ltd to continue its work in the regulatory and policy arena and to maintain the well established links the Centre has with regulatory authorities around the world. The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

Members of the Regulations Advisory Board

Dr David Jefferys - CEO, Medicines Device Agency, UK (Chairman)

Prof Gunnar Alván - Director General, Medicines Products Agency, Sweden

Dr Leonie Hunt - Director, Therapeutic Goods Administration, Australia

Dr Murray Lumpkin - Senior Associate Commissioner, Food & Drug Administration, USA

Dr Thomas Lönngren - Executive Director, EMEA, Europe

Dr Robert Peterson - Director General, Health Canada, Canada

Dr Hans Stocker - Director, Swiss Agency for Therapeutic Products, Switzerland

Dr Clarence Tan - Chief Executive, Health Science Authority, Singapore

Dr Kathy Zoon - Director, Food & Drug Administration, USA

Dr Graham Burton - Senior VP, Global Regulatory Affairs & Quality Assurance, The RW Johnson Pharmaceutical Research Institute, USA

Dr George Butler - VP & Head of Regulatory Affairs, AstraZeneca Pharmaceuticals, UK

Dr Mike Clayman - VP of Global Regulatory Affairs, Lilly Research Laboratories, USA

Dr Alexander Giaquinto - Senior VP Worldwide Regulatory Affairs, Schering-Plough Research Institute, USA

Dr Stewart Geary - Director, Medical, Regulatory Affairs & Pharma, Eisai Co. Ltd., Japan

Dr Christopher Towler - Director of Strategy Development, Imperial College London, UK

Prof Stuart Walker - CEO, Centre for Medicines Research International Ltd., UK

Members of the Institute for Regulatory Science

Allergan	Chugai	Merck & Co Inc	Sankyo
AstraZeneca	Eisai	Merck KGaA	Sanofi-Synthelabo
Aventis	Ferring	Millennium	Schering AG
Bayer	Fujisawa	Novartis	Schering-Plough
Boehringer Ingelheim	GlaxoSmithKline	Novo Nordisk	Servier
Bristol-Myers Squibb	Johnson & Johnson	Pfizer	TAP
British Biotech	Kyowa Hakko	Pharmacia	TEVA
Byk Gulden	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>

Hynes C, McAuslane JAN & Walker SR (2001). Building quality measures into the regulatory review process: assessing the needs of industry and regulators; CMR International. For further information visit <http://www.cmr.org/institute/qualitymeasures.html>

For further information please contact: Carly Anderson

CMR International Institute for Regulatory Science

Novellus Court 61 South Street Epsom Surrey KT18 7PX UK

Tel: +44 (0)1372 846100 Fax: +44 (0)1372 846101 Email: cmr@cmr.org Web: www.cmr.org