Risk Management:
The role of regulatory strategies in the development of new medicines

Meeting Report

C Anderson, JAN McAuslane & SR Walker

Woodlands Park Hotel, Surrey

25th- 26th April 2002

Mission Statement

CMR International Institute for Regulatory Science, an independent, not-for-profit research organisation, aims to establish the thought leadership role in the development and implementation of regulatory policy in the field of medicines innovation.

CMR International Institute for Regulatory Science
is a not-for-profit division of CMR International Ltd.

Workshop Objectives

The Risk Management workshop was held on the 25th and 26th April 2002 at the Woodlands Park Hotel, Cobham, Surrey, UK.

The meeting was attended by 46 delegates including representatives from 11 international regulatory authorities and 24 companies (including 13 leading and 11 other companies). See Appendix 1 for a listing of workshop attendees.

The primary objective of the meeting was to develop a global perspective on risk management from both regulators and companies. It was also the intention to develop recommendations to ensure that the number of medicines available world-wide is maximised by :

- A discussion of the regulatory, risk management strategies used in companies during the development of NASs and how these are changing.
- Reviewing benefit/risk decision making in agencies
- Sharing experiences of risk management techniques during product development, identifying areas for improvement and good practice, by a review of recent case-studies

The overall intention being that by the end of the meeting, delegates were able to provide recommendations for the future role of companies and agencies to increase partnering (company-company, agency-agency & company-agency) during product development and hence reduce risk.

The Workshop

The workshop began with a series of presentations under two main headings which included the following topics:

Industry Issues & Strategies

- Risk management: the new paradigm
- The use of models for risk-benefit assessment
- Strategies, practices and tactics for reducing risk during the development of a new medicine
- Industry Case Study

Improving partnering during product development

- Visions from a European perspective: the MCA
- Post marketing surveillance: Its role in risk management
- Panel discussion: Views on the FDA and MHLW
- Factors influencing risk management in EU
- Risk Management: a government auditors perspective

Copies of the slides presented at the workshop can be found in appendix 2.

Syndicate Discussion

Following each presentation, a Chairman moderated discussion and debate between speakers and delegates, then all attendees were divided into four allocated syndicate groups. Each group was given one of two topics to discuss and debate in detail, hence two groups covered the same topic:

- Improving communication between companies and agencies during a product's life-cycle (transparency of decision making)
- How can regulatory strategies improve risk management practices in order to decrease attrition rates and hence increase the availability of new medicines?

The objective of each group was to produce a definitive list of recommendations and proposals for industry and regulatory authorities based on the subject of their title. In order to stimulate and focus the discussions towards specific recommendations, a list of questions were provided by CMR International. Responses to the list of questions provided have been amalgamated for the two groups designated to debate each topic. These key points are summarised below under each question heading.

Summary of syndicate discussions

Improving communication between companies and agencies during a product's life-cycle (transparency of decision making)

? **Information Gaps**

- Information exchanged between companies and regulatory authorities and between authorities themselves world wide needs to be shared.
- Greater access to scientific advice from some agencies is needed in terms of timing, frequency and ease of access, in particular within the EU.
- There needs to be greater simultaneous interactions between stakeholders (including international experts who may be independent of authorities and companies), not only during development but also post-launch with continuous information flow.

? **Company Collaboration**

- Companies should share methodologies with other companies, regulatory authorities and other stakeholders providing their commercial interests and intellectual property are protected.
- Companies should make joint efforts on risk management involving all stakeholders (patient organisations, healthcare providers etc) regarding types of risk, mechanisms of risk and preventative methods for risk.
- Companies could learn from the publication of negative data and learn from each other via regulatory authorities.

? **Incident Management**

- Contingency plans should be created for both natural events (e.g. safety issues) and malicious events (e.g. poisoning or media attacks).

- Responsibility for patients needs to be defined in preparation of unpredictable events.
- Companies should develop risk management plans early in development which are revised over time and include the assessment of:
  (i) The possible risks;
  (ii) Possible changes in the frequency of these risks;
  (iii) The unidentified risks;
  (iv) Strategies for solving risks.

? **Alignment of Agencies' Perspectives**

- On scientific grounds there is good alignment between agencies on their perspectives and principles but on cultural and medical practice aspects there is not. However, is it reasonable to expect complete alignment?
- The differences in agency alignment need to be identified and then evaluated as to whether or not these are acceptable for the future.

? **Science versus Public Acceptability**

- It is unrealistic to expect only science to prevail with respect to risk management. Scientific understanding needs to be boosted to minimise and dispense with politics, perception and gossip.
- There needs to be a more realistic regulatory, social and political setting as well as more realistic expectations.
- Communication and education are needed to put a realistic operational framework in the public domain.
- To improve public acceptability of risk management, patients, carers, practitioners and politicians must understand:
  (i) The concept of benefit/risk;
  (ii) The issue of access to medicines (i.e. cost/benefit ratios);
  (iii) Some licensed medicines only benefit society as a whole rather than the individual, e.g. vaccines.
- To achieve improved understanding there needs to be:
  (i) 'Friendly' information exchange using modern communication tools; with agreement on the minimum amount of digestible information that can be given to a patient to eliminate 90% of the misuse of a drug (perhaps the use of flash card as opposed to the summary of product characteristics (SPC));
  (ii) Targeting of multiple educators: media, practitioners;
  (iii) Pressure on governments to create more resources for regulatory authorities;
  (iv) Forums and workshops for discussion and debate;
  (v) Definition of clear communication strategies for the sales force so that the 'total product' is presented, i.e. not just positive aspects but also the risks and management of risks;
  (vi) Identification of best communication strategies (letters are not considered to be the most effective) and goals with respect to risk management.
- Principles for communication strategies are:
  (i) Good faith;
  (ii) Early, open discussion of outcomes;
  (iii) Full and detailed information for all stakeholders;
  (iv) Early sharing of differences in perspectives and recommendations, so that these can be solved.

? **Information Available to Companies and Regulatory Authorities**

- The same information is not available to companies and regulatory authorities with respect to an individual product.
- Companies have more information than a regulatory authority on a specific drug during development.
- Regulatory authorities have much more post-marketing safety data than a company on drugs of the same class.
- All data that are not commercially sensitive should be available in the public domain.

How can regulatory strategies improve risk management practices in order to decrease attrition rates and hence increase the availability of new medicines?

? **New Paradigm**

- Are the new products referred to as 'lifestyle drugs' actually drugs for emerging diseases where it is harder to quantify benefit (and hence benefit/risk ratio)?
- Assessment and development are the same for all drugs but the challenge is to maximise existing sources of information by:
  (i) Looking at pre-clinical results carefully before going into clinical development;
  (ii) Partnership between agencies, consumer groups and companies;
  (iii) Early involvement of agencies and patients to ensure that development is focussed.

? **Product Development Practices/Models**

Attrition Rates:

- Is the aim to decrease attrition rates or to have appropriate and earlier attrition?
- To decrease attrition rates, we need to:
  (i) Manage the risks with all groups (including those not directly involved with the project);
  (ii) Involve consumer groups earlier, particularly for 'lifestyle drugs';
  (iii) Link pre- and post-marketing development more closely in companies and regulatory authorities to maximise the use of existing knowledge;
  (iv) Consider the intended population, i.e. healthy/very sick, short term/chronic therapy (trials are artificial);
  (v) Plan from Day 1 how the product will be used in the market place, so that a plan is prepared for the following:
    - Known risks where signals were seen in development that should be monitored;
    - Theoretically possible risks (based on scientific knowledge);
    - Unknown risks where no signals were seen in development.
  (vi) Understand what is happening in the market place regarding adverse consequences such as deaths and hospitalisations due to adverse events. What medication errors are involved? For example, is there brand name confusion? It is only by understanding the causes of risk management that interventions can be designed.
- The Risk Management Team should not only be comprised of the Pharmacovigilance Group but should include the Communications Group and others.

Trial Design:

- Early scientific advice, prior to clinical trial initiation, is needed from regulatory authorities (already formalised in US) and experts outside the company.
- Data from early trials can be used to identify risks for the population; these can be taken into account in Phase III to generate more information. In turn, this information can be used to identify how risk will be managed when the product is on the market.

Learn from Collective Experience:

- There is the opportunity of learning from experience which could be enhanced by authorities sharing collective experiences they have gathered from multiple companies.
- Regulatory authorities are now in dialogue with each other more about adverse events and product withdrawals but, for better understanding, they could talk simultaneously to multiple companies and share information.

Companies to Share Approaches to Risk Management:

- Need to understand:
  (i) How companies are organised/structured?
  (ii) What governance is there?
  (iii) Are there focussed risk management groups? If so, how are they working and are they effective?
- Can tools for safety and risk management be shared?
- Can companies learn from products that are submitted to regulatory authorities with a negative outcome?
- When products reviewed by an advisory committee in the US are subsequently not approved, companies could learn from the information in the briefing documents but this can be controversial.

Tools:

- Need to consider Bayesian statistics and sharing placebo controlled data to understand drug responses which may be difficult to do but still a possible option.

? **Patient Information**

- Patient focus is important; in addition to the draft label companies should also have a draft patient leaflet early in development for discussion with regulatory authorities; this would help to focus the regulatory authority on patient benefit.

? **Education of Physicians and Patients**

Who Educates?

- Many people educate, but companies and regulatory authorities have responsibilities as a source of information to ensure patients are receiving correct, reliable information.
- It is important that new legislation contains proposals about sharing and providing information.
- Physicians and patients also have joint responsibilities for the management of doctor/patient interactions, management of current diseases and learning about medicines being taken.

How Is Education provided?

- Paper leaflets are used for education but there must be other ways of communicating, e.g. IT advances; two-way communication; use of intermediaries such as patient careers to educate patients about new therapies.
- For lifestyle drugs the relative benefit/risk is difficult to understand; the challenge is to use alternative methods of communication with physicians and patients, e.g. risk scales.

What Education Do We Give?

- Are patients' expectations all related to benefit and no risk?
- No drug is without risk and regulatory authorities have a role to communicate this with credibility.
- Risks need to be conveyed relative to every day activities, e.g. crossing the street, and relative benefits, e.g. the drug only works in three-quarters of the population.
- Positive messages are as important as negative in reaching the right decisions.
- The side effects are emphasised too often.
- The media are into risk; the industry and regulatory authorities need to get them back into benefit.

? **Off-label Use of Medicines**

- Companies and regulatory authorities should have a good idea of how a product will be used off-label; this is where there is a great deal of risk and potential for adverse events.
- Off-label usage requires education; regulatory authorities and companies have a responsibility to develop information on this.

? **Pharmacogenomics**

- There is a need to understand pharmacogenomics and how this might play a role in risk management.

Meeting Outcomes

- Task force/workshops for companies and regulatory authorities to share risk management information, methodology and 'best practice'.
- For CMR to hold a workshop involving regulatory authorities, companies, media and communication experts to re-design communication tools, e.g. Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL). Perhaps a risk benefit statement should be included in SPC.
- Is there a pan-industry, pan- regulatory authority body, such as the WHO, that could create signal detection software or a common epidemiological database in a concerted way?

Risk Management – The Next Steps

June 2002.

- CMR to generate and distribute a **meeting report.**

October 2002.

- CMR to generate and distribute the **workshop proceedings.**

To be announced.

- CMR to hold a **discussion meeting on communication strategies between companies and regulatory authorities.**

Delegate feedback: quotes

"Excellent interaction with experienced people."

"The workshop met my expectations regarding exchange of information and exceeded my expectation regarding open dialogue (especially with Agency members)."

"Very good presentations / excellent opportunity to network."

"Very useful discussions with good balance of Industry & agency representatives."

Appendix 1 : Workshop Attendees

Dr E Abadie	Directeur du Département Pharmaco Toxico Clinique des Médicaments	Agence Francaise de Securite Sanitare des Produits de Sante, France
Dr P Branagan	Director, Medical Affairs & Clinical Services	Allergan Ltd, UK
Dr P Porter	Vice President, Drug Regulatory Affairs	Amersham Plc, UK
Dr G Butler	Senior Vice President World-wide Regulatory Affairs	AstraZeneca Pharmaceuticals, USA
Dr C Sunstedt	Director, Global Clinical Science	AstraZeneca, Sweden
Dr N Pauly	Global Pharmacovigilance & Epidemiology	Aventis Pharma, France
Dr B Gansewendt	Global Regulatory Affairs	Bayer AG, Germany
Miss C A Anderson	Research Associate	Centre for Medicines Research International Limited, UK
Mr Hajed Hashan	Research Fellow	Centre for Medicines Research International Limited, UK
Dr C Lumley	Senior Vice President	Centre for Medicines Research International Limited, UK
Dr J A N McAuslane	Director, Institute for Regulatory Science	Centre for Medicines Research International Limited, UK
Prof. S R Walker	Chief Executive Officer	Centre for Medicines Research International Limited, UK
Dr M Clayman	Vice President, Global Regulatory Affairs	Eli Lilly & Company Limited, USA
Dr T Lönngren	Executive Director	EMEA, UK
Dr G Kreutz	Head, Dept Clinical Pharmacology 1	Federal Institute for Drugs and Medical Devices, Germany
Dr F Frattini	Site Head, International Drug Regulatory Affairs	F. Hoffmann-La Roche Limited, Switzerland
Dr M Foulkes	Deputy Director	Food and Drug Administration - CBER, USA

Dr P Huckle	VP, European Regulatory Affairs	GlaxoSmithKline, UK
Dr R Peterson	Director General	Health Canada, Canada
Dr C Towler	Director of Strategy Development	Imperial College London, UK
Dr G Burton	Senior Vice President, Global Clinical Research	Johnson & Johnson Pharmaceuticals Research & Development, USA
Dr S Larkin	Director Regulatory Affairs & Safety	Kyowa Hakko UK Ltd, UK
Mrs T Cemeli	Regulatory Affairs Department	Laboratorios D. Esteve, SA, Spain
Dr U Franken	Regulatory Affairs Head	Laboratories Uriach, Spain
Dr H Harrison	Medical Writer	Langton Biomedical Ltd, UK
Dr D Jefferys	Chief Executive	Medical Devices Agency, UK
Dr J Raine	Director of Post Licensing	Medicines Control Agency, UK
Mrs T Janse-de-Hoog	Deputy Secretary	Medicines Evaluation Board, The Netherlands
Mr F Mussen	Associate Director, Regulatory Affairs	Merck Sharp & Dohme (Europe) Inc, Belgium
Dr R Pietrusko	VP Worldwide Regulatory Affairs & Pharmacovigilance	Millennium Pharmaceuticals Inc., USA
Dr B Gerdén	Pharmacovigilance Assessor	Medical Products Agency, Sweden
Dr N Lacy	Auditor Manager	National Audit Office, UK
Dr F Møllgaard	International Regulatory Affairs	Novo Nordisk A/S, Denmark
Prof. A Broekmans	Director International Pharma Policy	NV Organon, The Netherlands
Mr R de Leeuw	Head of Medical Biological Section	NV Organon, The Netherlands

Dr P Farrow	Vice President, Clinical Research	Pfizer Inc., UK
Dr R Spivey	Senior VP, Corporate Technical Policy	Pharmacia Corporation Worldwide HQ, USA
Mr D Gilbert	Head of Global Regulatory Affairs	Pharmacia Limited, UK
Ms J Shott	Regulatory Affairs	Procter & Gamble Pharmaceuticals Inc, UK
Dr T Hughes		Roche Products Limited, UK
Dr G N Thompson	Director, Corporate Regulatory Affairs	Sanofi-Synthélabo, France
Prof. B Schulz	Head Global Regulatory Affairs	Schering AG, Germany
Dr J Saillot	Vice President Clinical Research Operations, Medical & Safety Services	Schering-Plough Research Institute, USA
Prof. S Vožeh	Head of Medical Division	Swiss Agency for Therapeutic Products, Switzerland
Ms D Helms	Regulatory Affairs	TAP Pharmaceutical Products Inc, USA
Dr L Hunt	Director, Drug Safety & Evaluation Branch	Therapeutic Goods Administration, Australia