

R&D Briefing

The changing regulatory environment: Reality and Perception



42

Survey on

The changing regulatory environment: Reality and Perception
undertaken by CMR International Institute for Regulatory Science

Key points	1
Background	2
Reality and Perception	
Has the regulatory environment changed?	3
Changing regulatory requirements	4
Changes in the Review Process	5
Major hurdles in bringing a new medicine to the market	6
Impact of changes on development	6
Risk management	7
Achieving success	
Critical Success Factors	8
Improving the current regulatory environment	9
The next five years	9
CMR International Institute Regulations Advisory Board	back cover

Authors:

Neil McAuslane
Carly Anderson
Stuart Walker

Briefing prepared by
Margaret Cone

August 2004

**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*).

Further information on Institute Activities

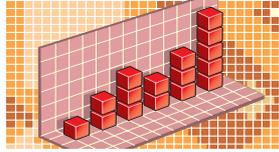
For information on forthcoming Workshops and current and future studies and publications visit the website: www.cmr.org/institute

The Institute programme of activities is published in the Institute Agenda, available from the website

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: institute@cmr.org Web: www.cmr.org/institute



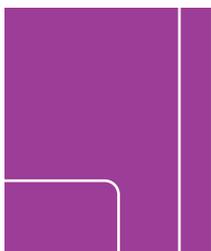
The Changing Regulatory Environment: Reality and Perception

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

Key points

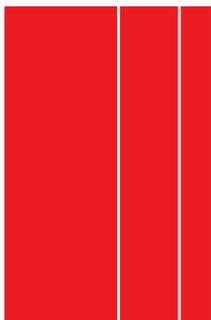


There was consensus that the regulatory environment has changed over the three years between 2000 and 2003 compared to the late 1990s. Whilst 65% of companies felt that the changes had increased the time and cost in bringing new medicines to market, only 23% thought the changing regulatory environment to be directly responsible for the decline in new active substance (NAS) submissions.



Both companies and authorities share the view that the regulatory agencies have become more risk-averse and are requesting more safety data for compounds compared with the late 1990s.

Most companies believed that there had been an increase in the number of conditions attached to authorisations and a majority were of the view that differences in scientific opinion between regulatory agencies had increased the cost and time of clinical development.



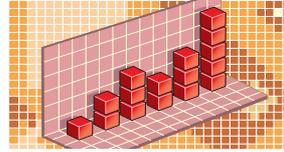
The authorities acknowledged the increase in the rate at which regulatory guidelines have been published and greater stringency in their application. They felt, however, that global development is being facilitated by the increasing harmonisation of regulatory requirements across regions compared with the late 1990s.

The need to develop a risk management plan prior to submission was seen, by companies, as a factor in increasing the cost and time of development but the majority have yet to be convinced that early strategies for risk management enable clinical development plans to be improved.



Asked to identify the critical factors for achieving successful registration, companies gave priority to communication, a company's overall strategy for development and how the regulatory function performed within the company.

The three key critical success factors identified by agencies were: communication with companies and the level of such interaction; companies' strategy and ethos in approaching development programmes; and the robustness and quality of the data submitted.



Background



The widespread observation of a significant decline in the number of new molecular entities reaching the market in the last few years, has been confirmed by CMR International data from studies in the major global markets for the decade 1993-2003 (Figure 1). The lowest number of NMEs for well over a decade was recorded in 2003 when only twenty-six were marketed. Whilst the development time has remained fairly constant at around 10-12 years over the decade the figures indicate an increase in the last few years.

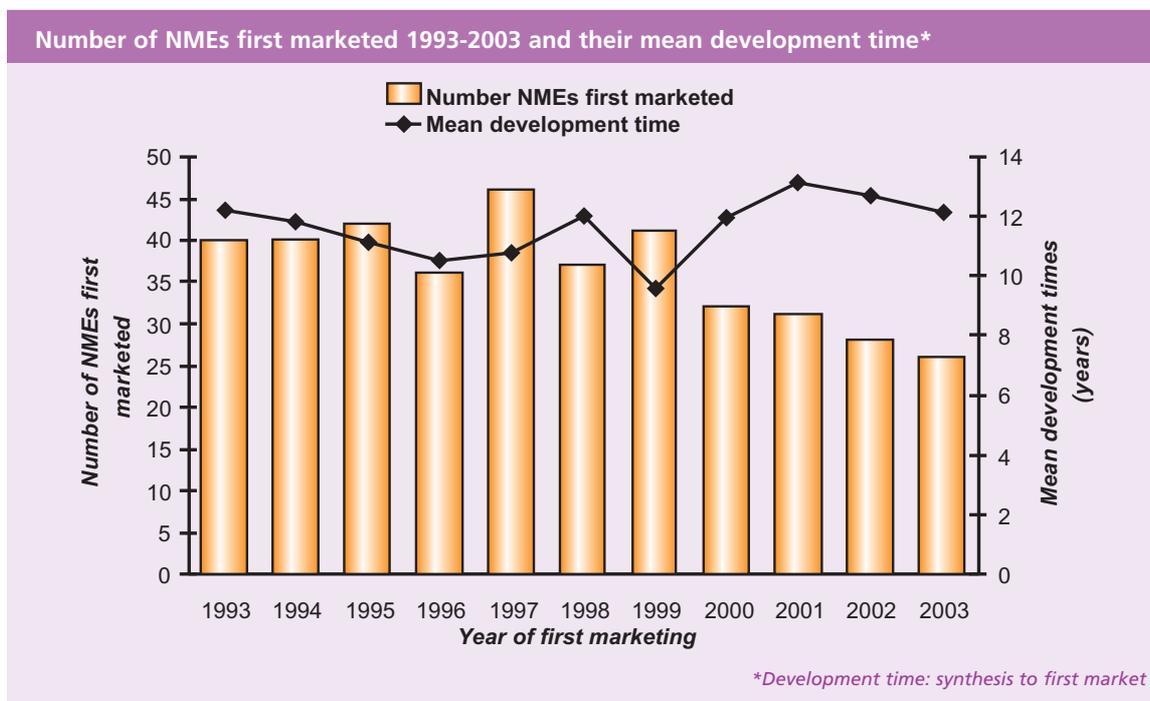


Figure 1

CMR International Institute Survey

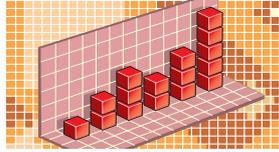
Against this background, the CMR International Institute for Regulatory Science carried out a survey in 2003, to study the 'reality and perception' of changes in the regulatory environment over the designated three years. This was undertaken in response to industry and authority requests to investigate the extent to which regulatory factors were having an impact on R&D productivity and also in preparation for a CMR International Institute Workshop on *Critical Success Factors for Regulatory Performance* held in Washington, September 2003 (see R&D Briefing No 41).

This project attracted the support of 20 leading pharmaceutical companies and 10 international regulatory authorities. The combined data set provides professionals working in the regulatory field with an overview of how industry and authorities perceive recent changes in the environment.

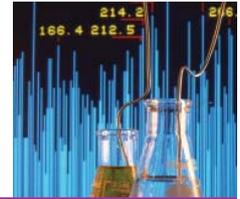
For the purpose of this study, the regulatory environment relates to all activities in the ICH regions (Europe, Japan and USA) that involve the generation, submission and review of data for a new medicine in terms of safety, quality and efficacy.

Section 1 contained a list of statements regarding the current regulatory environment and respondents were asked to 'strongly agree', 'agree', 'disagree', 'strongly disagree' or record a response of 'indifferent'.

Section 2 aimed to identify the regulatory factors that industry and authorities believe are critical to achieving success in today's environment.



Reality and Perception



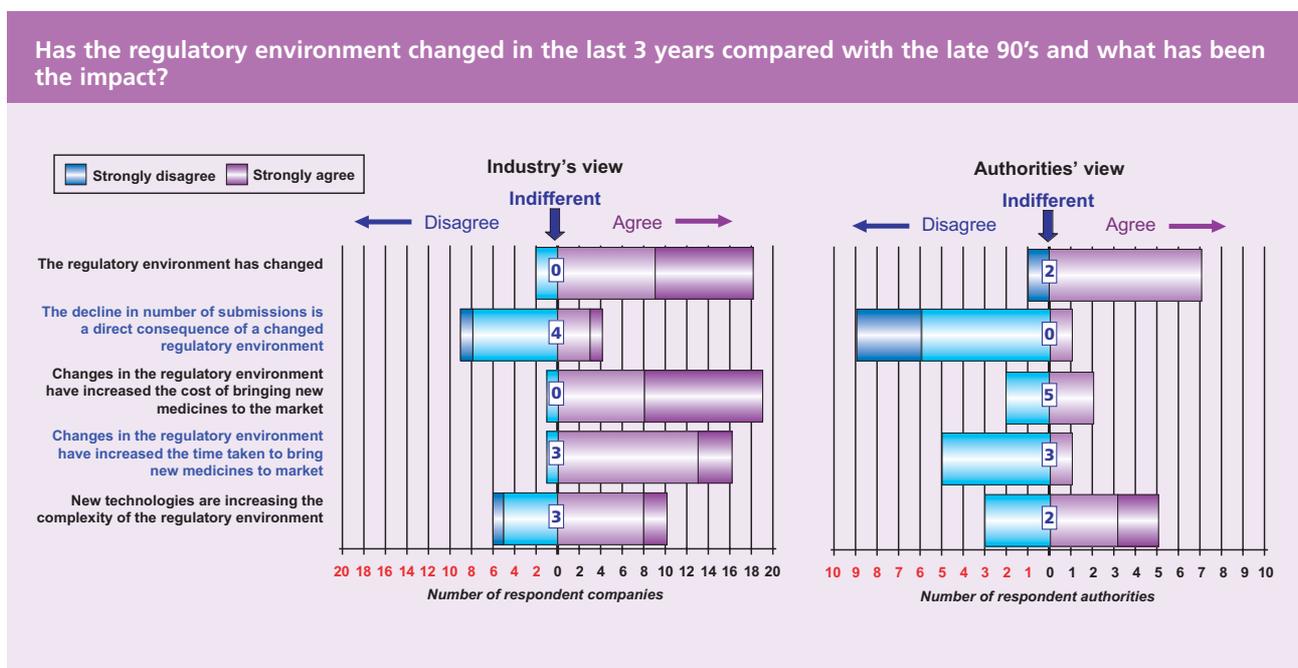
Has the regulatory environment changed?

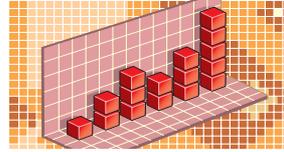
Five of the statements in Section 1 of the questionnaire referred to perceived changes in the regulatory environment and how these had impacted the development and review process (Figure 2).

- Ninety percent of companies (18/20) agreed or strongly agreed that the regulatory environment had changed in the previous three years compared to the late 1990s, but only 23% (4/17 companies) agreed that the decline in submissions were a direct consequence of this change.
- The majority of companies perceived that the change in the regulatory environment had increased the cost and time in bringing new medicines to the market.

- In the case of the regulatory agencies, 70% agreed that the regulatory environment has changed, and 90% felt that the decline in submissions was not directly related to this change.
- Fifty percent of the agencies did not agree that the change in the regulatory environment had increased the time to bring a new medicine to market. On the question of increased costs half the agencies were unable to express a firm view ('indifferent'), since they lack first-hand information on development costs

Figure 2





Reality and Perception



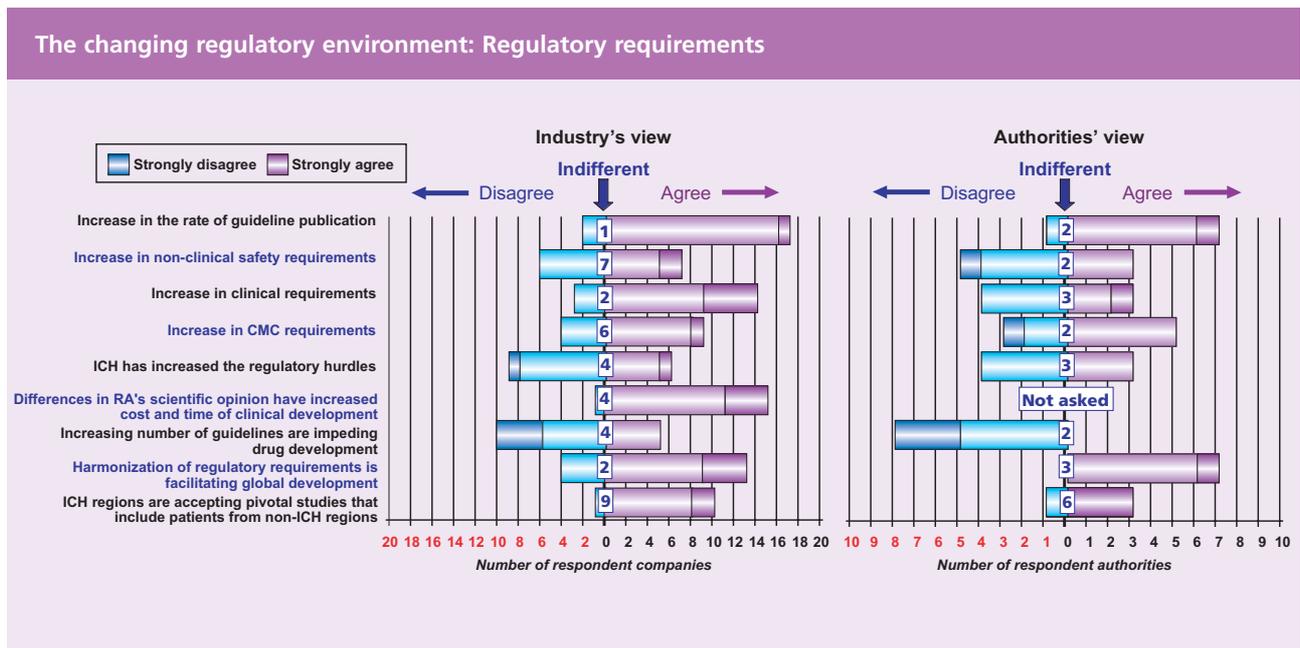
Changing regulatory requirements

The industry perception (Figure 3)

- In response to questions on changes in regulatory requirements, the majority of companies reported an increase in the clinical requirements, with just under half believing that both CMC and preclinical requirements had increased.
- On guidelines, a large majority of companies agreed that there had been an increase in the rate of guidelines published, but this was not perceived by industry as impeding drug development

- Seventy five percent of companies (15/20) believed that differences in scientific opinion between regulatory agencies had increased the cost and time of clinical development.
- Harmonisation was viewed by most companies as having facilitated drug development, although three 'major' companies (those spending more than US\$ 1 billion on R&D in 2002) did not agree. Ten of the top companies strongly agreed for the USA but disagreed in relation to Japan.

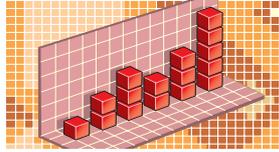
Figure 3



How the agency responses compared (Figure 3)

- Fifty percent of agencies felt that CMC requirements had increased but views were mixed in relation to increases in safety and efficacy requirements.
- The authorities were in agreement that there had been an increase in the rate of guidelines published but were of an even stronger view than industry (80%) that they did not impede drug development.

- Among regulatory authorities there was a mixed perception as to whether or not ICH guidelines had increased the regulatory hurdles although the majority of agencies agreed (70%) that global development was being facilitated by harmonisation of requirements across regions.



Reality and Perception



Changes in the Review Process

Section 1 of the Survey included nine statements related to the way in which the review process had changed. The results for the way in which these statements were ranked are shown schematically in Figure 4 and summarised below:

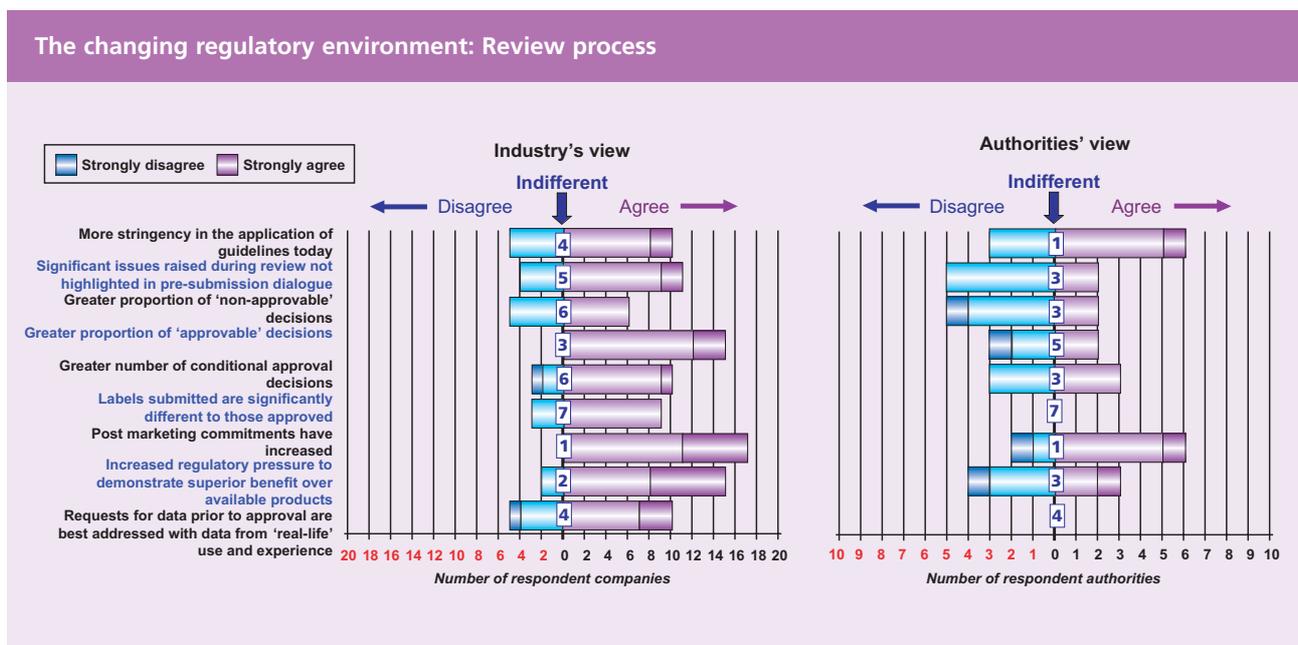
Industry's Perception

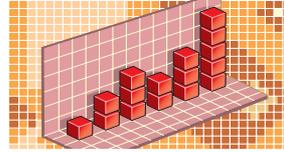
- In general, it was perceived that the regulatory environment has changed with increased post marketing commitments as well as a greater proportion of decisions being made, subject to the provision of further data ('approvable' decisions).
- Seventy-nine percent of companies believed that there was increased regulatory pressure to demonstrate superior benefit over available products, although some companies commented that this was not an issue in the USA.
- Just over 50% of companies believed that significant issues were being raised during the regulatory review process that had not been highlighted in pre-submission dialogue.

Authorities' Perception

- Sixty percent of the authorities agreed that guidelines were being applied more stringently, and most authorities did not feel that significant issues were being raised during the review that had not been highlighted during pre-submission dialogue.
- There was a mixed view in terms of whether, within agencies, there was increased regulatory pressure to demonstrate superior benefit over available products, however two of the ICH agencies agreed with this statement.
- Sixty percent of the authorities agreed with the statement that guidelines were being applied more stringently than in the past, but, in contrast to the industry view, only 20% believed that significant issues were being missed during pre-submission dialogue.

Figure 4





Reality and Perception



Major hurdles bringing a new medicine to the market

Companies and authorities were asked to rank, from highest to lowest, where the perceived hurdles lay, choosing between *Finance; Logistic; Regulatory; and Scientific*

■ Scientific hurdles were believed by both industry and regulators to be the highest hurdle faced by companies in bringing a new medicine to market.

■ The second highest hurdle for companies was regulatory while authorities felt it to be financial.

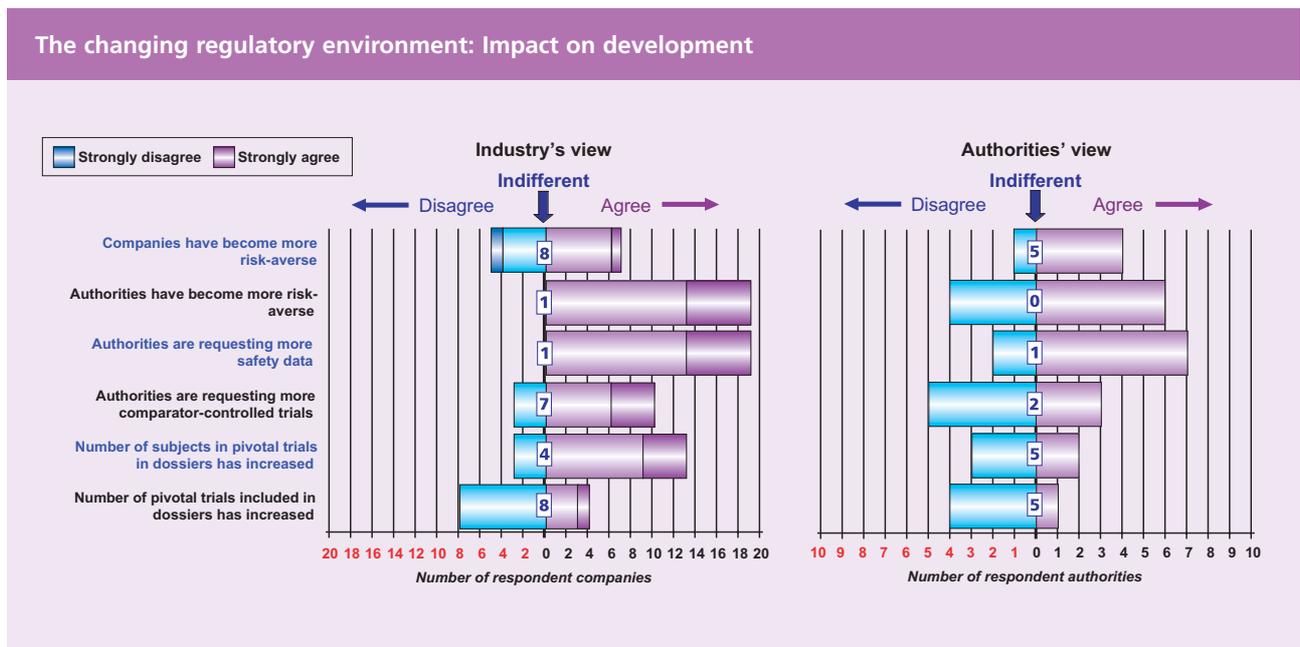
■ Both authorities and companies agreed that logistics were the least important of the hurdles in bringing a new medicine to market.

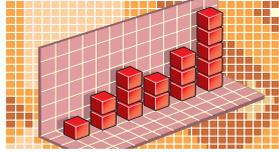
Impact of regulatory changes on drug development

Six of the statements in Section 1 of the questionnaire refer to the impact of the changing regulatory environment on the development of new medicines. The results, summarised in Figure 5, indicate agreement in the perception that authorities have become more risk averse and are requesting more safety information.

The authorities do not, however, all share the industry view that more comparator controlled trials are being requested, or that the number of subjects in the pivotal clinical trials reported in the dossier has increased.

Figure 5





Reality and Perception



Risk management

Figure 6

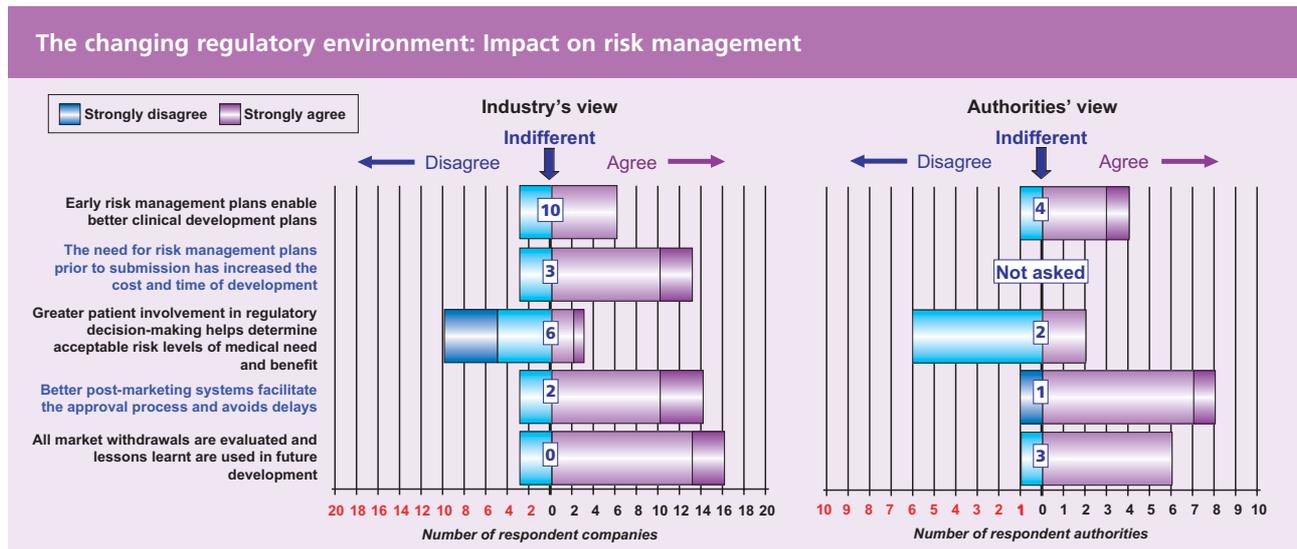
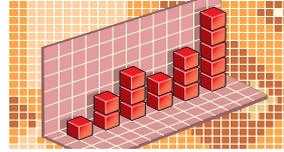


Figure 6 summarises the responses from companies and authorities to five questions in the survey on subjects related to risk management. These included the impact of early risk management planning on the clinical development programme and whether risk management increases the cost and time of development. Views on the benefits of greater patient involvement and the need for more robust post-marketing systems were also sought.

- Most companies believed that the need for risk management plans prior to submission has increased the cost and time of development, but are yet to be convinced that early risk management plans enable better clinical development plans.
- A large majority of companies agreed that better post marketing systems would facilitate the approval process and avoid delays and this view was shared by regulatory agencies.

- There was a similar, positive response from both industry and agencies to a question on the importance of learning from experience when product withdrawals occur.
- Neither industry nor regulatory agencies, however, agreed with the suggestion that greater patient involvement in regulatory decision making would be of help in determining acceptable risk levels.



Achieving success



Critical success factors

In the second section of the Survey, companies and authorities were asked to identify the regulatory factors that they believe are critical to success in today's environment. These were:

Companies

Company strategy: Strong science based decision making; Clarity of company goals early in drug development; Focus on products which satisfy unmet medical needs or superiority in terms of efficacy and safety.

Technical data: Robust scientific data; Well thought out clinical programme; A good understanding of regulatory precedents; Clearly defined, measurable, validated endpoints in well powered studies.

Communication: Early and open dialogue with agencies; Good contact and frequent interactions; Continuity and consistency in the regulatory advice from authorities.

Regulatory Affairs Function: Influence and status within the company; Early involvement in the development process; An effective understanding of authorities' interpretation of regulations and guidelines; Anticipation of potential regulatory questions early in clinical development.

Authorities

Strategy and Ethos: Well designed integrated development programme; Asking the right clinical questions; Focus on products that meet medical need; No over ambitious claims; Comprehensive risk management strategy and PMS programmes.

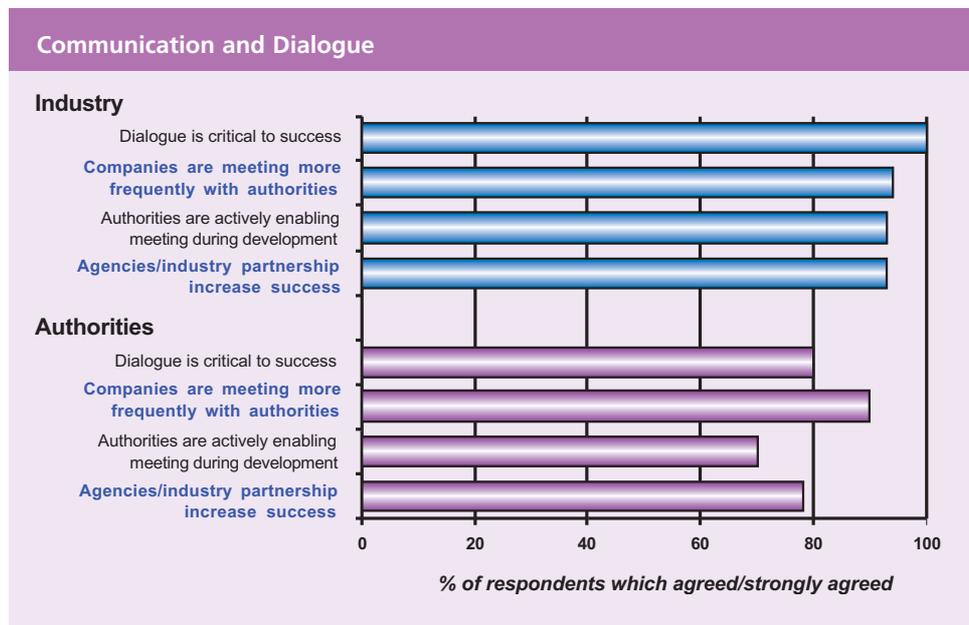
Dossier and Data: Complete dossiers; Robust documentation; Adequate datasheets supported by well organised applications; High quality data

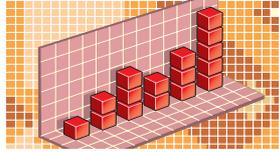
Communication: Early identification of regulatory view on product development plan; Early and continuous dialogue with agencies; Scientific advice before submitting Phase II; Co-operative, open and honest discussions; Pre-submission consultation; Capacity to respond to questions

Figure 7

Communication and Dialogue

Both companies and regulators identified communication and dialogue as key factors for success. A further analysis of perceptions of the role such interactions is shown in Figure 7.





Achieving success



Improving the current regulatory environment

Companies and regulatory authorities were asked to answer the question 'To improve today's regulatory environment where would you suggest that efforts be focused initially?'

Similar answers were grouped, as shown in the table. There was good agreement between agencies and companies that priority should be given to communication and dialogue with international cooperation and harmonisation as the next priority

<i>Where should efforts be focused in order to improve today's regulatory environment?</i>			
Regulatory Authorities		Companies	
Areas for Improvement	Number of Agencies	Areas for Improvement	Number of Companies
Dialogue between reviewers and companies	6	Greater interaction and dialogue between reviewers, companies and end users	7
International cooperation	4	Greater global harmonisation	6
More efficient IT use	1	Conditional approvals	3
Adequate funding of regulatory agencies	1	Greater adoption of mutual recognition agreements	2
Increased transparency	1	Sharing information	1
Quality of the review process and quality of regulatory science	1	Clear expectations	1

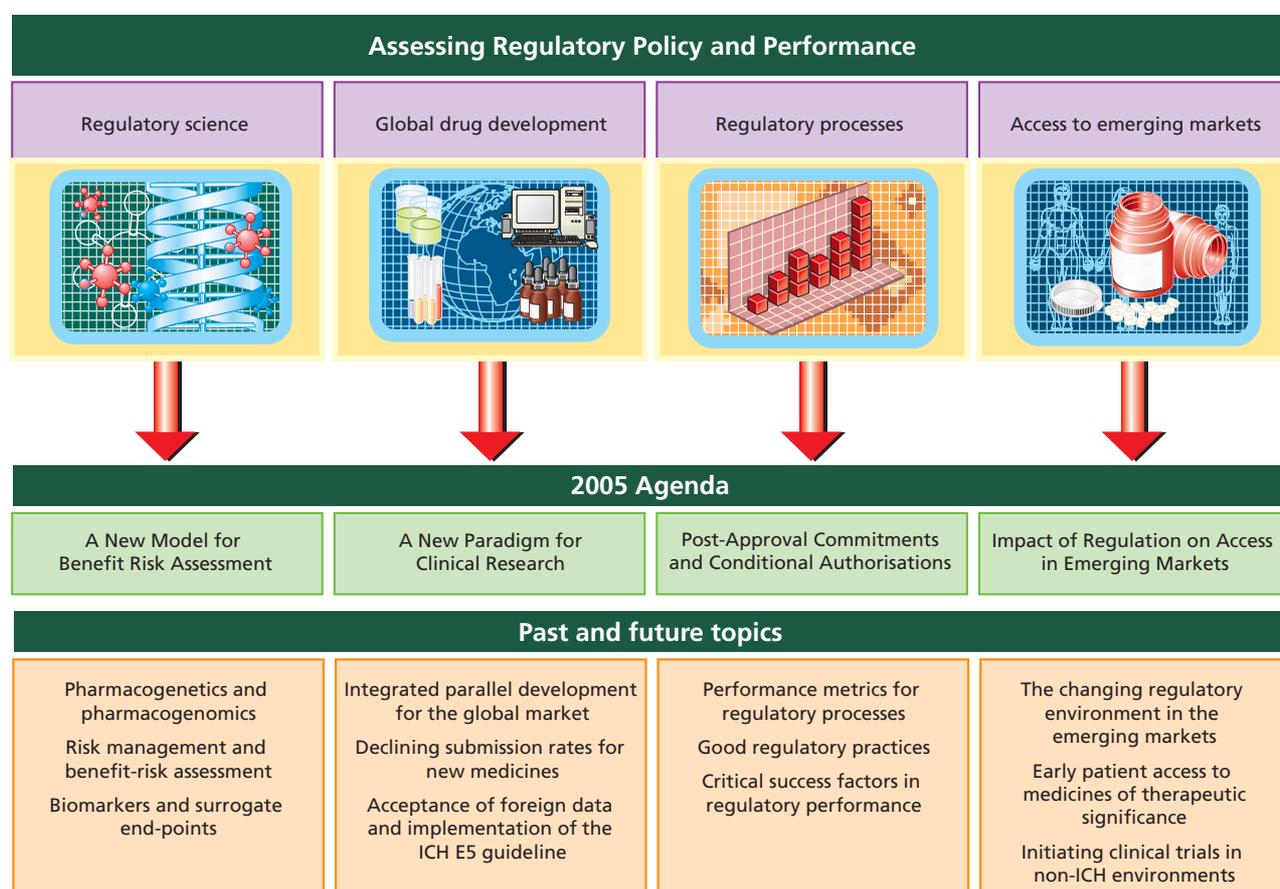
The next five years

The survey asked how companies and regulators perceived the regulatory environment changing in the next five years and some of the key factors are summarised below:

- Trend to electronic submission and analysis of data
- Increased proportion of biotech products and rise of generics in marketplace
- Increasing dialogue and transparency especially in relation to new technologies
- Shift of focus from pre-authorisation data analysis to post authorisation information management
- Increased complexity of submissions because of new technology
- More focus on safety especially for new active substances
- Simultaneous filings in different regions (facilitated by ICH and the Common Technical Development - CTD)
- More focus on international harmonisation and cooperation
- Regulatory performance and cost measured more tightly with greater attention to patients and public views

Responses from companies emphasised an increased reliance on risk management plans. Regulators cited an increased focus on safety but also believed that the methodology for filing and assessing the increasingly complex submissions would have a major influence on future developments.

CMR International Institute for Regulatory Science



Members of the Regulations Advisory Board (2004)

Dr David Jefferys (<i>Chairman</i>), Senior Adviser - Healthcare Industries, Department of Health	UK
Dr Robert Peterson (<i>Vice Chairman</i>), Director General, Medical Products Directorate, Health Canada	Canada
Prof. Gunnar Alván, Director General, Medical Products Agency	Sweden
Dr. Osamu Doi, Senior Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Dr Leonie Hunt, Director Drug Safety and Evaluation Branch, Therapeutic Goods Administration	Australia
Dr John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research (CDER), Food and Drug Administration	USA
Dr Murray Lumpkin, Principal Associate Commissioner, Food & Drug Administration	USA
Thomas Lönngren, Executive Director, European Medicines Agency (EMA)	EU
Dr Milan Smid, Director, State Institute for Drug Control	Czech Republic
Prof. Samuel Vožeh, Head of Business Unit, Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic	Switzerland
Dr Graham Burton, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, Celgene Corporation	USA
Dr George Butler, Vice President and Head, Worldwide Regulatory Affairs, AstraZeneca Pharmaceuticals	USA
Dr Christine Cioffe, Vice President Project Management, Merck and Company Inc	USA
Dr Tim Fransen, Vice President of Global Regulatory Affairs, Lilly Research Laboratories	USA
Dr Stewart Geary, Deputy Director, Corporate, Regulatory Compliance and Quality Assurance Headquarters, Eisai Co. Ltd.	Japan
Dr Edmund Harrigan, Senior Vice President, Worldwide Regulatory Affairs, Pfizer Inc.	USA
Dr Paul Huckle, Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline R&D	UK
Prof. Stuart Walker, President and Founder of CMR International	UK

CMR International Institute for Regulatory Science

Novellus Court, 61 South Street, Epsom, Surrey KT18 7 PX, UK

Tel: +44 (0) 1372 846 100 Fax: +44 (0) 1372 846 101 E-mail: institute@cmr.org, Web: www.cmr.org/institute