RISK MANAGEMENT WORKSHOP 12-13 DECEMBER 2002

IDENTIFYING AND DEVELOPING EFFECTIVE STAKEHOLDER COMMUNICATION DURING DRUG DEVELOPMENT

MEETING REPORT

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1. OVERVIEW

Risk is complex and in managing it we must be aware of public perception, social expectation and acceptance. Every day we undertake activities that carry a far greater risk than we are prepared to accept from a new medicine.[1]

This quotation from the first CMR International Workshop on Risk Management, April 2002, encapsulates the starting point for the second Workshop, held in Washington in December 2002. The focus of discussions had moved on from the predominantly scientific and regulatory aspects of risk assessment discussed at the first Workshop to the broader topic of risk communication as part of the management strategy. Whilst 'risk management' has been a subject of discussion for many years, industry has been slow to introduce formal risk management programmes into the drug development process.

By holding a second workshop on the topic, within a year of the first, CMR International underlined the urgent need for both industry and regulators to build risk management into the fabric of the product approval process. The workshop highlighted the need for a paradigm shift away from the traditional model, where product information intended for those who will be using the medicine (Summary of Product Characteristics in the EU, product labeling in the US) is only discussed at the end of the approval procedure and involves only the company and regulatory agency. A clear message from the Workshop was that risk communication strategies needs to be implemented at a much earlier stage and involve a far wider range of stakeholders.

Pivotal to such communication strategies is the need to develop better communication skills in order to put the risks and benefits of new medicines into perspective for health care providers and patients. At the Workshop, the old adage that 'the patient is waiting' was revisited. The patient is *not* waiting, participants were warned, when it comes to seeking information about medicines and if the information they require is not forthcoming from the authorities and companies, patients will be looking elsewhere.

The 'traditional' preoccupation with identifying serious but rare side effects and adverse reactions to drugs was also a subject for discussion. Whilst this aspect of pharmacovigilance is vital, in reality patients are at far greater risk, statistically speaking, of being harmed by inappropriate prescribing, prescribing errors and by not following instructions for dosage and use. These aspects need to be included and addressed in developing risk management strategies.

Among the other messages from the meeting was the suggestion that both industry and regulators might be over cautious in their approach to risk 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.

[1] Towler, C, *Risk Management: The new paradigm,* Proceedings of the CMR International Risk Management Workshop: *The role of regulatory strategies in the development of new medicines*, April 2002

A feature of the Workshop was the opportunity for participants to contribute to round table discussions at the end of each Session.

Section 2 of this report summarises the main points from the discussions

Section 3 gives further details of the individual presentations and the subsequent questions and answers that they generated.

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science has been set up as a not-for-profit division of the Centre for Medicines Research International Ltd in order to continue its work in the regulatory and policy arena, and to maintain the well established links that the Centre has with regulatory authorities around the world. The Institute will operate 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.

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SECTION 2. OUTCOME OF THE DISCUSSIONS

SESSION 1: COMMUNICATING TO THE USERS OF MEDICINES

In this Session, chaired by Dr Katherine Zoon, FDA, there were presentations giving: the patient and system/stakeholder perspective (Dr Eleanor Vogt, Institute for the Advancement of Community Pharmacy); describing an information system set up by the UK industry (Mr Steve Mott, Datapharm Communications Ltd); discussing the communication channels used by the FDA (Dr Susan Ellenberg); describing the revised product monograph system in Canada (Dr Robert Peterson, Health Canada), and explaining how the new Swiss pharmaceutical law impacts on advertising medicines (Dr Hans Stocker, Swissmedic).

The round table discussions at the end of this Session included the following points and recommendations:

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, again through a procedure involving all stakeholders, information for the public on disease management and the use of interventions other than prescription drugs.

Discussion points

- 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.
- 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.
- 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 audiovisual methods of communication need to be explored.
- 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.
- Discussions on direct to consumer information (DTCI) 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.
- 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.
- Whilst the focus is on 'empowering' the patient this must not overlook the need for physicians' attitudes to change in order to accept and interact with better informed and assertive patients.

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 outcome and improved compliance as a result of better information.
- Methods are also 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 and there must be commitment from Senior Managers and Senior Executives in industry and the regulatory authorities in order to move forwards.
- A good business case needs to be made demonstrating 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.

SESSION 2: COMPANY/AGENCY INTERACTIONS

In this Session, chaired by Dr Murray Lumpkin, FDA, there were presentations: giving a regulatory perspective on communicating risk assessment data during the drug development process (Dr Leone Hunt, TGA, Australia and Dr Murray Lumpkin, FDA); and on communicating the views of regulators within companies (Dr Mike Clayman, Lilly Research Laboratories).

The round table discussions at the end of this Session included the following points and recommendations:

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 giving scant attention 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.
- 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. Education on this aspect would encourage a 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.

Discussion points

- 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.
- 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.
- 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.
- There is a need to develop communications strategies in association with the people who do this for a living, for example colleagues in the media and in education.

- There is a critical interface between evaluating safety in clinical trials, when the populations are so tightly controlled that they do not reflect the actual exposure in the real world, and in the post-launch period. This can be especially dramatic and, in some cases damaging when there is an almost simultaneous global launch of a new product.
- There was discussion on curtailing the scope of the global launch of a new drug and hence controlling sudden exposure to large patient populations, but this would need to include provisions that would give something back in terms of patent life.
- There was a proposal that the concept of 'conditional release' should not be confined to drugs that represent a major therapeutic advance, but should be extended to a wider range of products once clinical efficacy has been established. This would enable early controlled release and exposure to the target population, and 'Phase III' trials designed to confirm the safety hypothesis would be carried out as a condition of the authorisation.
- 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 challenging the physicians' authority.
- 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.
- Both industry and regulators may be underestimating the degree of risk that patients are prepared to accept for medicines, including so-called 'life-style' 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.
- 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.
- The generation of data from signal detection has its strengths and weaknesses and it is important that signals from such systems can be verified. (The WHO system was cited as one that has not been found to be very fruitful as many of the signals cannot be verified).

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.

SESSION 3: THE COMMUNICATION OF COMPANIES' RISK MANAGEMENT PLANS

In this Session, chaired by Dr George Butler, AstraZenica Pharmaceuticals, there were two presentations, the first describing the development of a risk management plan (Dr Cathy Bonuccelli, AstraZenica Pharmaceuticals) and the second discussing communication of risk management plans within companies and to the public (Dr André Broekmans).

The round table discussions at the end of this Session included the following points and recommendations:

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 standard BS EN ISO 14971: 2001 (see Section 3) 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.

Discussion points

- 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.
- The trend towards massive 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 of 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.
- 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.
- 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.

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 needs to be closely involved in such discussions.

- Useful lessons could be learned by working with patients' associations on case studies of potentially valuable drugs 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 or workshops, involving a wider spectrum of stakeholders, in particular, patients associations.

Closing the meeting, Professor Stuart Walker noted the proposal for a further workshop at a later date. He confirmed that this important topic would remain on the agenda of the CMR International Institute for Regulatory Science and be kept under review for future action.

Information on the programme of events for the Institute for Regulatory Science can be found on the CMR International website: http://www.cmr.org

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SECTION 3. MEETING SUMMARY

SESSION 1 COMMUNICATING TO THE USERS OF MEDICINES

Chairman: **Dr Kathy Zoon***, CBER, FDA*

Introducing the meeting, Dr Zoon suggested that risk management should be considered as a five-point programme:

- Risk assessment;
- Risk confrontation;
- Risk intervention;
- Risk communication;
- Risk management evaluation.

She stressed that 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 his/her 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, the likelihood that the physician will read it thoroughly is 'approaching zero'. 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

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Guiding Principles for Improving the Effectiveness of Patient Stakeholder Communication

Dr Eleanor Vogt*, Institute for the Advancement of Community Pharmacy*

One of Dr Vogt's primary messages was the need to build, or in some cases re-build, the necessary 'trust' between those who develop, regulate and provide medicines and the patients that use them. A new generation of patients and patient associations are actively seeking information on medicines and greater involvement in the development of information systems. Surveys have indicated that the concerns of patients about interactions, side effects and using medicines correctly came above the concerns about cost that often pre-occupy healthcare providers.

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. It is not just a question of what to communicate but, more importantly, how to ensure that all the stakeholders are at the table. The patient is no longer 'waiting' but is actively seeking better information and greater involvement, especially through patients' associations. Patients need to be placed at the centre of healthcare delivery. In the necessary learning and educational processes, the old

teaching proverb should be remembered: 'Tell me and I will forget; Show me and I may remember; Involve me and I will understand' (*Anon.).*

Points from the discussion

Need for a new structure: The traditional approval system is based on two parties, regulators and industry, and there is not a structure that facilitates industry, government, patient/consumer groups and healthcare professionals getting together earlier to discuss relevant issues. New systems should be evolving but who should be the catalyst for this? Dr Vogt suggested that, in theory, anybody can be the catalyst, but in the real world we have to recognise that it is the industry that has the resources to support these kinds of endeavours and it is the regulators who have the mandate to make this happen.

Practicality of involving patient group: Using a new stroke drug as an example, it was questioned whether it was realistic to expect the developer to engage the stroke community in discussions of how the patients and providers could best use the product during Phase III trials before the results of the studies are known. Dr Vogt acknowledged that this is new territory but stressed that the community that is going to benefit from the product should be involved in its 'ownership' as early as possible.

Another discussant suggested that companies should consider having 'patient benefit advisors' in the way that they have outside medical advisors and pharmaceutical development advisors. This could start in a small way and be worked up.

Example of AIDS patient groups: It was suggested that there were some lessons to be learned from the way that the AIDS groups have demanded to be involved in issues relating to treatment of the disease. Dr Vogt reminded participants that the initial industry reaction had been very negative but the outcome had been more money for AIDS, more recognition and more resources for treatment.

Medwatch and learning without 'blame': Dr Vogt had cited the Federal Aviation Agency (FAA) scheme as an illustration of how to learn from reports of errors without involving blame and she was asked whether FDA's Medwatch also provided an example of this. She agreed that it was, but felt practitioners did not get feedback and so lose the incentive to report. It did not, in her opinion, provide a 'learning system' in the way that FAA did. Dr Zoon added that FDA had carried out an 'experiment' with biological deviation reports where trend analysis was carried out on the data received by the agency and this was then reported out.

Patients at the centre: The UK National Health System (NHS) is being redesigned to put the patient at the centre. One illustration where this is working well is in the devices area where companies are involving patient groups in the development of user manuals. Medical devices are a somewhat special case, as patients are much more involved as part of their treatment. The scheme has, however, been particularly valuable in addressing issues of user error and how these are taken forward both in the development phase and in the early launch of a product.

Potential conflict of interest: A system that involves all stakeholders and encourages 'trust' between the parties could run into problems of conflict of interest since the companies that are trying to sell their products will be working with their customers. Dr Vogt acknowledged this as a factor that needed to be recognised from the outset so that discussions could move beyond it.

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

Mr Steve Mott, *Datapharm Communications Ltd.*

Mr Steve Mott described the work of Datapharm Communications Ltd, a not-for-profit company set up by the ABPI which, through the *electronic* Medicines Compendium (e-MC), makes UK product information freely available via the Internet (*http:www.medicines.org.uk*).

He discussed how industry was responding to patients' information requirements and questioned whether some of the fundamental issues in communicating effectively with patients over the correct use of medicines were being addressed. Working in a highly regulated environment and within the constraints of legal liability, the industry has not yet focused on the collaborative processes and systems needed to address the real issues of developing effective 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.

Among the initiatives for delivering information in novel ways are proposals for interactive digital television, use of videos, spoken versions of patient information, more creative presentation of information on websites (e.g., using video clips to illustrate drug delivery systems) and 'paperless labelling', whereby the latest revision of product information is printed out at the time of dispensing. There remain, however, some basic issues to be addressed including the distinction between advertising and technical regulated information. Industry needs to demonstrate that it can be responsible and committed to ensuring that its products are used effectively and the critics of the industry need to understand that there are 'credible boundaries' that need to be drawn up.

Points from the discussion

Quality Assurance: Asked about the quality control used for the e-MC, Mr Mott explained that reference document for information in the compendium is the Summary of Product Characteristics approved by the Medicines Control Agency (MCA) or the European Medicines Evaluation Agency (EMEA), and that Datapharm had worked with medicines information pharmacists to refine QC processes. Ultimately, however, the responsibility rests with the contributing companies whose data and updates are signed electronically.

A company participant noted that the company's responsibility is delegated to the regulatory affairs department which has a similar responsibility for controlling the prescribing information that appears on its corporate websites.

Language and understanding: FDA has a requirement that the readability of information and instructions on products that have been switched from prescription to OTC must be tested 'in the Malls of America'. How does Datapharm address similar aspects of communication? Mr Mott hoped that, now that the e-MC was established, they would be able to look at this aspect. The example used in the presentation, where video clips are used to illustrate technical issues, was certainly worth exploring further.

A regulatory agency participant drew attention to the EU requirement that new applications in the centralised procedure must comply with readability testing requirements for all patient leaflets. Feedback from patients on the quality of patient information leaflets had highlighted concerns about the rigid requirements for the order in which information is presented. With greater flexibility, information could be reorganised and presented in a more suitable format.

A participant from industry also commented on the problem of getting information out to the public in a way that enables them to understand the concept of risk benefit and to put this into the correct perspective. Patient groups are more receptive but communicating with the general public remains an unmet challenge. The chairman pointed out, however, that communicating risk benefit information to members of the public was at the centre of the process of obtaining informed consent from patients in clinical trials and presented similar challenges.

Differences in product information: Mr Mott was asked how the e-MC deals with products where the approved indications and adverse event information differ in different countries or regions. He replied that the Datapharm was looking at these issues across Europe, but not

globally. Data processing using XML means that information can be broken down into discreet elements making it relatively easy to present the different variations in different markets.

Mature patients: It was suggested that older patients were less likely to be comfortable with internet technology and obtaining information from the Internet. It was pointed out, however, that some of the most involved and well informed patients are those seeking information on hormone replacement therapy (HRT) and breast cancer.

Involving all stakeholders: Dr Leone Hunt reported on a project in Australia to mandate the supply of patient information when medicines were prescribed. The scheme ran into trouble, however, because the physicians had not been included in the early consultations and were resistant to handing out the information or making sure that patients had access to it. The industry had been closely involved in drawing up user guidelines and requirements for language, but all the effort was wasted if the information did not reach the consumer. A lesson was learnt on involving all parties at an early stage.

FDA Communication to Health Care Providers

Dr Susan Ellenberg, *CBER, FDA*

Dr Susan Ellenberg reviewed the way in which FDA's Center for Biologics and Research (CBER) addresses the problem of communicating vital information on biological products to busy physicians and providers in the light of knowledge that few will regularly read product information and circulars or visit the FDA website. Communication on the safety of biologics is of particular importance. On the one hand there is a new generation of biotech products where inherent safety issues relate to multiple mechanisms of action and complex manufacturing procedures. The emerging new products resulting from gene therapy and genotransplantation will also bring a 'whole new world' of risk management issues. On the other hand CBER regulates traditional biologics such as blood products and vaccines that are considered generally very safe. These, however, are administered to very large target population and there is much public concern about safety.

When there is important new or changed information to communicate CBER has explored a number of different approaches apart from the traditional ones of safety alerts, label changes and 'Dear Doctor' letters. Press conferences can only be used sparingly for matters of urgency but dissemination of information through the FDA Advisory Committee system has been found to be effective. Other CBER initiatives include the publication of journal articles that discuss new products and their risks, presentations at scientific meetings and the dissemination of summaries of initial post-marketing safety experience with new products.

Points from the discussion

Assessment of Physician's needs: Dr Ellenberg was asked whether FDA had carried out a survey of health care providers to find out what forms of communication they wish to receive, in view of the perception that typical modes of communication are not well accepted and practitioners are over-loaded with information. In reply, Dr Ellenberg emphasised that the different methods that were being tried were not a substitute for the routine methods of communication. On the question of a survey, this had not been undertaken. It is, in fact, extraordinarily difficult to carry out such a survey within the FDA, as any kind of survey involving more than ten people has to be agreed by the Office of Management and Budget and it takes considerable 'fortitude' to go through this process.

PDUFA III: Dr Ellenberg noted that there is a new focus on risk management under the Prescription Drug User Fee Act (PDUFA) phase III and it is hoped that resources will be made available for developing risk management plans. Working groups are looking at the format and content of product labeling and communications with health care providers and consumer groups.

Advisory Committees: The Chairman, Dr Katherine Zoon, noted that, in relation to vaccine safety issues, CBER works closely with the Center for Disease Control (CDC) and with the Advisory Committee on Immunisation Practices and the National Vaccine Advisory Committee, and has experience of outreach projects not only among health professionals but also involve some of the consumer groups and users. Dr Ellenberg added that similar approaches were planned for therapeutic biologic products, especially highly visible new products.

Assessing impact: Dr Ellenberg was asked about the impact of FDA's publication in medical journals, described in her presentation, relating to the incidence of tuberculosis in patients treated with infliximab and whether this could be could be assessed in terms of the number of reports received by Medwatch. She replied that this would be difficult to assess. Reports of tuberculosis associated with the drug appear to have gone down which would indicate that patients are being evaluated for latent disease before being treated. On the other hand, an increase in reporting could also indicate that the publication had been effective in drawing attention to the problem and in stimulating reports.

Asked if a specific study had been carried out on the impact of the publications and the number of physicians that were reached, Dr Ellenberg regretted that, again, resource constraints prevented this sort of evaluation although informal feedback from letters and other published articles had been positive.

Off label use: There is very little awareness in the community about the distinction between labels and off label use (the use of HRT for primary and secondary prevention of cardiac disease was cited as an example). Does FDA have any initiatives to highlight the issue? Describing this as a 'very sticky issue', Dr Ellenberg pointed out that companies are not permitted to discuss the off label use of their products and that the regulation of medical practice is not within the remit of FDA. The agency cannot require studies to be carried out to rationalise a situation where products are widely being used for unapproved indications. Many times, however, observational data is found to point in the right direction, for example suggesting that HRT reduces osteoporosis.

How Can Users Get the Information They Need or Want?

Dr Robert Peterson, *Health Canada* and **Dr Hans Stoker**, Swissmedic, Switzerland.

Dr Robert Peterson focused on the recent project carried out by the Health Products and Food Branch to revise the Canadian Product Monographs. Whilst the document has traditionally been used as a source of scientific and factual information for physicians, a new section of consumer information has been added to the revised format. Direct to consumer advertising (DTCA) is not allowed under Canadian law but one of the objectives of the product monograph project was to define a source of regulated information that could be used to delineate the information to be provided to the public. The revisions were made following research and consultations that have been carried out since 1998 through surveys and discussions by focus groups. A pilot project to make the monographs available via the Health Canada website will be undertaken and other ways are being explored to make the information more widely and readily available.

Dr Hans Stocker provided a review of the way in which the new Law on Therapeutic Products (LTP) in Switzerland deals with the subject of advertising prescription medicines. The Swiss authorities do not have a tradition of formal communication with consumers and patient groups but this is an area that can be expected to change. The LTP applies to both medicines and medical devices and has an overall objective of ensuring correct moderate and sensible use of medicines. The law and implementing ordinances prohibit the advertising of prescription medicines to the general public but allows companies to provide general health-related information that is not product specific. There are however, borderline issues,

particularly in relation to 'sponsored' editorial articles in publications and items on websites that are non-promotional in content but include links to product information.

Dr Stocker also described a project under discussion in a European Council working party to provide guidance to Internet users who seek information on health-, and medicine-, related issues. Flyers and information sheets intended to be distributed to patient organisations, consumer groups or to be posted on government websites will warn of the dangers of obtaining medicines other than through the normal regulated channels. They will also indicate sources of information that can be considered as 'safe' and those which should be regarded as unreliable.

Points from the discussion

Canadian product monographs: Dr Peterson was asked whether the EU standard formats for the Summary of Product Characteristics and patient information leaflets had been taken into consideration in the revision of the product monograph format. Dr Peterson replied that an international scan of other regulatory authority requirements had been carried out. Virtually all the elements from the EU requirements are included, although the sequencing of the information might be slightly different.

Scope of the product monographs: Dr Peterson was asked whether the monograph system also provided information for patients on the risks of the target disease if left untreated. He pointed out that the development of educational material for the public on disease management and the different options for treatment is outside the scope of a product-specific monograph. It is, however, an important area that needs to be developed and controlled. Health Canada would not wish to see promotional materials coming from many different sources all trying to inform, for example, on the appropriate management of heart disease.

Development of a product monograph: Asked about the process for developing a product monograph Dr Peterson stressed that the company always has the primary responsibility. The agency provides the template for the information and it is part of the regulatory process for approval of a product. It is recognised that companies work to a global core data sheet but that this can be accommodated within the monograph scheme.

Information via the Internet: There was general question on whether the European Commission might be prepared to sponsor a third party website such as WebMD in the US, which provides authoritative, but independent, information on both products and diseases. Dr David Jeffries, UK Medicines Device Agency referred to the National Electronic Library for Health in the UK which provides a similar service and covers both medicines and devices. There are direct links to 'NHS on line' which provides an information service for patients and attracts about a million hits per day.

The Chairman commented on the value of such 'data warehouses', provided there were suitable provisions quality assurance and keeping the information up-to-date. There was clearly a need for such systems especially in the light of Dr Peterson's description of physicians downloading information to their 'palm pilots' when discussing side effects and interactions with patients, rather than having to find the right piece of paper.

Information and advertising: Dr Stocker was asked whether those drafting the new Swiss laws had considered trying to define what constitutes information on medicines as distinct from the definition of advertising. He replied that this had not been carried out initially but that there was now a year's experience with the new legislation and it was apparent that further amendments were required, including a definition of what information is allowed on the Internet.

Credibility of industry information: The European Council project described by Dr Stocker had classified industry information among the 'less reliable'. This continues the negative perception of industry as a supplier of information and is somewhat surprising coming from the Council. Dr Stoker emphasised that this had been an early draft but acknowledged that there was scepticism about the industry as an information source on medicines, possibly because a clear distinction is not made between information and advertising.

Why single out information on the Internet? It was suggested that the Internet is not the only unregulated channel of information on medicines and that a case could equally be made for providing advice about obtaining information from other sectors of the publishing world including bookshops. Dr Stocker replied that there were regulations about what could be advertised in print that could be enforced relatively easily, but this is not the case with the Internet.

Dr Kathy Zoon and other participants expressed the view that the real hazard with the internet was the availability of fraudulent and unregulated products rather than poor information. When it comes to the quality and content of industry information, the industry is, to a large extent, self-policing. A company would be the first to make a complaint if a competitor was doing something it considered inappropriate.

SESSION 2: COMPANY/AGENCY INTERACTIONS

Chairman: **Dr Murray Lumpkin**, FDA

Risk Assessments During Product Development

Dr Leonie Hunt, *TGA*, *Australia* and **Dr Murray Lumpkin**, FDA

Dr Leonie Hunt gave an Australian perspective on the information on risk assessment that should be communicated to the regulatory authorities. Describing the Therapeutic Goods Administration (TGA) as a 'small' regulatory agency, Dr Hunt described the system for the notification and authorisation of clinical trials in Australia and the importance of open, relevant and timely communications with industry on safety issues arising from clinical investigations. This is particularly important in view of the fact that the amount of information that the authority receives, through formal channels, in advance of trials, is relatively small. 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. On the other hand, it is important not to overwhelm ethics committees and the authorities with information that is not directly relevant to the trials in Australia: the TGA does not wish to receive unblinded reports of adverse events from all around the world.

Discussion of safety issues and identification of risk must always be communicated in the context of the expected benefits of the product. Another critical issue is the need to plan trials, including Phase IV trials, to address identified risk, in particular to evaluate the use of the drug in target populations that are representative of patients likely to be at higher risk, including children, the chronically ill, those on other medications and elderly patients (well over 65).

Dr Murray Lumpkin addressed the question of communication and risk assessment from a US Regulatory perspective. He suggested that there needs to be a major paradigm shift in the way risk is evaluated and managed in the 21st century. 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 consideration of the concept of risk, and risk tolerance and whether this differs among stakeholders. Industry can have a bias in assessment of risk, and this is not necessarily a positive bias, because of liability issues. Regulators might be similarly cautious but, at the end of the day, it is the risks that the patients and the practitioners are willing to tolerate that will determine the success or failure of the drug.

Dr Lumpkin identified five areas where regulators are being faced with significant new challenges in terms of safety and safety assessment:

- 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

The globalisation of clinical trial programmes is having a major impact on safety assessment, with data becoming available from trials in patients from different medical cultures with differing nutritional and disease status. In 1991 FDA carried out five overseas clinical trial inspections; in 2001 there were over 70.

The whole 'new world' high tech customised biologic and pharmacogenetic products raise a completely different spectrum of safety and risk management issues. In the case of gene therapy there are long-term considerations of risk that need to extend beyond the immediate patient to future offspring. Such issues and other challenges of the 'empowered' patient who is seeking information and medicines outside the normal channels cannot be managed through a '1950's drug access scenario'. It is no longer a question of all medicines being available from the corner drug store with the physician prescribing and the pharmacist dispensing.

Points from the discussion

CT adverse reaction reports and blinding: The introduction of unblinding in clinical trial adverse reaction reporting in Europe and requirements, under the Clinical Trials Directive, for providing individual serious unexpected adverse reactions to all ethics committees and all investigators is obviously of concern to TGA. There is a risk of increasing the 'noise' so much that the ethics committees and the investigators will take little or no notice of the information that is being provided. Dr Hunt agreed that information overload is a serious issue for ethics committees and investigators. Data on adverse reactions from trials outside Australia may not be relevant to national trials and such data only serves to raise concerns without providing useful information. Furthermore there is the risk of diluting the data and missing genuine signals that indicate a problem with the use of the drug in a particular clinical setting.

Target patient populations and dose: Dr Hunt was asked to clarify her views on carrying out clinical investigations in high-risk populations and in such a way that risk factors, particularly in relation to dose, could be evaluated. In reply Dr Hunt emphasised that there was no question of designing or undertaking high risk trials. She believed, however, that in the early pre-marketing development phase there might be information on patient groups that are particularly at risk that is not collected because it has not been obtained from well designed trials in controlled populations. Such data might, however, have a value in terms of communicating risks, designing product information and developing the Phase IV marketing plan. On the question of dose, there was no suggestion of driving dose levels up in order to assess risk. On the contrary, there is often a need to ensure that the *minimum* effective dose is identified and used. Many drugs are currently used at doses well above this minimum.

Communicating the Views of Regulators Within a Company

Dr Mike Clayman, *Lilly Research Laboratories*

Dr Mike Clayman addressed internal company communications and in particular the role of the regulatory affairs group in representing the regulatory agency viewpoint to the company. There is a need to balance the 'enthusiasm and passion' of a team responsible for the development of a new product with the 'regulatory reality' of the obstacles likely to be encountered. One essential tool for keeping new drug development – which can take a decade to complete – on track is the 'draft launch label' or targeted package insert. This sets

goals for the product against which decisions on its viability can be made during the development process. Another tool that has been developed to facilitate the planning of the global launch of a new drug is the 'regulatory approval archetype', from which approval dates can be predicted based on timelines and past performance of the different regulatory agencies. There are, however, 'regulatory' risk factors that need to be anticipated in meeting the target launch date and a major factor in minimising these is a 'mock submission review'.

Returning to the risk assessment of the product itself, Lilly has developed a software system, *Automated Safety Signal Evaluation and Triage* (ASSET), to monitor and analyse post-marketing data, not only from the companies own database but from epidemiological data and regulatory information systems worldwide. This provides the basis for improved safety update reporting and risk assessment management. Another important safety tool is the company internal procedures for effecting labeling changes in a timely and consistent manner. The objective is to carrying these out, when the need is apparent, in a proactive manner and not only at the behest of a regulatory authority.

Points from the discussion

Label changes without justification: Regulatory Authorities, particularly the Japanese Ministry of Health, Labor and Welfare (MHLW), sometimes ask for information to be included in product information on the basis of 'class labelling' in the absence of any occurrence of the adverse event with the drug in question. How should the company react? If the MHLW is intransigent in its position, Dr Clayman suggested that the company would need to make a business decision that 'transcends the science'. Its position in believing the change unnecessary should be documented and made clear to MHLW. The documentation is also important in order to explain the situation to other agencies. With the speed of communication and use of the Internet a decision made by one agency will provoke immediate questions from the others and it is better to be proactive in providing information than to wait to be asked.

An industry participant from Japan added that the MHLW will normally allow a 'disclaimer' on class labelling to the effect that the particular adverse effect has not been observed with this particular drug. This, of course, has to be removed as soon as any relevant reports are received.

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.

Global Product Labelling Decisions: Asked whether business people were involved on the committee making decisions on global changes in labelling, Dr Clayman replied that they were not. The committee needs to address whether the data support label changes independent of business ramifications. The committee looks not only at the scientific basis for including an item in the core labelling but also at the wording and the way in which the information is expressed. The committee might also advise on how best to communicate important issues to the prescribing population. It is, however, the responsibility of the Labeling Department to actually communicate this information to affiliates around the world with line management responsible for local implementation including interactions as appropriate with regulatory authorities.

Global labelling and liability: One of the big issues in achieving truly harmonised labeling throughout the world is liability. In the US, additional safety information can be added at any time and there must be a temptation on the part of corporate lawyers to fill the US label with information that is there for liability rather than scientific purposes. Dr Clayman felt his company had moved beyond this and that, typically, changes would not be made in the US

that did not reflect a core data sheet change. Furthermore the legal counsel advising the Global Product Labeling Committee is of the view that the liability protection afforded by label wording is important but accepts that the drivers behind label changes are the views of regulatory, clinical and pharmacovigilance committee members.

ASSET: The question was raised of how effective the safety signal detection algorithm had been in terms of detecting problems leading to label change. Dr Clayman replied that there were cases initiated by signals from ASSET. It could be argued that these would ultimately be detected by other methods but the question is at what stage? ASSET should be regarded not only as an early warning system on potential problems but a means of placing the risk in context by providing information on how often the drug is actually being used in the market, and by providing background incidence of similar adverse events in the disease population.

Adverse events and risk evaluation: The Chairman addressed the role of the spontaneous reporting systems that have been developed, at enormous cost, over the last thirty years and questioned whether there was too much of a preoccupation with such systems. Whilst they have an important role in detecting the rare adverse event that would not have been detected in clinical trials, in terms of patient safety this is actually 'a very, very small piece of the pie'. There are other areas where misuse or erroneous use of drugs are causing more harm to patients than serious, rare adverse reactions, and managing patient safety needs to be seen in this broader context. Dr Clayman agreed and commented that that industry is only at the stage of 'cutting its teeth' on risk management plans, on a molecule by molecule basis. Much attention is, however, now being paid to how the drug is actually going to be used in the market place, who is the prescribing physician population, what is their level of familiarity with the potential adverse event profiles, and how can they best be instructed in such matters. Furthermore, industry is actively seeking participation of its experts in other multidisciplinary groups that are currently wrestling with similar issues.

SESSION 3 THE COMMUNICATION OF COMPANIES' RISK MANAGEMENT PLANS

Chairman: **Dr George Butler**, AstraZeneca Pharmaceuticals

In his introductory remarks, Dr Butler referred to the 'when, who and what' of risk management that 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.

He emphasised the importance of looking at the professionalism of risk management plans and the processes that manages them. 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.

The Development of a Risk Management Plan

Dr Cathy Bonuccelli, *AstraZeneca Pharmaceuticals*

Dr Cathy Bonuccelli continued the theme of 'who, what, when and how?' and emphasised the importance of developing, as early as possible, an inclusive risk management approach that puts the patient in the centre of 'thought, action, and learning'. An important message was that risk management is not only about reducing risk but also optimising patient benefit.

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. There are known side effects many of which may be avoidable if the product is used correctly and other preventable risks including medication errors resulting from confusing names and poor instructions as well as defects in the product quality. All are preventable and require a proactive approach in risk management plan. There are also uncertainties arising from unexpected side effects, unstudied uses and unstudied populations for which a reactive plan is needed.

The components for optimising patient benefit that were discussed included disease understanding, product knowledge, patient understanding, healthcare systems knowledge and continuous learning as well as the risk management and communication tools that are available or need to be developed. Industry's particular expertise lies in areas such as understanding diseases and particular products. Weaknesses lie in understanding patient characteristics, their perceived needs and expectations, and in aspects of healthcare delivery systems that impact on the safe use of medicines.

Among the risk management and communication tools that are available, partnering should be given greater attention as companies cannot operate management programmes alone. Credibility and trust needs to be built through honest relationships between industry and other stakeholders including patients, physicians, pharmacists and regulators. Communication strategies also need to include those who pay for healthcare. There is a preoccupation with demonstrating the cost effectiveness of medicines but one of the consequences of improving the safe use of medicines may be an increase in the required healthcare resources with patients undergoing more tests and making more frequent visits to the physician.

Communication of Risk Management Plans Within Companies and to the Public

Dr André Broekmans, *NV Organon*

Dr Broekmans described the way that Organon had addressed a specific issue requiring action to be taken following risk evaluation but also extended the concept of risk management to other risks that can impact on a company by adversely affecting public perception.

Dr Broekmans first gave the case history of Oganon's decision to withdraw, voluntarily, the product Raplon® (rapacuronium bromide), a muscle relaxant used in general anaesthesia. The decision was made following serious cases of bronchospasm that had not been expected from the clinical trials and where the specific risk factors for susceptible patients could not be clearly identified. The product was only marketed in the US and, although FDA would have supported measures other than a complete product withdrawal, a quick internal decision was made on the principle of 'patient safety first'.

The second example was the perceived threat to the company's security and reputation from the campaigns of animal activists against the use of animals in drug testing. Organon has undertaken a communication project to clarify the company position on animal welfare and the appropriate use of animals in essential research. Whilst material has been prepared to counteract unwanted media and public attention, an equally important internal communication campaign is being undertaken to make staff members aware of the company views.

The third example of risk management was the way that Organon had addressed the threat to its reputation and the integrity of its products through the misuse and abuse of the company's anabolic steroid products for body building in sport. The company had found Internet sites illicitly using the company brand and promoting misuse of anabolic steroids. There was also evidence that counterfeit products were in circulation and being sold via the Internet. Action had been taken to remove the offending sites, provide warnings of the danger of misuse of anabolic steroids, and enlist the help of international anti-counterfeiting agencies.

Returning to the theme of risk management during drug development, this is organised in Organon by empowering multidisciplinary, cross-functional project teams that have a responsibility for dealing with issues as they arise in the pre-, and post-, authorisation phase. Pivotal to the process is that the teams are not only empowered to act in the best interest of the patient but they are also given adequate support and training. Within the company's board of management the ultimate responsibility for public and patient safety rests with the Executive Vice President for medical affairs to whom both the safety and regulatory affairs divisions report.

Points from the discussion

Pre-set decisions on safety: Dr Bonuccelli was asked whether a pre-set decision on the incidence of adverse events that would result in the cancellation of a project could be overcome by commercial and marketing staff. She acknowledged that this could be a problem since the development of mandated risk management procedures is still at an early stage. There is always a tendency to wish to see a product with which one has been closely involved 'stay in the race'. This underlines the importance of involving different stakeholders in the action taken at the pre-set decision points.

Withdrawal of Raplon®: Using the example of Raplon® where safety issues emerged that were not predicted from the animal tests or clinical trials, Dr Broekmans was asked whether there were lessons to be learned and whether these could be shared with the rest of the drug development community. In reply, he noted that Organon had reanalysed the clinical trial results to see if there were risk factors that could be identified, and additional tests had also been carried out in animal models to see if similar adverse events could be simulated. With regard to sharing the experience, this is a sensitive issue as it would involve disclosing proprietary information in a field which is a research priority for the company. FDA however, had been provided with the full details.

Asked about the extent to which the decision to withdraw Raplon® rather than choosing some other risk management tools was influenced by legal liability considerations, Dr Broekmans acknowledged that this was a factor. He was, nonetheless, happy that the company had made the right decision in the interest of patient safety, and that the decision had been made quickly.

Agency attitude to product withdrawals: Referring to the FDA surprised reaction to the withdrawal of Raplon®, an industry participant noted that European regulators do not always support companies' decisions voluntarily to withdraw products as a result of adverse event reporting. One reason could be that there may be implications for other products in the same group where similar risk benefit considerations might apply and this could face the authorities with a dilemma. Dr Broekmans suggested that agencies may also be concerned that such withdrawals are a reflection on the validity of the original assessment and decision to approve the product. This needs to be viewed against media criticism, particularly in the US, of the user fee system and allegations that products are being approved too soon.

An industry participant commented on the predicament of having new products that have been subject to close scrutiny under risk management procedures whilst there are many older products on the market for which there is no similar database and little incentive to invest resources in further studies.

Countering misuse and counterfeits: Asked about the amount of effort the company had given to countering the abuse of its products, Dr Broekmans agreed that it had been resource-intensive but that it was justified because the products were so closely linked to the

company and because of the importance of defending the place of the legitimate products. In view of the counterfeit issue it had been possible to enlist the help of the government.

Dr Broekmans was asked about the effectiveness of removing the offending websites and ensuring that they are not immediately created elsewhere He replied that Organon had registered many different web names to try to block pirate activity but it required constant vigilance and monitoring to detect illicit use of the product names.

A participant commented on counterfeits and the difficulty of managing safety surveillance when reports may not relate to the authentic product. Dr Broekmans replied that the company policy was to register all adverse event reports but to alert the authorities, when providing safety updates, to the fact that counterfeit products could be involved.

Threat from animal activists: In response to a question, Dr Broekmans reasserted his view that the actions of groups such as SHAC (*Stop Huntingdon Animal Cruelty*) and the naming of companies on their website can pose a substantial risks to the public perception of a company. Public sympathy rests with the animals and there is a need to balance this by explaining the need to use animals in order to evaluate the safety of medicines.

Asked whether Organon had considered doing all animal work in-house and not contracting this out, Dr Broekmans replied that this was not an option because of managing development programmes and timetables.

Precautionary principle: Dr David Jefferys, Medical Devices Agency, UK, commented that the concept of 'proportionality' is being applied to risk management in Europe as can be seen in the adoption of standard BS EN ISO 14971: 2001[1] On the other hand, the 'precautionary principle' being enshrined, in various pieces of European legislation which can be regarded as contradicting the proportionality principle. Other participants agreed that the precautionary principle is in total contradiction to the ability to identify risks and then manage them effectively and could lead to potentially valuable products being denied to patients.. Dr Broekmans also commented that the 'precautionary' approach adopted by the CPMP can make it extremely difficult, once an authorisation has been suspended, for a company to meet the stringent requirements of the authorities and restore the product to the market.

Further information on the presentations

Workshop participants have been provided with copies of the slide presentations from the meeting and these will be made available when the final report is published on the CMR website (http://www.cmr.org).

[1] **BS EN ISO 14971: 2001 - Medical devices.** *Application of risk management to medical devices*
This standard specifies a procedure by which a manufacturer can identify the hazards associated with medical devices and their accessories, including *in vitro* diagnostic medical devices, estimate and evaluate the risks, control these risks and monitor the effectiveness of the control. (http://www. bsi-global.com)