R&D Briefing

Risk management

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Workshop Highlights

Identifying and Developing Effective Stakeholder Communication During Drug Development

Workshop on Risk Management held by the CMR International Institute for Regulatory Science, Washington DC, 12-13 December 2002

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

The Proceedings of the first CMR International institute Workshop on *Risk Management: The role of regulatory strategies in the development of new medicines* is available as a 90-page publication, priced £95.00.

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Risk Management: Identifying and Developing Effective Stakeholder Communication During Drug Development

Highlights from the Second Workshop on Risk Management held by the CMR International Institute for Regulatory Science, Washington DC, 12-13 December 2002

Key points

Risk communication strategies need to be implemented at a much earlier stage and involve a far wider range of stakeholders.

Better communication skills must be developed in order to put the risks and benefits of new medicines into perspective for health care providers and patients. The old adage that 'the patient is waiting' must be revisited as the patient is *not* waiting when it comes to seeking information about medicines. If the information they require is not forthcoming from the authorities and companies, patients will be looking elsewhere.

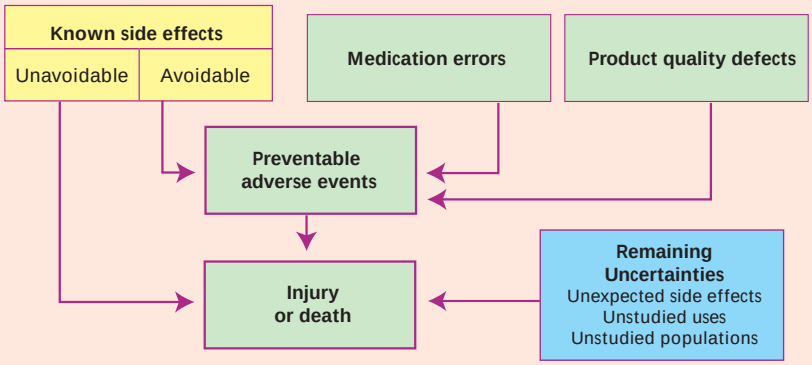
There is a 'traditional' preoccupation with identifying serious but rare side effects and adverse reactions to drugs whilst, statistically, patients are at far greater risk of being harmed by inappropriate prescribing and medication errors or by not following instructions for dosage and use. These factors need to be included and addressed in developing risk management strategies.

Both industry and regulators might be over cautious in their approach and may be under-estimating the degree of risk that patients are prepared to accept for medicines that offer a clear improvement in the quality of life. Such issues need to be discussed in an open and transparent manner with all the stakeholders at the table.

Sources of risk from drug products

One of the fundamentals is that there are two types of risk to be addressed, those which are avoidable and those which cannot be anticipated in advance.

Presentation by
Dr. Catherine Bonuccelli

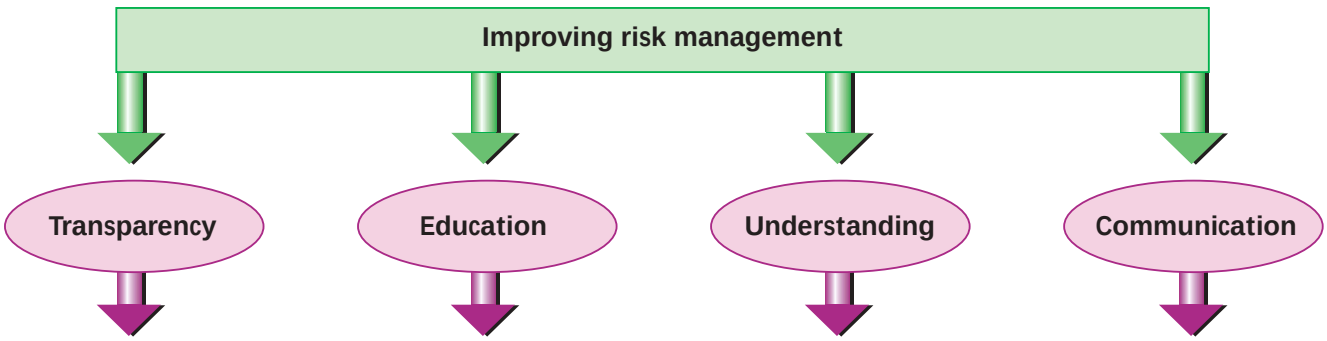


Risk management plans will include both proactive and reactive elements

Background

Following a number of high profile product withdrawals, risk management has an increased priority for the pharmaceutical industry. Whilst the concept of risk management for medicines has been under discussion for many years, few companies have yet built specific risk management strategies into their drug development programmes. Similarly, benefit/risk assessment is becoming an increasingly important factor in the drug approval process, but regulatory authorities have yet to develop clear guidance on the parameters for such assessments.

Against this background the Centre for Medicines Research (CMR) International's Institute for Regulatory Science held two workshops in 2002 at which participants from senior management in industry and regulatory agencies explored the need to develop a clearer framework for risk management throughout the life cycle of a medicine. The first workshop, held in the UK in April 2002 focused on regulatory strategies and models for benefit/risk assessments. One of the main recommendation was that industry and health authorities together should look more closely at their current communication strategies and assess where improvements could be made to meet the requirements of all stakeholders.The Institute therefore convened a second Workshop to look specifically at '*Stakeholder Communications during Drug Development*' in order to implement best practices for the benefit of all parties. The highlights of the second Workshop, which took place in Washington DC, 12-13 December 2002, are summarised in this briefing



- Learn from collective experience
- Share approaches
- Share best practice

- Increased information sharing
- Off-label use of medicines
- More 'user friendly' information, use of IT opportunities

- Reasonable balance of benefit & risk
- Identification of responsibility
- Expectations from medicines

- Improved communication tools
- Early scientific advice
- Greater interactions

Improving Risk Management Strategies as represented in the recommendations and conclusions from the first Risk Management Workshop *(see inside cover)*

Communicating to the Users of Medicines

Session 1. Communicating to the Users of Medicines

PROGRAMME

Chair: **Dr Kathy Zoon**, Director, Centre for Biologics Evaluation and Research, Food & Drug Administration, USA

Guiding Principles for Improving the Effectiveness of Patient Stakeholder Communication.

Dr Eleanor Vogt, Senior Fellow, Institute for the Advancement of Community Pharmacy

The Role of the Pharmaceutical Industry in Minimising Risk Through Better Product Information

Mr Steve Mott, Executive Director, Datapharm Communications Ltd, UK

FDA Communication to Health Care Providers

Dr Susan Ellenberg, Director of Biostatistics and Epidemiology, Centre for Biologics Evaluation and Research, Food & Drug Administration, USA

How Can Users Get the Information They Need or Want?

Dr Robert Peterson, Director General, Therapeutic Products Directorate Health Products and Food Branch Health Canada and Dr Hans Stocker, Director, Swissmedic ,Switzerland

Highlights from the Discussions

Risk evaluation and management of communications must start early in the product development cycle and cannot be left to the approval stage. Risk communication needs to be considered not only by companies and regulators but also by the community that will be using the products. The traditional regulatory approach is to focus on including risk information in the product labeling for healthcare providers and patients, but novel methods of communication need to be developed. The needs of the healthcare provider must also be considered. It is their role not only to evaluate the risk-benefits of the different treatments available but also to communicate the information in a way that the patient can understand.

Establishing and planning a risk communication strategy and deciding how to utilise data to develop the appropriate messages about a product is of paramount importance. Whilst much effort goes into the preparation of the package insert, busy physicians rarely have time to study them. Better ways to communicate timely, relevant and targeted messages are required and the way forward lies in networking and information exchange. No one group – industry, regulators, physicians or consumers – has sole responsibility, it has to be a partnership.

Short and long term goals

The short term goal is a better informed and more involved patient who uses medicines correctly and avoids unnecessary risks arising from misuse. The long term goal is to improve clinical outcomes and hence the business success of new medicines. The overall goal is to protect and improve public health.

A key issue is to build trust between all stakeholders – industry, regulators, health care providers and patients – by involving all parties in the discussion of ways to improve communication and the dissemination of information.

Along with improved product-related information, there is a need to develop information for the public on disease management and the use of interventions other than prescription drugs.

Discussion points

- Timing: Initiatives to involve physicians, patients and consumers in the development of a communication strategy for a new medicine must start at an early stage and not wait until the product is approved for marketing.
- Inherent Risk: Patients need to be educated to understand that all medicines carry risks, but information on the risk of a particular medicine must always be put in the context of the risk of the disease itself and the consequences of not using the medicine correctly.

Teaching Proverb

"Tell me and I will forget;
Show me and I may remember;
Involve me and I will understand"

Anon.

Communicating to the Users of Medicines

Discussion points *(cont.)*

- Mode of communication: Whilst it is acknowledged that patient leaflets need improving, this alone will not satisfy the patients' demands for more and better information. Use of the media and different electronic and audio-visual methods of communication need to be explored.
- Websites: A system for the accreditation of websites is needed either by professional or governmental organisations or trade associations to certify that the information is authentic and can be trusted.
- DTCI: Discussions on direct to consumer information frequently become confused with the more controversial issue of direct to consumer advertising (DTCA) and clear (regulatory) guidelines and definitions are needed to separate information from advertising.
- Sharing information: The interpretation of safety information from the databases of different regulatory bodies needs to be made more transparent and information held by industry and regulators needs to be shared.
- Physicians: Whilst the focus is on 'empowering' the patient, the attitude of physicians also needs to change in order to accept and interact with better informed and assertive patients.

Patient Information

The recent debate in the European Parliament on revision of the EU pharmaceutical legislation had highlighted some of the conflicts and controversies, in particular the question of whether a company can make information on prescription medicines available to the public without breaching EU advertising regulations. It was also apparent that whereas patient groups would welcome access to information from industry, with appropriate controls, consumer groups argue that there is no role for industry in providing patient information. Datapharm is working with patient groups in the UK to identify where industry could legitimately and understandably have a role in delivering information.

Steve Mott

Action items

- Both companies and regulatory authorities should establish departments or groups within their organisations that include educationalists who can advise on communicating information to physicians, patients and consumers. (There was a suggestion that providing appropriate educational programmes could become part of the conditions of approval for a medicine).
- Suitable benchmarks need to be developed to enable progress to be measured in terms of improved clinical outcomes and improved compliance as a result of better information.
- Methods are needed to test communication tools and assess whether they achieve their objectives in terms of increasing knowledge and ultimately improving outcomes.
- There are funding issues that need to addressed. There must be commitment from Senior Managers and Senior Executives in industry and the regulatory authorities in order to move forward.
- A good business case needs to be made to demonstrate that failure to communicate adequately with providers and patients in the short term will cost companies and healthcare providers more in the long term due to the failure of risk management programmes

A 'new look' in risk communication

Many of the problems encountered with medicines are not related to inherent risks of the product but arise from the system that delivers the product to the patient such as medication errors and a lack of understanding on the part of the patient about the correct use of the medicine. In addressing such problems society needs to get away from the culture of 'blame' and move towards a 'new look' in risk communication, using the expertise that is spread throughout society in order to learn better ways to minimise avoidable risk and understand intrinsic risk factors associated with medicines.

Dr Eleanor Vogt

Company-Agency Interactions

Session 2. Company-Agency Interactions

PROGRAMME

Chairman: Dr Murray Lumpkin, Principal Associate Commissioner, Food & Drug Administration, USA

Risk Assessments During Product Development

Dr Leonie Hunt, Director, Drug Safety & Evaluation, Therapeutic Goods Administration, Australia

Dr Murray Lumpkin, FDA

Communicating the Views of Regulators Within a Company

Dr Mike Clayman, Vice President, Global Regulatory Affairs, Lilly Research Laboratories, USA

Highlights from the Discussions

Traditionally there has been a preoccupation with identifying safety issues on the basis of pharmacological and toxicological data and the management of adverse drug reaction reports. The emphasis needs to move not only to managing patient safety but also to a consideration of the concept of risk, and risk tolerance and whether this differs among stakeholders. Industry can have a bias in assessment of risk, but this is not necessarily a positive bias, because of liability issues. Regulators might be similarly cautious but, ultimately, it is the risks that the patients and the practitioners are willing to tolerate that will determine the success or failure of the drug.

Observations

Both industry and regulators are well versed in risk management when this involves handling data on relatively rare adverse reactions, but the same does not apply to managing the risks of misuse of products through poor prescribing practices and patient non-compliance.

Millions are spent looking for rare events whilst scant attention is given to estimates that up to fifty percent of patients are not following product administration instructions correctly. Communication initiatives and risk management strategies need to address this.

Discussion points

■ Limitations of safety data: Practitioners and patients need to understand the nature of the data that is available at the time of authorisation, and its potential limitations in relation to assessing the safety of the medicine. This would lead to better informed dialogue between practitioners and patients on the choice between a new product with (inevitably) unknown safety factors and an older drug that is better known but may be less effective.

■ Sharing data: There needs to be greater transparency and information-sharing in relation to safety information. Industry has in-depth knowledge about its own products but regulators have the advantage of seeing safety information and signals across a range of related products.

■ Global strategies: Both industry and regulators need to learn from the fact that we are dealing with global markets and to ensure that communication strategies are not limited to specific geographical areas.

■ Global launch: Evaluating safety on the basis of tightly controlled populations in clinical trials can never reflect the 'real world' situation of the post-launch period. Dramatic and, in some cases, damaging situations can arise when there is an almost simultaneous global launch of a new product.

Curtailing the scope of the global launch of a new drug might be an answer but any such restrictions would need to include provisions for pay-back in terms of patent life.

Company-Agency Interactions

Discussion points *(cont.)*

■ Cultural factors: Differences in the willingness of patients to accept risk become more apparent when clinical trials are carried out at a global level. Differences in culture, however, can also affect the readiness of patients to report adverse effects which may be perceived as a challenge to physicians' authority.

■ Addressing all ADRs: It is important not to try to 'explain away' individual adverse events that appear in clinical trials, by citing exceptional circumstances. There have been high-profile instances where safety issues identified at the clinical trial stage, but not fully explored, have led to the withdrawal of the product after launch.

■ Scope of communications: In the global arena it is equally important to ensure that communications extend beyond the interface between the regulators and the regulated industry and involve consumers and physicians in an effective manner.

Global harmonisation of risk management:

Asked whether it is feasible for a company to think in terms of a global risk management strategy for a new product, Dr Clayman felt that it was too early to think in such terms. Even within the EU it is difficult to agree a single risk management plan to meet the needs of all European regulators. Whilst a harmonised plan is desirable, at the present time it needs to be designed on a case by case basis because of differences in medical practice and the perception of acceptable risk. This affects the definition of useful and relevant information in terms of best use of the product and 'educating' physicians. There is no single paradigm and it is highly influenced by differences in culture.

Extract from the discussion in Session 2

■ Risk and lifestyle: Both industry and regulators may be underestimating the degree of risk that patients are prepared to accept for medicines, including so-called 'lifestyle' products where the health problem may not be perceived as sufficiently serious to justify any risk. Laser eye surgery was cited as an example of a procedure which carries specific risks: these are clearly spelt out to patients and the demand for the treatment is, nonetheless, escalating.

■ Summaries: Information overload is becoming a serious problem for investigators in clinical trials but there is a potential conflict for companies. Providing clinicians only with targeted extracts and summaries of data may not fulfil regulatory obligations to provide, for example, unblinded reports on all adverse events.

New Regulatory Challenges

- **The globalisation of clinical trials;**
- **The shift in the design of clinical trial programmes, from efficacy hypothesis testing to safety hypothesis testing;**
- **The development of products to counter the threat of bioterrorism;**
- **The trend towards combination products, including drug-device, drug-biologic and drug-nutraceuticals combinations;**
- **The emerging gene and tissue derived therapies; and gene therapy**

Regulators are being faced with significant new challenges in terms of safety assessment

Presentation by
Dr Murray Lumpkin

Company-Agency Interactions

Action Items

- The practice of drawing up 'target' product information (labeling) from the outset and before product development commences is gaining acceptance and should become a routine tool for measuring whether a new product is meeting expectations as the research and development phase proceeds.
- The criteria for target labeling should be established in discussion with epidemiologists and the 'safety hypothesis' for the drug must always be written into the document. (The concerns of liability lawyers about including such information at an early stage must be overcome).
- Decisions on whether to proceed with a research project should be made by an 'independent' group within the company and should not involve marketing personnel (although marketing will be closely involved in establishing the initial target labeling).
- Traditionally, clinical trials have been designed primarily to test the efficacy hypothesis but a clinical trial programme that also tests the safety hypothesis is essential.

Programme rationale

All stakeholders, and particularly the investigators and ethics committees, need to be given a clear insight into the rationale of the development programme for a new product, including risk management. This will enable adverse event reports and other safety issues that arise in the course of the trials to be evaluated in context and in a more understanding way, and should avoid 'reactive' situations.

Dr Leonie Hunt

PPR Calculation

Proportional Reporting Ratio (PRR) used in signal screening and trend analysis

Presentation by Dr Mike Clayman

	Event of interest	All other events
Drug of interest	a	b
All other drugs	c	d

$$PRR = \frac{a(c+d)}{c(a+b)}$$

The Communication of Companies' Risk Management Plans

Session 3. The Communication of Companies' Risk Management Plans

PROGRAMME

Chairman: ***Dr George Butler,*** *Vice President and Head, Regulatory Affairs, AstraZeneca Pharmaceuticals, USA*

The Development of a Risk Management Plan

Dr Cathy Bonuccelli, Drug Development Business Strategist, AstraZeneca Pharmaceuticals, USA

Communication of Risk Management Plans Within Companies & to the Public

Dr André Broekmans, Vice President Regulatory Affairs & Pharma Policy, NV Organon

Highlights from the Discussions

The 'when, who and what' of risk management spans the whole life of a drug:

- **When:** Risk assessment cannot start too early in the three phases from discovery through development to marketing, although it is doubtful whether any company yet has experience of a risk management plan for a new drug that started at 'Phase 0';
- **Who:** Risk management plans should not only involve cross-functional teams within the company, but also patients, physicians and, perhaps, the purchaser;
- **What:** This involves testing the total hypothesis of safety and reviewing the pre-set decisions which determine when a project should be cancelled' as well as other tools such as 'black box' labels, changes in labeling, reviewing the database and communicating.

New ways of communicating must be sought to help convey the right messages and to overcome the problem of ensuring that prescribers and patients listen to those messages. Industry may find itself working in a more transparent environment but this should help the decision-making process when it comes to comparing the public perception of an acceptable risk against the industry perception, which might, in some cases, be more cautious.

Observations

Although a number of risk management tools and methodologies exist there has been little movement in the last five to ten years and there is an urgent need for companies to establish risk management programmes, making better use of the knowledge that has been gained.

Integrating risk management procedures into the drug development cycle has financial implications that have not yet been addressed. If risk management becomes a mandatory requirement, resources may need to be deflected from other areas.

Since risk management programmes will involve a major investment it is critical that resources are not only directed to the essential issues but also kept in proportion in relation to the benefits that can be expected for patients.

The development of risk management tools is at an early stage and feedback on the effectiveness and validation of different strategies is essential. This should not be confined to information exchange among companies since feedback from the regulatory agencies is equally important.

Concerns about a lack of communication and information sharing were highlighted by the fact that the standard[1] relating to risk management of medical devices is now the European standard and is being taken forward as an International standard, but little is known about it in pharma circles.

[1] BS EN ISO 14971: 2001 - Medical devices. Application of risk management to medical devices

The Communication of Companies' Risk Management Plans

Discussion points

■ Understanding risk: One of the problems in communicating with the public about risk is the fundamental lack of understanding about what an authorisation means in terms of the 'safety and efficacy' of a product. Safety is, at best, provisional at the time of approval and is, of necessity, based only on observations from the limited number of patients included in the clinical testing programme.

■ Patient exposure: The trend towards large-scale global launches for new products with rapid patient uptake as the goal needs to be questioned.

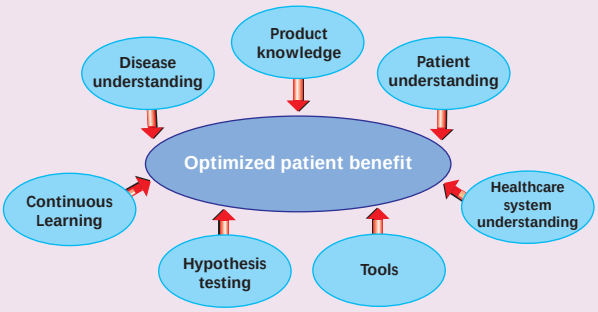
Senior management and marketing colleagues need to be persuaded that it is in the best, long term interest for new products to have a slower launch with greater control over the patient population that is exposed to the drug in the critical early stages.

■ Proactive communications: The first several months after the launch of a product are a critical time when companies should be proactive in communicating with the authorities to ensure that potential safety concerns are placed in perspective against the background incidence of events in the patient population and the data accumulated during product development.

■ Unexpected interactions: Discussion of the situation in Singapore raised the issue of the use of traditional, complementary medicines and the potential for interactions that would not normally have been addressed in the development programme.

Optimised patient benefit is the central focus for risk management planning

Presentation by Cathy Bonucelli on The Development of a Risk Management Plan



Action items

■ Whilst the larger companies have been relatively slow to introduce risk management functions into their organisation, the majority of small and medium companies have not even begun to address the subject. Communication of the issues among the industry as a whole is needed and there is a clear role for the industry associations in this.

■ Companies should address any internal misconceptions, particularly among commercial departments, that the admission of risk presents an automatic barrier to the success of a product. The rational and open discussion of risk is fundamental to the success of a risk management programme.

■ Healthcare providers in different settings need to be engaged in discussions of the manpower and resource implications of managing innovative new technologies effectively and monitoring their safety. Longer term planning is needed to meet information and education needs and industry must be closely involved in such discussions.

■ Useful lessons could be learned by working with patients' associations on case studies of potentially valuable medicines that have been withdrawn from the market on safety grounds, to see whether better communications might have prevented this outcome.

■ The regulatory barriers and uncertainties, in Europe, with regard to the information that companies can provide to patients about their products need to be addressed by the authorities as a matter of urgency, in the interests of patients and to meet expectations for more open and transparent communications.

The next steps

The Workshop recognised the need for a 'best practice' guide on risk management but noted that its development would require further sharing of experience from companies' risk management programmes and further feedback from regulatory bodies. Such guidance could be developed in a future workshop involving a wider spectrum of stake-holders, in particular, patients associations.

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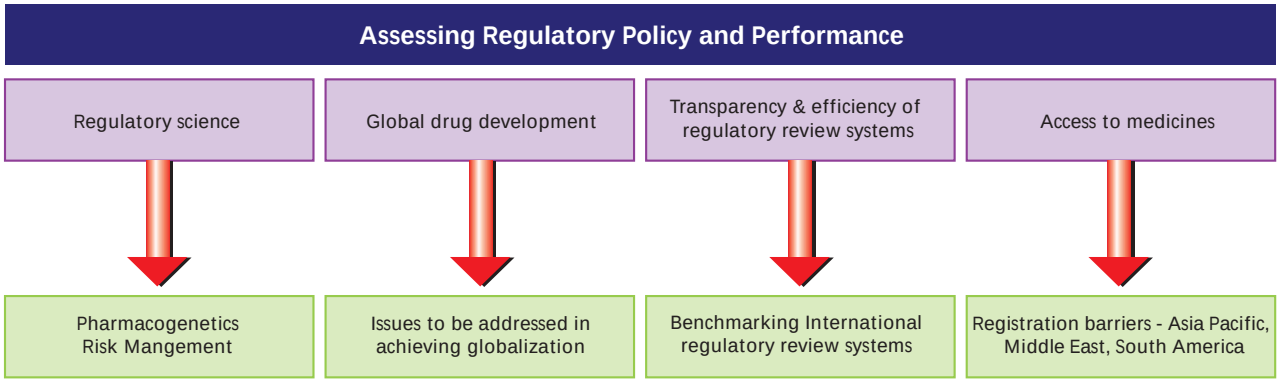

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