

R&D Briefing

Regulatory Performance



41

Highlights from the Workshop on

Regulatory Performance: Critical Success Factors in Today's Environment

Organised by the CMR International Institute for Regulatory Science, in Washington D.C., 15-16 September 2003

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**CMR 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

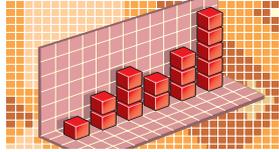
For information on forthcoming Workshops and current and future studies and publications visit the website: www.cmr.org/institute

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

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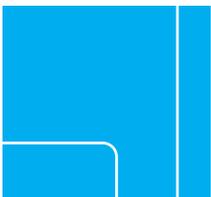
Regulatory Performance: Critical Success Factors

Highlights from the workshop held by the CMR International Institute for Regulatory Science in Washington D.C., 15-16 September 2003

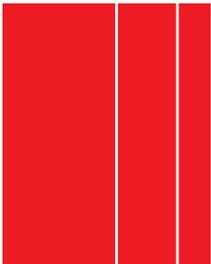
Key points



There was consensus that one of the most important success factors for regulatory performance is good communications and the exchange of information between experts in companies and agencies. Such exchanges can streamline the product registration process and make new medicines available to patients more efficiently. The Workshop therefore welcomed the new FDA/EMA confidentiality agreement* and called for cooperation from all sides to expedite its implementation.



A related theme that emerged from the Workshop was the need for a radical re-examination of the limits and constraints of confidentiality placed on regulatory agencies. Whilst commercially valuable information and intellectual property must be fully protected, there are many instances where the authorities have information on general scientific issues that, if shared, could help company researchers to avoid pitfalls, dead ends and, more importantly, potential safety hazards.



These issues were discussed against a background of data on the ever-increasing investment in new drug research whilst the output of new medicines has declined dramatically in recent years. Although the research pipeline appears to remain full, products are staying for longer in the early phases of development where the attrition rate is high. Whilst it was acknowledged that it is far more economical to abort a project at an early stage than later, there were concerns that valuable products could be lost as a result of increasing the regulatory and research hurdles in Phases I and II.

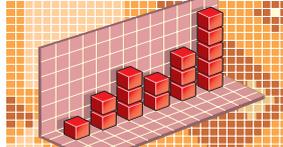


An examination of the extent to which the regulatory environment had changed was one of the objectives of the meeting and, in accordance with the working practices of the Institute, a survey had been carried out among regulators and industry, in advance of the Workshop. Among the many conclusions and inferences that could be drawn from the data was the perception that regulators had become more risk averse in recent years



Another issue that was highlighted was the increasing commitments to conduct further studies as a condition of authorisation. One of the recommendations from the Workshop suggested that the CMR International Institute should carry out a study to quantify the impact of conditions and commitments attached to authorisations

**Participants at the Workshop found themselves in the unique position of receiving first hand reports, from FDA and EMA, of the confidentiality agreement that was finalised between the two parties on Friday 12 September 2003. The agreement, which will facilitate the sharing of regulatory information on pre- and post-authorisation issues, underlined one of the main themes that ran throughout the Workshop.*



Background



In recent years all regulatory agencies and companies have invested considerable time and resources in major initiatives to improve their review performance, both in terms of efficiency and quality. This activity is ongoing against a background of high profile withdrawals, a decline in the number of new medicines being submitted for marketing authorisation by companies, and a growing perception that the regulatory environment is changing.

The CMR International Institute Workshop was designed to explore the trends and drivers behind these changes and to identify the key elements that are having an impact - positive or negative - on the approval rates of new medicines. A study on *'The changing regulatory environment: Reality and Perception'* was undertaken among companies and regulatory authorities, in preparation for the workshop, and the outcome is reported separately in R&D Briefing No. 42.

Workshop recommendations on critical success factors

Towards Global Scientific Advice

The signing of a confidentiality agreement between FDA and EMEA was welcomed as a significant step forward and it was hoped that this would pave the way for increased multi-lateral consultation on drug development projects. The importance of having the sponsor 'at the table' was stressed.

- It was recommended that industry give its full support and cooperation to this initiative. It was hoped that success in information exchange at an international level could be seen as a move towards global scientific advice. The use of video conferencing, web conferencing and electronic communications were advocated to facilitate the procedures.

Sharing Agency Experience

There is a wealth of knowledge and experience contained in the closed files held by the regulatory agencies but confidentiality constraints prevent this from being shared.

- A scheme was envisaged under which companies could allow the agencies to share information on pre-clinical, clinical and chemistry, manufacturing and control (CMC) issues related to drug development. Participating companies could identify and clear anonymised information for sharing and would, in return, receive other information through the scheme.

Primary objectives would be to avoid waste of resources and the ethical issues involved in allowing companies to pursue research where the agencies have knowledge of specific hazards or where the undertaking is known to be a 'blind ally'. Without compromising intellectual property it should be possible to enhance drug development by

allowing unsuitable products to be terminated earlier and promising ones to be accelerated, to the ultimate benefit of the patient. It was suggested that unpublished information on abandoned projects and clinical trials with a negative outcome could also be added to this data resource

Post-marketing commitments

Commitments to carry out post-marketing studies and investigations, entered into at the time of product authorisation, must be realistic, achievable and likely to yield usable and useful data.

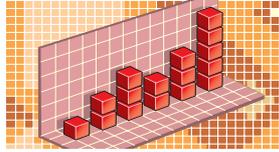
The procedures for setting conditions for post-marketing studies need to be reviewed to ensure that companies are not being pressured to agree to accept conditions at short notice as the 'price' of obtaining an authorisation. Not only is there a major resource issue but also one of monitoring such commitments and ensuring compliance within specified time limits.

- It was recommended that a study be carried out, to quantify post-marketing commitments in terms of resources and compliance levels. Such a study would pave the way for a review of the procedures for assigning and agreeing post-marketing conditions at the time of authorisation.

Global Risk Management

- Companies were recommended to plan proactively in order to develop a global risk management programme.

Such a plan will drive post-marketing commitments and should involve all parties, including health care professionals and pharmacoepidemiologists.



Workshop recommendations *(continued)*



Continuity in the dialogue

Acknowledging that there are frequent personnel changes within both companies and agencies, there is nonetheless, a need for a greater continuum in the advice given to companies by regulators and the companies' teams of experts that deal with regulatory issues.

- It was recommended that:
 - Agencies should ensure greater continuity between the advisory teams and review teams dealing with specific projects;
 - Companies should not disband, completely, their teams of experts once a marketing authorisation is obtained and hand the post-marketing care of a product to a new group who do not have the same background knowledge of the product.

Whilst continuity is important, however, it must not be dependent on the views of specific individuals; it must not be 'personality driven'. Within the EU Centralised Procedure, there may be advantages in identifying the rapporteur and co-rapporteur at an earlier stage, say Phase IIb, and involving them in the scientific advice discussions.

Resolution of global issues

Major scientific issues, which impact on global drug development, require a coordinated approach to consensus building.

- It was recommended that workshops should be established between regulators, industry, academia and practitioners to create consensus on issues as a basis for drawing up global guidance and guidelines.

The example was cited of the ICH Guidance on QT interval prolongation where a major consultation had been held, involving all interested parties, as part of the development of the guideline.

Risk based approach to regulatory requirements

With the advance of science there are increasing demands to gather more and more information and data in Phases I and II of development, a fact that is reflected in the metrics showing that pipeline drugs are remaining longer in these phases. These include pharmacokinetic, pharmacodynamic and pharmacogenomic issues. There is always more information that could be obtained but research cannot be sustained on this basis.

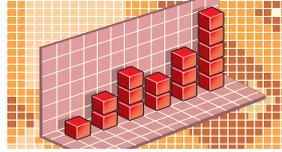
- It was recommended that requirements should be defined for the safe and effective therapeutic use of new medicines. This should be a risk-based approach to essential data and must avoid the growing tendency to include 'nice to have' information.

From the presentation by Bonnie Goldmann (Session I)

Critical factors for the successful review and approval of new medicines: TACTICS

There are several critical factors which can facilitate timely review and approval of an application for a new medicine - described by the acronym, TACTICS

- T**ransparency
- A**nticipation
- C**ommunication
- T**imeless
- I**ntegrity
- C**ompliance



Workshop recommendations *(continued)*

Relationship between industry and agencies

A partnership between industry and agencies is an important success factor but there is a need for education to improve the relationship, which can be marred by a lack of trust and ‘arrogance’ on both sides. There is a need for companies to convey more open and consistent messages with greater transparency.

Drug development projects must be discussed, ‘warts and all’, bringing all issues into the open without attempts at concealing difficult issues. Regulatory agencies must be equally open and the outcomes of meetings need to be recorded better than at present.

Electronic Submissions

A major success factor is the realisation of the potential of fully electronic, ‘paperless’ submissions. The common standard for the ICH electronic Common Technical Document (e-CTD) is obviously a major step towards this, but other tools and developments are required to recognise and accommodate the different ways that submissions are reviewed by the different agencies.

A further commitment and investment was required by the agencies to implement electronic data management that supports the review procedure.

Beginning with the end in mind

The practice adopted by many companies of defining, from the outset of development, a target package insert, setting out the desired, ultimate label claims is a useful way to structure discussions, not only within companies but also with regulators. It creates the basis for a well-delineated and clearly linked clinical development programme and allows critical discussions on the way in which a project is proceeding.

Syndicate Sessions

In Session 3 of the Workshop, four Syndicate Groups were convened and each was asked to identify key changes that are affecting drug development and regulation and to propose *critical success factors* for optimising regulatory performance, in response to these changes.

Session Chairman: **Dr David Jefferys**, Head of Devices Sector, Medicine and Health products Regulatory Agency (MHRA), UK.

■ **Topic A: Pre-submission:** Changes and responses to change in the discovery and clinical development phases of drug development.

Syndicate 1

Chair: **Dr Mike Clayman**, Vice President, Global Regulatory Affairs, *Eli Lilly & Company Limited, USA*

Rapporteur: **Margaret Cone**, Director of Regulatory Science, *CMR International Institute for Regulatory Science*

Syndicate 2

Chair: **Professor Samuel Vožeh**, Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, *Swissmedic, Switzerland*

Rapporteur: **Dr Graham Burton**, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, *Celgene Corporation, USA*

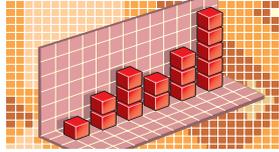
■ **Topic B: Post-submission:** Changes and responses to change in the regulatory review and post-authorisation phases

Chair: **Dr Leonie Hunt**, Director, Drug Safety and Evaluation Branch, *Therapeutic Goods Administration, Australia*

Rapporteur: **Dr Steve Caffé**, Vice President, Head GDDC/US Regulatory Liaison, *Aventis Pharmaceuticals Inc, USA*

Chair: **Professor Stuart Walker**, President and Founder of *CMR International, UK*

Rapporteur: **Dr Stewart Geary**, Director, Medical, Regulatory Affairs and Pharmacovigilance, *Eisai Co. Ltd, Japan*



Points from the syndicate discussions



Changing Regulatory Environment

CMR International data, presented by Dr Neil McAuslane in Session 2 examined the declining submission rate for new molecular entities in relation to the development pipeline. This had shown that, whilst there are an increasing number of NCEs entering Phase I, they are staying longer in Phases I and II with an increasing attrition rate and a consequent decrease in the numbers in Phase III of the pipeline. The following were proposed as factors influencing this observation:

Regulatory environment

- The implementation of the Centralised Procedure in the EU and the accompanying changes in procedures and requirements, including the greater emphasis on comparative efficacy and safety;
- High profile withdrawals in the last six years, and the resulting changes in testing methods and requirements. Examples include QT interval prolongation;
- Increased risk aversion in companies and authorities leading to earlier abandoning of drugs during the clinical development stages;

- Increased complexity of the drug development process resulting from advances in technology and factors such as new privacy rules and their impact on the conduct of clinical studies;
- A changing clinical trial environment including the role of IRBs/ethics committees, controversy over the use of placebos vs. active comparators and the introduction of the EU Clinical Trials Directive.

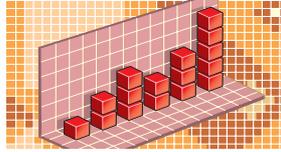
Company environment

- 'Regulatory creep' resulting from companies carrying out tests that are not necessarily requirements, e.g., in the interests of achieving a 'harder' end point;
- Early abandoning of 'me too' drugs where there are no specific advantages over others on the market;
- The increasing need to take pricing and reimbursement into consideration as well as considerations of return on investment;
- The increased sophistication of targets and therapies, for example the statins, and treatments for diabetes.

Observations on 'Quality'

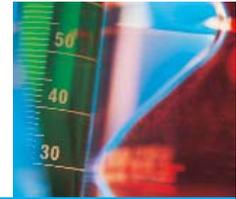
The meaning of 'quality' in terms of drug submissions and regulatory review needs to be better defined. Regulatory review times can be measured relatively easily but this may simply be a measure of efficiency, which ignores whether the review reached the correct conclusions. From a company point of view, avoiding a 'refuse to file' action is a relatively low standard for quality. An analysis of the lists of questions sent to companies may be a better measure of the quality and completeness of the original application.

There is a danger that there is a greater focus on the speed of review, and on achieving filings and approvals by specific dates than the more important goal of bringing good medicines with appropriate prescribing information to patients, in a timely manner.



Points from the syndicate discussions

(continued)



Observations on scientific Advice

- A formal procedure for obtaining Scientific Advice exists in the EU but there is a perception that it could be more flexible and the scientists more accessible. It is often more useful for companies to go to national agencies for advice than to use the EMEA process. The system is also open to criticism because of the non-binding nature of the advice, in contrast with the system under which FDA provides advice.
- Situations might arise where changes in background information have a major impact on the scientific advice previously given to a company. Under such circumstances, agencies should be proactive in informing the company. If the change is prompted by a safety issue that has been highlighted by a competitor's application, questions of confidentiality need to be addressed, as discussed in the earlier recommendation.
- As a general observation, the quality of scientific advice can be improved by ensuring that the agency understands the company's development plans as early as possible, for example whether the aim is 'first in class' or 'best in class' for a new drug. There should be open dialogue on the full plan as it goes forward, not just in relation to the next protocol. A clinical development plan should be submitted between Phase IIa and IIb.

Responding to Requests for Information during Review

Most companies are establishing 'rapid response teams' to ensure that requests for further information are dealt with promptly. Success can be improved by setting targets for how quickly responses are generated and by anticipating questions rather than a 'wait and see' attitude.

What Constitutes Success?

Patients

- Earliest availability worldwide of new medicinal products

Purchasers

- Fast availability of multiple therapy choices

Health Authorities

- Right first time submissions allowing efficient review and decision-making process; no emerging major safety issues post-launch

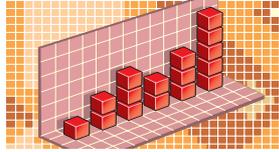
Commercial

- US approval with competitive labelling within 12 months
- Non-US approval (technical plus "reimbursement") at the same time or soon after?

Regulatory

- Indications approved consistently worldwide
- Dosage minimum ~ same in all countries (PK / PD dependant)
- Contraindications, warnings, precautions and safety statements are data-driven
- Conditional approval work is realistic
- No imposed additional preclinical studies
- Sources of manufacture secure
- Agreement with authorities to re-review label impositions with 2 years of marketing data
- Regulatory dialogue door remaining "wide-open"

*From the presentation
by Dr George Butler
(Session 2)*



Workshop Programme



PROGRAMME

Chairman: Dr Robert Peterson
Director General, Therapeutic Products Directorate, Health Canada

EU regulation at a turning point
Dr Marisa Papaluca Amati
Deputy Head, Safety and Efficacy of Medicines Sector, European Agency for the Evaluation of Medicines (EMA), EU

Changing horizons for clinical development, and the regulatory implications
Dr Tim Franson
Vice President, Global Regulatory Affairs, Lilly Research Laboratories, USA

Health Canada: Meeting the need for change
Dr Robert Peterson
Director General, Therapeutic Products Directorate, Health Canada, Canada

Session 1: Changes and Challenges in the Current Regulatory Environment

Quotes and extracts from the workshop report

In emphasising the need to 'make accessible, efficacious, high quality and safe medicines, including the more recent and innovative ones, to all those who need them regardless of their income or social status', G10 had highlighted the need for regulators to think not only in 'traditional' terms of the safety, quality and efficacy of medicines but also about the so-called 'fourth hurdle' of achieving access to new medicines.

Dr Marisa Papaluca Amati

We may be moving to a stage of agreement between sponsors and regulators that the throughput of products based on pharmacogenomics can be significantly improved by allowing approvals to be based on validated surrogate markers. Since outcomes are expected for reimbursement, this could, however, raise problems if the surrogate markers do not have a clear link with the final outcome.

Dr Tim Franson

The introduction of regulatory project management has been a pivotal move, with the establishment of milestones for tracking progress and identifying when and why applications are going off track and timelines are being missed.

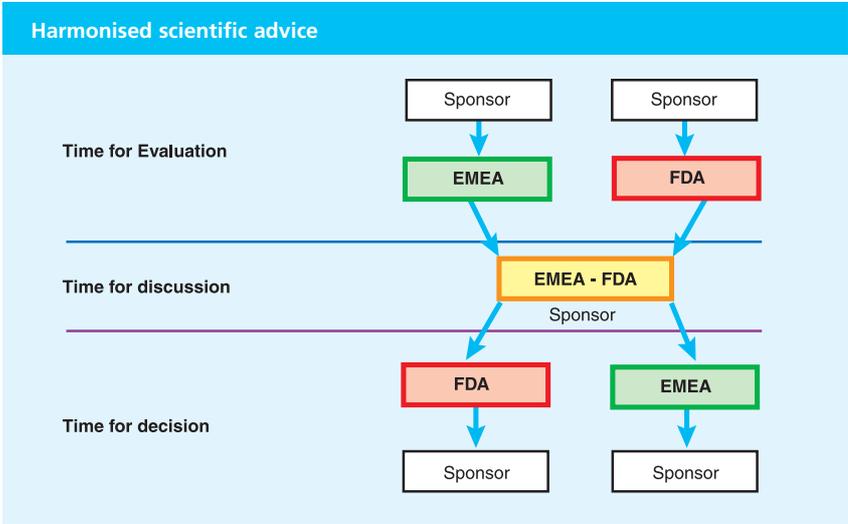
Dr Robert Peterson

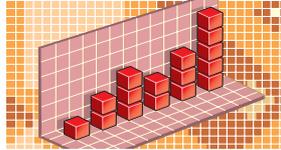
Dr Jenkins reported that FDA had looked at the drugs that had come off the market in the last decade and found that the primary reasons were issues of QT prolongation and liver toxicity. In some cases potential problems had been identified before the drug came to market and the sponsor tried to implement risk management strategies that had failed.

Discussion session

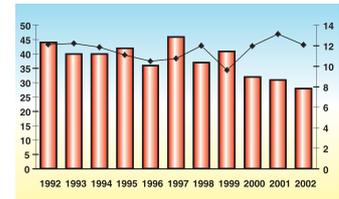
EMA/FDA Confidentiality agreement

On the subject of scientific advice, Dr Papaluca Amati made the important announcement that, on the previous Friday, 12 October 2003, the EMA and FDA had finalised a confidentiality agreement that would facilitate the exchange of information between the agencies and could pave the way to greater consistency and transparency in the advice that is given. Perhaps, she suggested, simultaneous, joint advice could become a reality. In the meantime, each agency would remain responsible for the advice it provides.





Workshop Programme



PROGRAMME

Chairman: Dr Robert Peterson
 Director General, Therapeutic Products Directorate, Health Canada

What do trends and indicators tell us about the changing regulatory environment?

Dr Neil McAuslane
 Chief Scientific Officer, CMR International Institute for Regulatory Science, UK

The relationship between regulation and innovation: a help or hindrance? An industry viewpoint

Dr Declan Doogan
 Senior Vice President, Clinical R&D and Project Management Pfizer Inc., USA

The relationship between regulation and innovation: a help or hindrance? A regulatory response

Dr Eric Abadie
 Director of Registration and Clinical Strategy, AFSSAPS, France

Session 2: The Declining Submission Rate for New Medicines

Quotes and extracts from the Workshop report

Fourteen of the sixteen companies (or 88%) agreed that the regulatory environment had changed but only 27% (4 of 15 companies) saw the declining submission rate as a direct consequence of these changes. In the case of the authorities, seven of the ten that participated (70%) agreed that the environment had changed but only one (10%) related these changes to the declining submission rate.

Dr Neil McAuslane

The increasing regulatory burden on companies that may have an impact on drug development does not result from the marketing authorisation regulations but is related to the increased focus on comparative benefit and cost effectiveness. The rejection rate for marketing authorisations had not changed significantly and he did not believe that changes in regulations had resulted in increased requirements for clinical testing.

Dr Eric Abadie

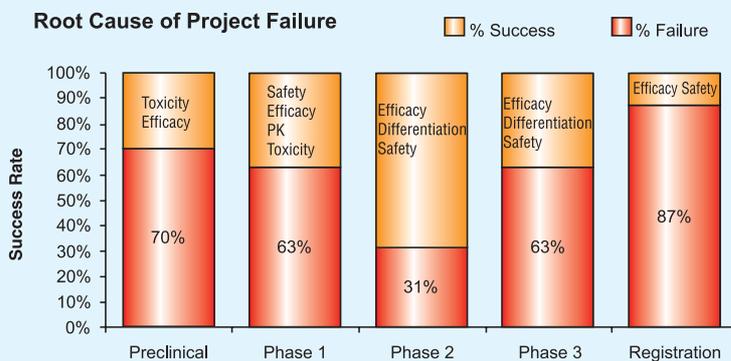
Increasingly, there are two types of regulation impacting the introduction of new medicines in Europe. Whilst the marketing authorisation procedures have the primary place, the national regulations and procedures for determining which products are reimbursed by the public sector are having an increasing influence on the business environment.

Dr Eric Abadie

There is too much emphasis on negative aspects of pharmaceutical R&D and not enough concomitant positive commentary. The question of the yields should not be measured only in terms of the number of chemical entities going into development but whether those emerging at the other end are considered to be not only safe but also value added medicines for patients.

Dr Declan Doogan

Root cause: Improving success rates requires continuing study of our failures

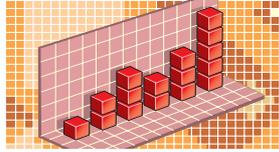


- There are four (major) reasons why drug projects fail
- Which of these can we influence?

From the Presentation by Dr Declan Doogan

It would be interesting to have better information on the extent to which commercial factors influence decisions to abandon drug development projects. Presumably, if there are sufficient molecules in the pipeline it is easier to decide to stop a project at Phase I and move the next product into early Phase II.

Dr Robert Peterson (discussion session)



Workshop Programme



PROGRAMME

Chairman: Dr Alex Giaquinto
Senior Vice President, Global Compliance, Schering Plough, USA

Keys to Success and Failure: An Industry Perspective
Dr Bonnie Goldmann, Senior Vice President, Global Strategic Regulatory Development, Merck Research Laboratories, USA

Keys to Success and Failure: A Regulatory Perspective
Dr John Jenkins, Director, Office of New Drugs, CDER, FDA, USA

Keys to Success and Failure: Industry Experience
Dr George Butler, Vice President and Head, Worldwide Regulatory Affairs AstraZeneca Pharmaceuticals Ltd, USA

Session 3: Keys to Success and Failure in the Review Process

Quotes and extracts from the Workshop report

All aspects of interactions with agencies, as well as the data itself, should reflect the highest degree of integrity. In dealings with agencies it is essential to create mutual respect and trust through open and honest communications which, as mentioned earlier, must work both ways. Data integrity requires not only a complete application but also well designed clinical trials with validated endpoints that meet the necessary standards of evidence and clarity of presentation required by the reviewer.

Dr Bonnie Goldmann

FDA is working on pilot programmes involving more end of Phase IIa meetings. This would mean greater involvement in dose-ranging and pharmacokinetic trials to try to formulate better advice when the end of Phase II is reached and the Phase III programme is being discussed.

Dr John Jenkins

FDA has no expectations that drugs are perfect but if the reviewers find out, during review, about a problem that has not been revealed openly they will immediately be suspicious that there are other matters that have not been revealed. This can 'kick the reviewers into overdrive' with a result that they dig deeper and deeper into the submission looking for concealed data. Once trust and credibility has been lost it is hard to retrieve the situation

Dr John Jenkins (Discussion session)

In terms of the company portfolio, the parallel launch is a means to maximise patent life but also makes best use of the commercial and technical expertise in the company. An enormous amount of planning goes into the launch of a product but, once the product is approved, the project team may be reassigned to other projects. It is inefficient and impractical to repeat a major launch year after year in different regions.

Dr George Butler

Institute survey on The changing regulatory environment: Reality and Perception

In preparation for the Syndicate discussions, the survey had asked companies and agencies what they believed were the main critical success factors for achieving a successful registration. The responses could be summarised under four main areas:

■ **Company strategy:** Strong science-based decision making at all stages of the development process and a focus on products that satisfy unmet medical need or demonstrate

superiority in terms of efficacy and safety;

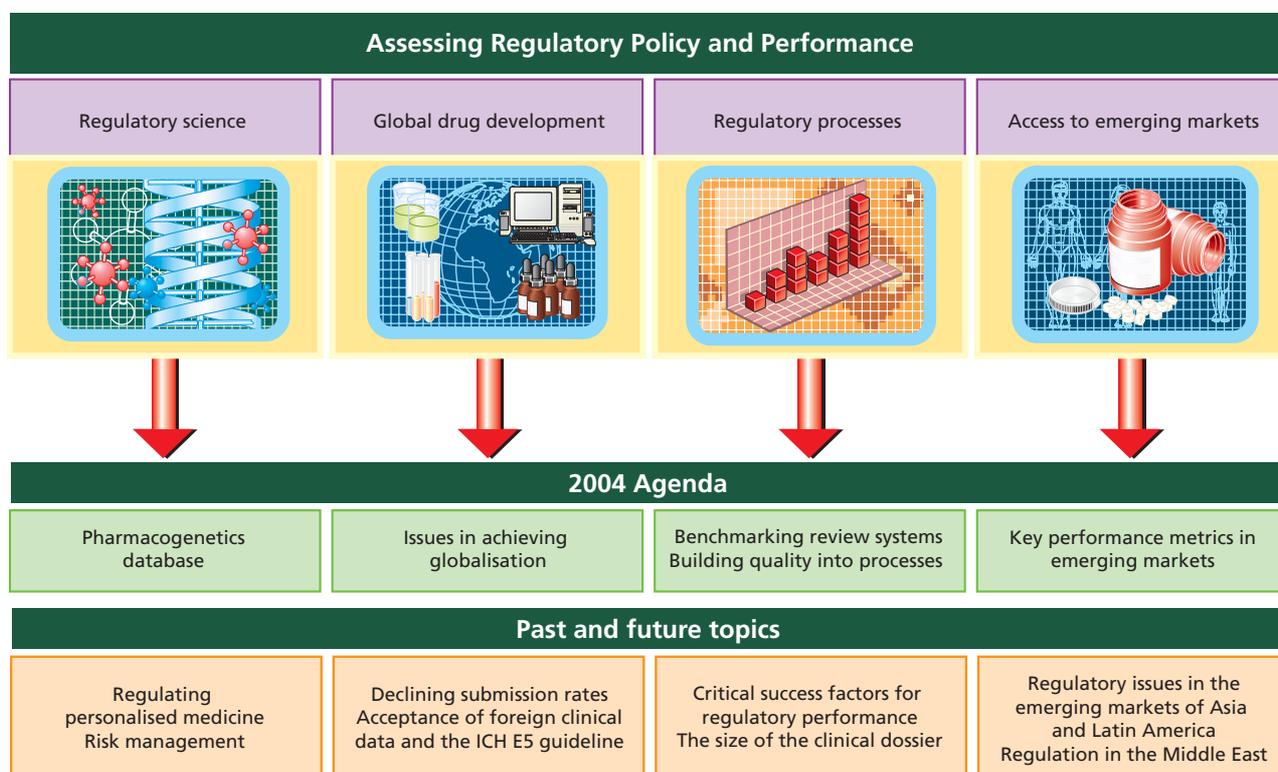
■ **Technical data:** Well thought out clinical programme that strongly supports the desired label and a good understanding of regulatory precedents;

■ **Regulatory Affairs function:** The need for the department to have adequate influence and status within the company and be

involved at a suitably early stage in the development process. The need for the function to have an effective understanding of the authorities' interpretation of regulations;

■ **Communication:** Early, open and frequent dialogue between companies and agencies with continuity and consistency in regulatory advice, aligned to clinical and regulatory strategies.

CMR International Institute for Regulatory Science



Members of the Regulations Advisory Board (2004)

Dr David Jefferys (<i>Chairman</i>), Head of Devices Sector, Medicines and Health products Regulatory Agency (MHRA)	UK
Prof. Gunnar Alván, Director General, Medical Products Agency	Sweden
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 Agency for the Evaluation of Medicinal Products, (EMA)	EU
Dr Milan Smíd, Director, State Institute for Drug Control	Czech Republic
Dr Robert Peterson, Director General, Therapeutic Products Directorate, Health Canada	Canada
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, Senior Vice President, 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, Director, Medical, Regulatory Affairs and Pharmacovigilance, Eisai Co. Ltd	Japan
Dr Paul Huckle, Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline R&D	UK
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