

# R&D Briefing

## Current strategies in Global Drug Development

43

### Survey on

#### **Regulatory factors that impede or assist the global development of medicines**

undertaken by the CMR International Institute for Regulatory Science

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**Centre for Medicines  
Research International  
Institute for Regulatory Science**

The CMR International Institute for Regulatory Science has been established as a not-for-profit division of the Centre for Medicines Research International Ltd, in order to continue CMR's work in the regulatory and policy arena and to maintain the well-established links that the Centre has with the pharmaceutical industry and 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 (see back cover)

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## Current strategies in Global Drug Development

A summary of the outcome of a survey carried out by the CMR International Institute for Regulatory Science among pharmaceutical companies.

### Key points

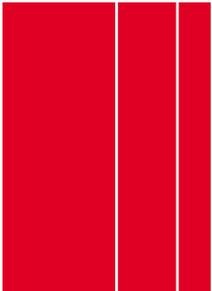


Although the pharmaceutical industry is moving towards integrated global development of new medicines and simultaneous submission to regulatory authorities, this has yet to be achieved routinely and, for many companies, remains a vision for the future.

The need for additional clinical programmes, coupled with companies' development and filing strategies have resulted in the so-called 'Japan gap' whereby patients in Japan may not have access to new products until two or more years after marketing in the US and Europe.



The majority of companies predicted that, by 2010 they would be filing new drug applications simultaneously in the three ICH regions, but the current situation shows applications first being filed in the US and Europe, with submissions to Japan being much later in the order of filing, after Canada, Australia and other countries. Some 60% of companies reported that they filed applications more than two years after the first submission in the rest of the world.



When asked about clinical development strategies in an 'ideal' scenario where clinical endpoints were not an issue, 70% of companies indicated that, in the current environment, they would carry out an integrated development programme in the US and Europe with development in Japan at a later time. For 75% of companies, however, the vision for 2010 was for integrated development with the same clinical protocols in all three regions.



Asked about perceptions of the major barriers to global development the issues that were identified as most serious were differences in medical practice and culture, the cost of patient recruitment, clinical trial infrastructure, regulatory hurdles and patient availability.

Productive communications with regulatory agencies are a key factor in achieving global development strategies. The survey found that the US FDA was the agency most frequently consulted, especially at the pre-clinical stage. For all agencies (US, EMEA, EU Member States and Japan) consultations were most frequently held at end-of-Phase 2 and at the pre-submission stage.

Of concern is the high percentage of companies (87%) that had experienced significantly differing scientific advice from different agencies. The areas highlighted were clinical endpoints, comparator agents and dose levels.

It was apparent that industry would welcome discussions on a fundamental paradigm shift to move away from the 'traditional' approaches to drug development and review. This might include the integration of risk management plans into drug development in order to reduce Phase III studies, and the establishment of a globally coordinated safety database. The ultimate aim, however, would be to move towards joint reviews and decision-making.



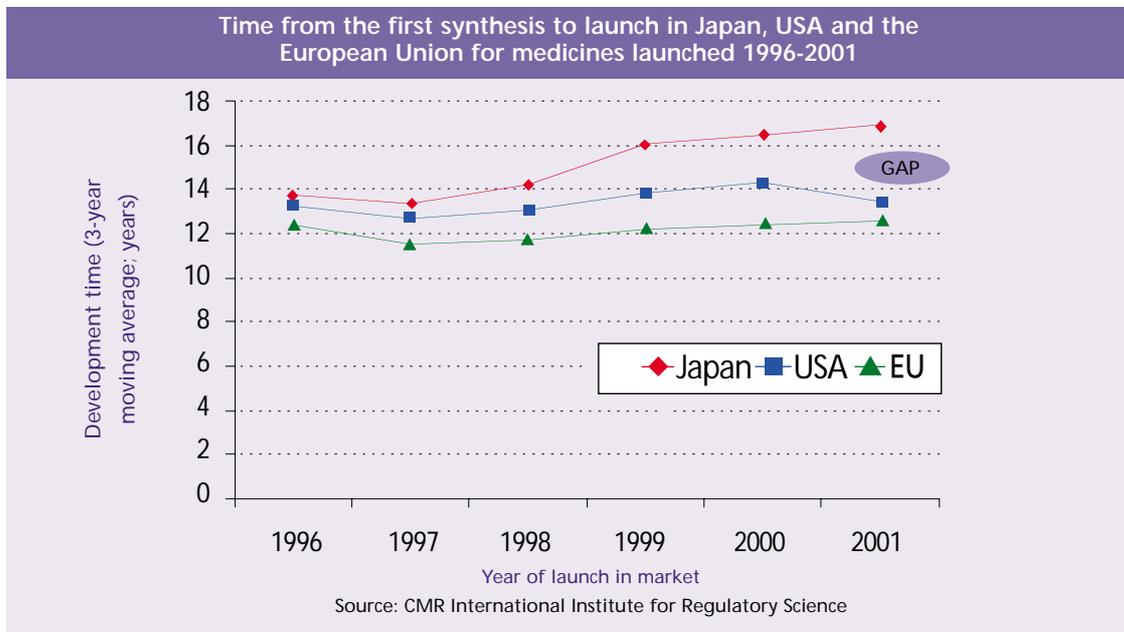
## Background



Simultaneous development of new medicines and concurrent submissions in the three main ICH regions is the goal of most major pharmaceutical companies. The integration of Japan into global development plans has, however, been a relatively recent development for some companies, but harmonisation initiatives and the adoption of the ICH guidelines by agencies mean that this is now achievable.

Historically, companies first adopted an integrated approach to development and registration in the US and Europe, in advance of clinical development for submission to the authorities in Japan. The lag time between the first human dose anywhere in the world and the start of clinical studies in Japan has resulted in the so-called 'Japan Gap' which, as shown in Figure 1, meant products were reaching the market in Japan between two and four years later than in the US and Europe. Patients in Japan were therefore waiting a considerable time to benefit from new medicines launched in other major markets.

figure 1



## CMR International Institute Survey

The 'Japan Gap' was one of the items investigated in a survey on Current Strategies in Global Drug Development carried out by the CMR International Institute, in preparation for the Workshop on Global Drug Development held in Tokyo, May 2004<sup>1</sup>. Responses to the survey were received from 17 multinational pharmaceutical companies, which included eight out of the top 15 (classified by R&D investment).

**Objective:** To identify companies' current development strategies and their perception of the regulatory and clinical factors that are a help or a hindrance in pursuing the goal of global drug development.

The survey had three sections:

**Section 1:** Submission and development strategies.

What does global drug development mean today; How close to integrated drug development and simultaneous submission is the industry now; Where will it be in 2010?

**Section 2:** Regulatory strategies, interactions and issues

What does a current 'regulatory development roadmap' look like for simultaneous development today, where are the hurdles and what are the practical solutions?

**Section 3:** Looking towards the next 10 years,

With advances in technology, continuing resource constraints and increased globalisation, what would an ideal regulatory landscape look like and how could this be achieved?

*In the context of this study, the majority of questions relate to a company's general strategy for activities in the ICH regions (Europe, Japan and USA) that encompass the generation, submission and review of data for a new medicine*



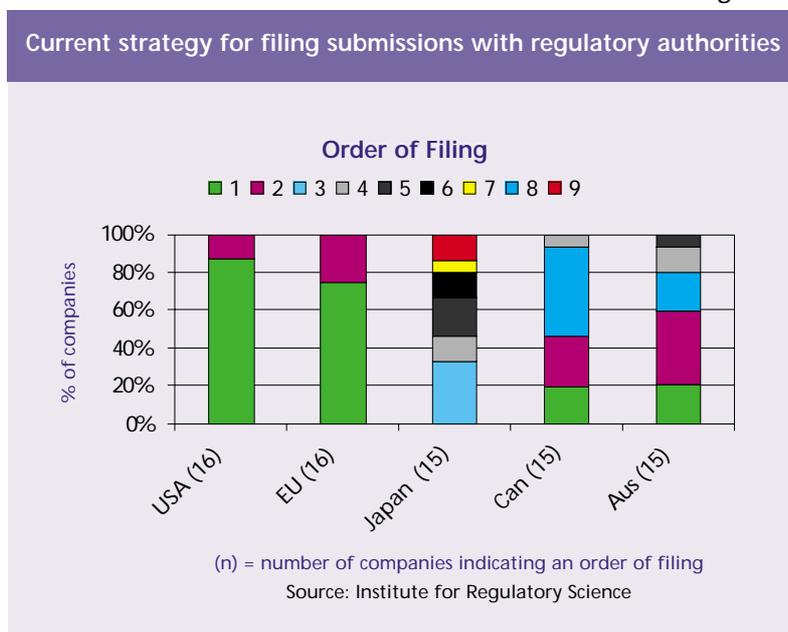
# Submission strategies



## Timing and sequence of submissions

Asked about strategies for the timing of submissions to regulatory authorities in the three ICH regions, about one third of companies gave simultaneous filing as their current preference, one third indicated a sequential approach and the remainder preferred to decide on a case-by-case basis. When asked to predict their strategy in 2010, however, the vision of the large majority of companies was that they would be filing simultaneously in the three regions.

figure 2



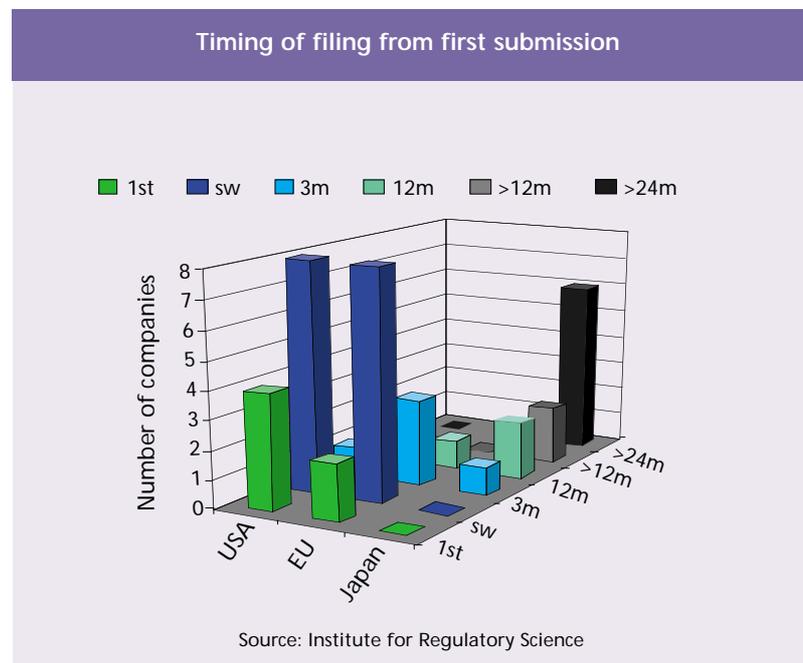
When the order of filing was examined (Figure 2) it was found that a large majority of companies submit to the US and Europe first and this is often followed by submissions to Canada and Australia. Applications were rarely, if ever, submitted to Japan as the first country and, for many companies, it appears that Japan is fourth to sixth or even ninth in terms of the order of filing applications.

Asked about the extent to which differences between agencies (e.g., the availability of fast tracking in the US) was a consideration in determining the filing strategy 15 of the 17 companies agreed it was a factor, of which two indicated it was a key driver.

figure 3

When the timing of submissions was examined (Figure 3), a similar pattern emerged with applications often being filed within the same week (SW), in the US and Europe, whilst some 60% of companies reported that they had filed applications in Japan more that two years after the first submission in the rest of the world.

All respondents believed that their submission sequence and timing will differ in 2010, moving towards simultaneous submission and a closing of the international market gap.





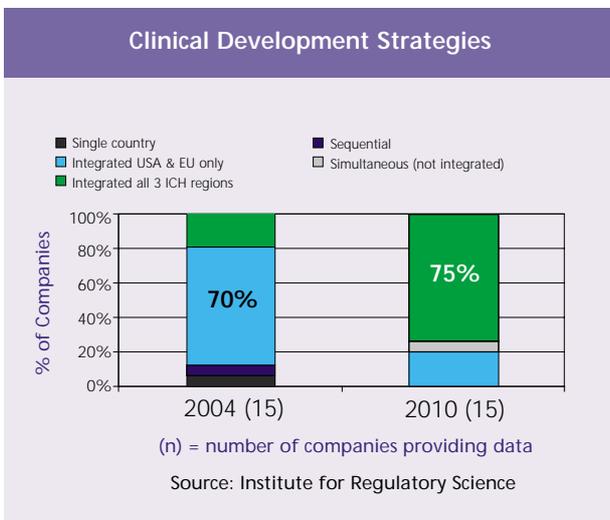
# Development strategies

## Clinical development strategy

Companies were presented with the scenario of a compound coming into development for which the clinical endpoints are harmonised and acceptable in the three ICH regions. They were asked which of the clinical development strategies shown in Figure 4 were most likely to be adopted at present and for compounds entering the development pipeline in 2010. Seventy percent of companies indicated that they had an integrated approach but only for the US and Europe. It is not, however, only Western companies that are studying new drugs in the US and Europe first and then bridging into Japan at a much later stage; Japanese companies are also following this strategy.

For 75% of companies the vision for the future (2010) is a single global development plan with simultaneous data collection and submission, allowing timely approval and access to new medicines for all patients.

figure 4



### Key

#### Single country/region only

An independent programme aimed at registration in only one ICH region

#### Sequential development

The new active substance (NAS) being developed for all ICH regions, but in one country/region at a time

#### Integrated development in USA and Europe with development for Japan at a later time

A pre-defined programme using the same protocol, with the same expected claims. Data generated by one region is pivotal in submission to the other

#### Simultaneous but not integrated

The NAS is developed in parallel in all three ICH regions with the intention of filing in each within a 12 month period, but not using integrated data

#### Integrated development the three ICH regions

Definition of integrated development as described above

## Clinical development in Japan

Companies were asked to indicate the type of studies (full, integrated or bridging) that they believe are essential for each Phase of clinical development, in order to register products in each of the three ICH regions. An analysis of the results for clinical development in Japan is given in Figure 5.

figure 5

### Key

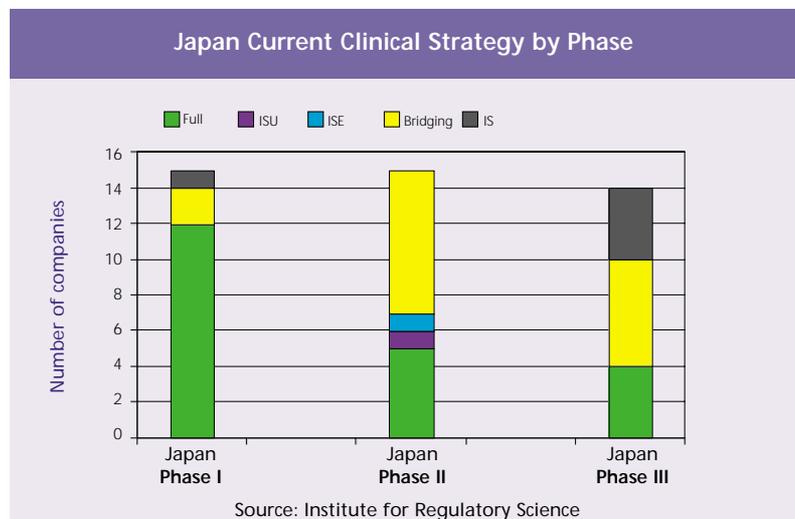
**Full:** full studies conducted solely in the region

**Bridging:** bridging studies conducted solely in the region

**IS:** integrated studies (one protocol across more than one region) involving all three regions

**ISU:** integrated studies involving only Japan and USA

**ISE:** integrated study involving only Japan and EU





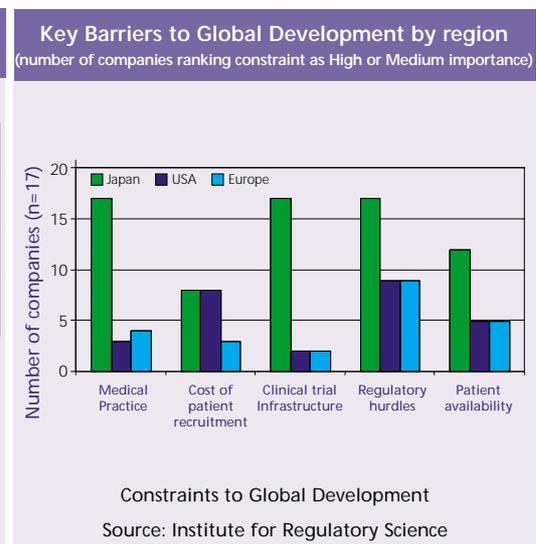
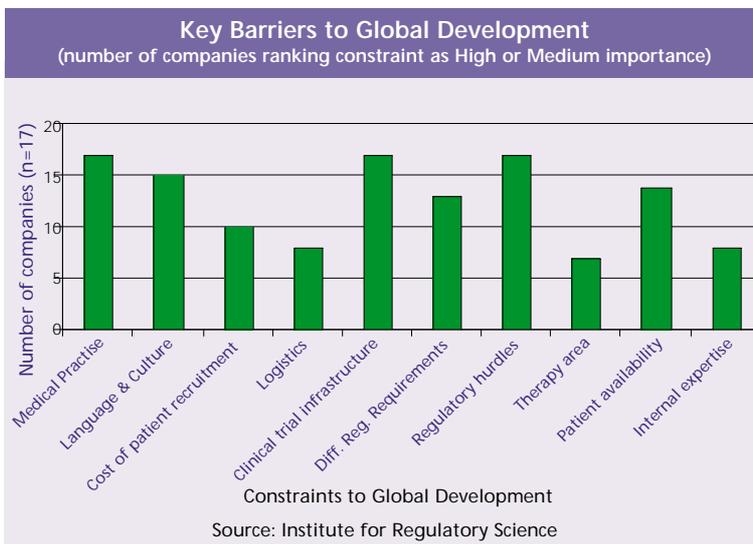
# Barriers to global development



In the Survey, companies were asked about the key constraints in undertaking a global development strategy in the ICH regions. A list was suggested and respondents were asked to rank them as high, medium, low and zero importance. The overall results are shown in Figure 6. The potential barriers were differentiated according to their importance in the US, Europe and Japan and the results, by region are given in Figure 7.

figure 6

figure 7



In addition, companies were invited to identify other obstacles and, specifically the major regulatory hurdles in the way of global drug development. Some of the points identified in the responses are highlighted here:

### ICH Harmonisation

- Objectives not yet fully achieved:
- The ICH E5 guideline is subject to restrictive and differing interpretation
- A more aggressive focus required on CMC in the ICH process
- Need to cascade information on ICH progress effectively throughout the agencies to reviewers not directly involved in the harmonisation decisions

### Scientific Advice

- Scientific advice given by different agencies during a global drug development programme is not harmonised
- Simultaneous requests for scientific advice and better communication between agencies would help
- Advice given by authorities should be binding

### Transparency of the review process

- Regular feedback on the progress of reviews
- Earlier scientific discussion to permit post marketing issues to be handled better

### Communication with regulatory agencies

- More flexibility and cooperation in arranging meetings between health authorities and companies
- Lack of awareness by regulators of new technologies
- Over-conservative attitude to biomarkers and surrogate end points

### Medical/Clinical

- Harmonisation of definitions for diseases and clinical endpoints for pivotal trials is advocated
- Issues with the size of clinical trials and more flexibility is needed in relation to CT design
- Acceptance of foreign clinical data, the use of bridging studies and the need to repeat pivotal studies remain an issue

### Regulatory review

- Assessment of risk and benefit to take account of medical need and the size of the target patient population
- Extension of programmes for exchange of regulatory information and of personnel among the major agencies
- Need for increased commitment to agreed evaluation timelines, by agencies

### Policy and politics

- Social and economic constraints on the Regulatory Bodies
- System that allows differing Scientific Advice given by EU member states and the EMEA/CHMP
- On-going issues related to comparators for clinical studies (placebo in the US vs. active comparator in EU)
- Need to streamline post-approval commitments especially for new products undergoing simultaneous review

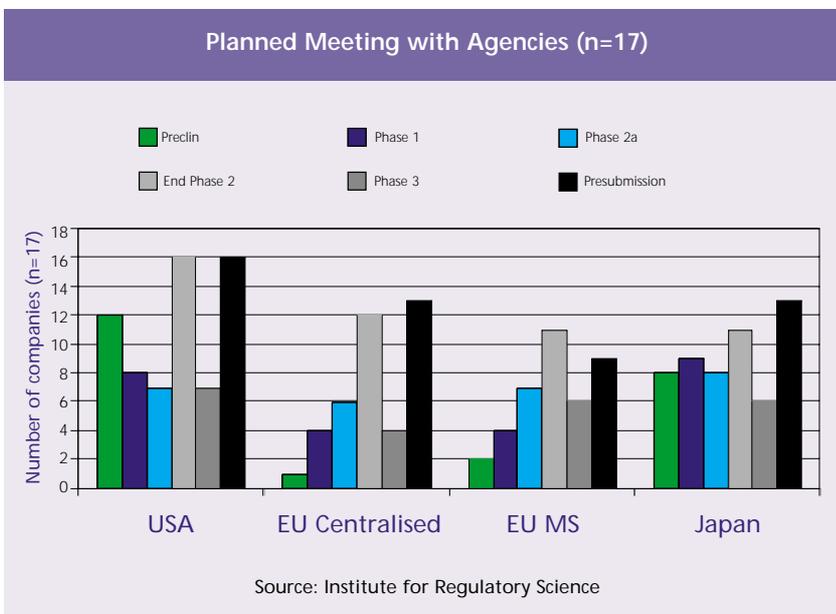


# Regulatory strategies

## Interaction with agencies

An earlier CMR International Institute study that looked at critical success factors for regulatory performance<sup>2</sup> had identified, as a key factor, good communications between companies and agencies, leading to early and open dialogue, good contacts and frequent interactions resulting in continuity and consistency of regulatory advice. This was followed up in the current survey and companies were asked about their plans for arranging meetings with the authorities, during drug development (Figure 8).

figure 8



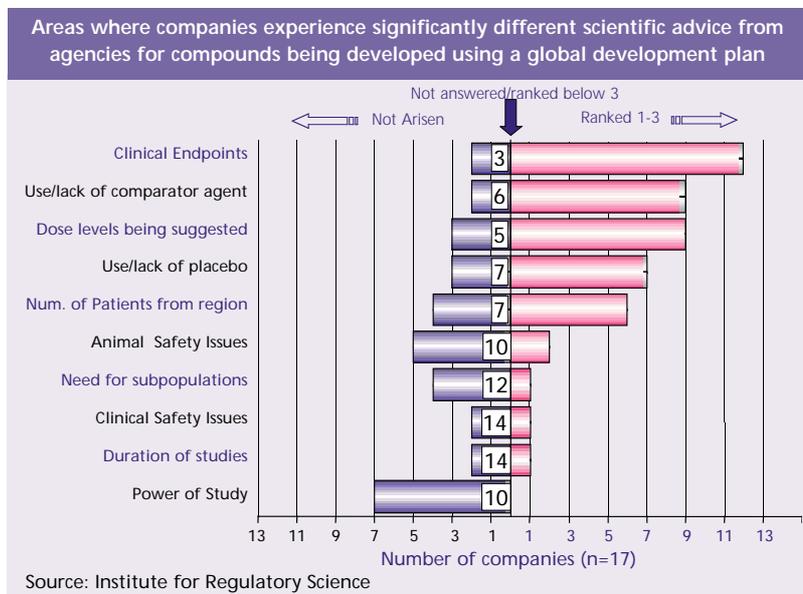
- In the early development stages (preclinical to Phase 2a) about 50% of the companies plan on having some kind of meeting with the authorities.
- Overall, the highest rates of meetings are held with the FDA, particularly at the end-of-Phase 2 and pre-submission stages.
- In the EU, a comparison of interactions with the EMEA, for centralised applications and with agencies in member states (MS) shows a similar profile with little consultation before Phase 2.

## Differing scientific advice

When asked whether they had the experience of receiving significantly different scientific advice from agencies for compounds being developed using a global development plan 14 out of 16 companies (87%) replied that they had.

figure 9

Companies were asked to rank the main sources of conflict, as set out in Figure 9, or indicate that the issue had not arisen. As shown, the three areas where differences in scientific advice arise most frequently are in relation to clinical endpoints, use of comparators and dose levels.



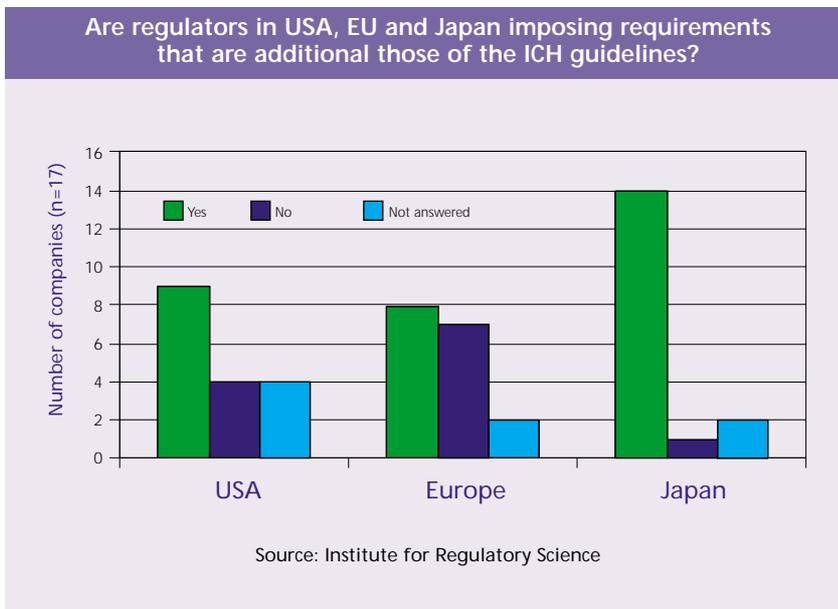


# ICH harmonisation



International harmonisation of the technical requirements for studying new medicines has been an important factor in enabling global development programmes to be pursued. The tripartite initiative between the US, EU and Japan, the International Conference on Harmonisation (ICH) has been pivotal in bringing about regulatory harmonisation but there remain concerns about the consistency with which the ICH guidelines have been adopted, utilised and implemented.

figure 10



- In the survey, companies were asked whether they believe that regulators in the USA, Europe and Japan are currently imposing requirements that are additional to those agreed in ICH guidelines, in a way that is an impediment to global development.
- As shown in Figure 10, this is considered a potential problem in all three regions, but the perception is particularly strong for Japan.
- The topic was discussed at the CMR International Workshop on Global Drug Development, Tokyo, May 2004, when it was recommended that the Institute carry out a study on the implementation and interpretation of ICH guidelines in the different regions<sup>1</sup>.

In the current survey companies identified the following areas of concern, in relation to harmonisation of requirements:

## USA

- Clinical safety studies
- Quality (CMC) issues

## Europe

- Different interpretation of ICH guidelines between Member States
- Comparator products for clinical trials

## Japan

- Interpretation of the ICH E5 guideline on acceptance of foreign data
- Use of Asian data generated in the countries around Japan

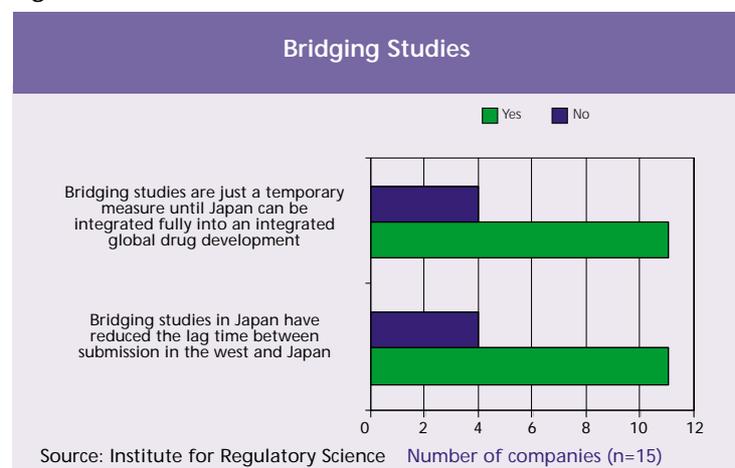
## Bridging studies (ICH 5)

Companies were asked whether they agreed or disagreed with the statements shown in Figure 11.

As indicated, most companies saw bridging studies as an interim measure but acknowledged that they had reduced the lag time in registering products in Japan.

Companies were also asked about the timescale before the infrastructure, time and cost of undertaking clinical development in Japan allows project teams to have confidence that Japan can be fully integrated into global drug development. The responses indicated a median time of 5.5 years in a range of 0 to >10.

figure 11



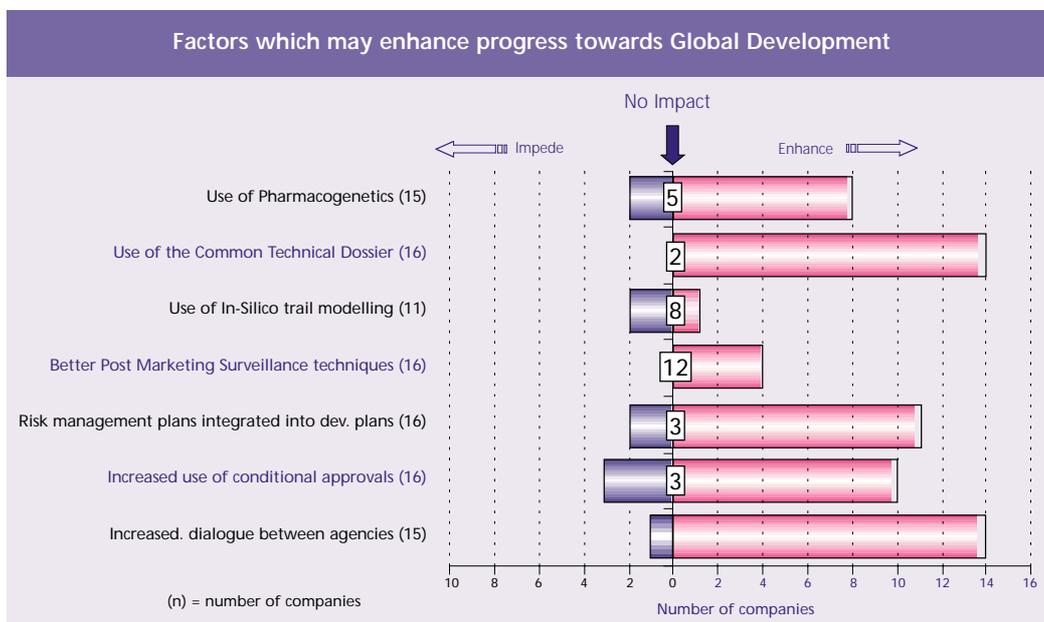


# Looking to the future



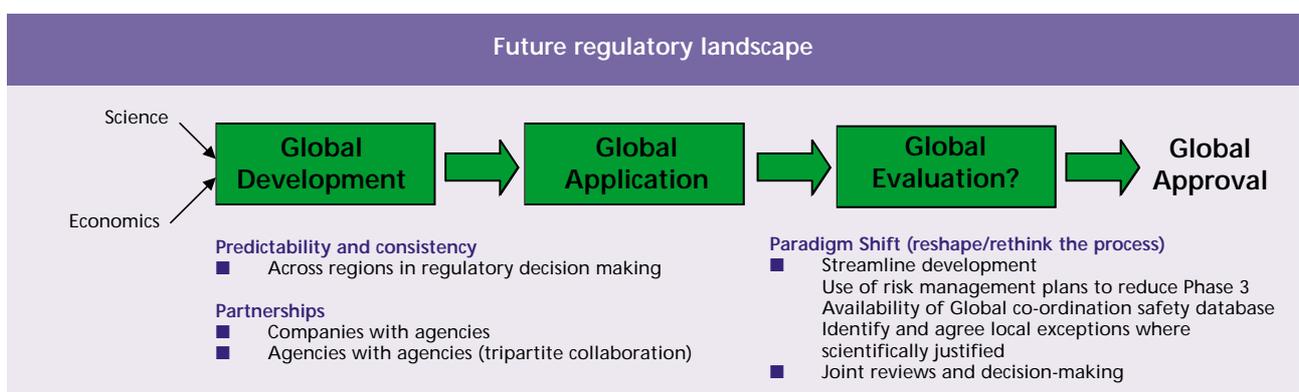
Companies were asked rate the factors shown in Figure 12 according to whether they felt they would enhance, impede or have no impact on progress towards global development.

figure 12



In response to an open-ended question in the survey, on future developments (see opposite), companies indicated that they would be looking for predictability and consistency, partnerships and a paradigm shift to reshape and rethink regulatory processes.

Predictability in the timing and outcome of regulatory decisions across regions is the key to successful global drug development. Partnership is a word that is now frequently used in relation to agencies working together and to the relationship between industry and regulators. Industry would welcome strengthened tripartite agreements between agencies to facilitate the exchange of information and coordination of regulatory advice. A move away from the 'traditional' approaches to drug development and review might include the integration of risk management plans into development in order to reduce Phase III studies, and the establishment of a global, coordinated safety database. The ultimate aim, however, is to have the quality measures in place that will allow a move towards joint reviews and decision-making.





## Looking to the future



The survey included the following question:

Looking towards the next 10 years, with advances in technology, continuing resource constraints and increased globalisation, what, in your opinion, would be an ideal 'regulatory landscape' and how could this be achieved?

A summary of the company responses is given below. These formed the background to the Syndicate group discussions at the CMR International Workshop on Global Drug Development, Tokyo, May 2004 (see reference 1 below), when some far-reaching recommendations were made for a 'new paradigm' for the development and regulatory review of medicines.

## Discussion points for the future of drug development and review

### Streamlined drug development

- Development times could be shortened if some aspects of regulatory assessment could be transferred from pre-marketing approval to post-marketing commitment.
- The development of compounds identified as a significant therapeutic 'breakthrough' should be coordinated in all regions, with parallel processing and sharing of information amongst regulatory bodies.
- Enhanced risk management plans should be adopted as a way of reducing the Phase 3 programme.
- There should be more flexibility in accepting smaller development programmes that allow access to limited market sectors.
- A reduction in the resources required for routine authorisation maintenance would allow agencies and sponsors to focus on more productive activities.

### Joint reviews and decision-making

The future vision of greater regulatory collaboration would be helped by:

- Developing procedures for collaborative and joint assessments between the regions, which include full involvement of the companies;
- Recognition of the review by a major authority, among other authorities;
- Partnership between regulators in US, Japan and Europe from end of Phase 2a, to help bring the product to the market faster and more efficiently.

### Real partnership with regulatory authorities

The development of a culture of shared objectives and partnership between agencies and companies would be assisted by:

- Increasing trust between the two parties and avoiding a 'risk aversion' approach by the agencies;
- Achieving true harmonisation of advice and regulatory expectations internationally;
- Adopting 'rolling' review procedures in the EU and other major regulatory agencies;
- Interactions with regulators that start before the first human dose and begin discussion of targeted labelling during Phase II;
- Implementation of pre-clinical advice from agencies;
- Availability of a globally co-ordinated safety data base for regulators and industry that will increase confidence in the ability rapidly to detect safety issues in the post marketing phase.

### Electronic data exchange

The full benefits of electronic data exchange need to be promoted through:

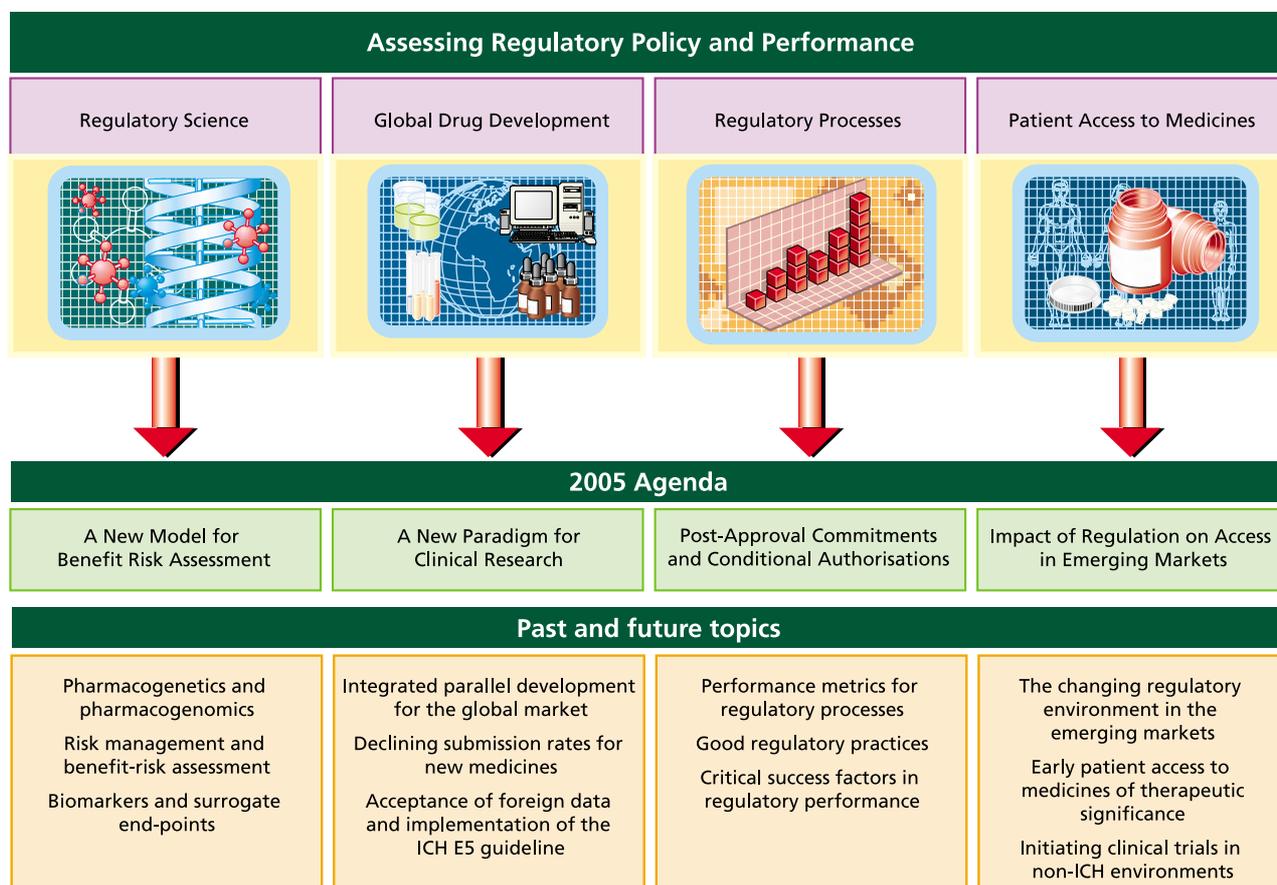
- Elimination of requirements for paper in regulatory submissions;
- Implementing seamless transmissions between electronic IND and CTD, enabling sponsors to submit a given document only once;
- Adoption of a truly standardised eCTD.

### References

1. **R&D Briefing 44:** Global Drug Development and Regulatory Review: Is there a new paradigm?, Highlights from the CMR International Institute Workshop held in Tokyo, May 2004
2. **R&D Briefing 42:** The changing regulatory environment: Reality and Perception

Publications available from the CMR International Institute for Regulatory Science (institute@cmr.org) or via the website, <http://www.cmr.org/institute>.

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