



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

Meeting Report

C Anderson, JAN McAuslane & SR Walker

Woodlands Park Hotel, Surrey

25th - 26th April 2002



Mission Statement

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

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

Workshop Objectives

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

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

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

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

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

The Workshop

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

Industry Issues & Strategies

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

Improving partnering during product development

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

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

Syndicate Discussion

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

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

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

Summary of syndicate discussions

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

? Information Gaps

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

? Company Collaboration

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

? Incident Management

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

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

? **Alignment of Agencies' Perspectives**

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

? **Science versus Public Acceptability**

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

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

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

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

? **New Paradigm**

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

? **Product Development Practices/Models**

Attrition Rates:

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

Trial Design:

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

Learn from Collective Experience:

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

Companies to Share Approaches to Risk Management:

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

Tools:

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

? **Patient Information**

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

? **Education of Physicians and Patients**

Who Educates?

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

How Is Education provided?

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

What Education Do We Give?

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

? **Off-label Use of Medicines**

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

? **Pharmacogenomics**

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

Meeting Outcomes

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

Risk Management – The Next Steps

June 2002.

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

October 2002.

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

To be announced.

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

Delegate feedback: quotes

“Excellent interaction with experienced people.”

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

“Very good presentations / excellent opportunity to network.”

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



Meeting Report
June 2002

Appendix 1 : Workshop Attendees

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

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

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

Appendix 2

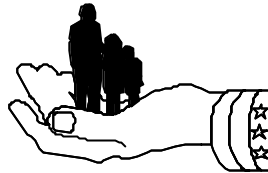
Presentation slides from:

Dr Chris Towler, Imperial College London, UK
Mr Filip Mussen, Merck Sharp & Dohme (Europe) Inc, Belgium
Dr Mike Clayman, Lilly Research Labs, USA
Dr Mary Foulkes, Food and Drug Administration - CBER, USA
Dr Thomas Lönngren, EMEA
Mr Nick Lacy, National Audit Office, UK

Unfortunately, it has not been possible to include the slides from Dr Graham Burton's and Dr June Raine's presentations in this report.

Please also be reminded that the slides included in this report are **not** for general distribution.

Risk Management



April 2002
Chris Towler

Scope of my talk

- The nature of risk
- Risk as a consequence of complexity and information overload
- The statistical issue
- Social expectations
- Selective ignorance
- The Regulatory Angle
- The solution

Whose risk should be managed?

- Patients / Public Health
 - Beneficiaries of appropriate strategies
- Politicians
 - Stakeholders
- Industry
 - Stakeholders and Major Beneficiaries of “getting it right”

The Nature of Risk



“Doctors prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of which they know nothing”

Voltaire

Janet Woodcock (FDA) has reported on current appraisal

- System of risk management in USA is poorly integrated and outdated
- Substantial preventable harm occurs
- Up to 98,000 people may die each year from medication errors in hospital
- Not a “regulatory issue”
- Not a consequence of faster approval
- Needs concerted effort by all constituents

UK Experience



18th December 2001

Approximately 1200 people died last year in England and Wales as a result of medical mistakes – a rise of 500% over the past decade.

Statistics suggest that one in 10 people in hospital suffer some kind of adverse event, half of which are preventable

Mistakes found in one hospital
Cancer patient prescribed sleeping tablet temazepam instead of anti-cancer drug tamoxifen
A toxic medicine was prescribed to be given daily instead of weekly
An anti-cancer medicine prescribed at 1,000 times the correct dose
A contraceptive steroid prescribed in the place of an anti-psychotic drug

The American Hospital Association lists the following as some common types of medication errors:

- Incomplete patient information (not knowing about patients' allergies, other medicines they are taking, previous diagnoses, and lab results, for example);
- Unavailable drug information (such as lack of up-to-date warnings);
- Miscommunication of drug orders, which can involve poor handwriting, confusion between drugs with similar names, misuse of zeros and decimal points, confusion of metric and other dosing units, and inappropriate abbreviations;
- Lack of appropriate labelling as a drug is prepared and repackaged into smaller units;
- Environmental factors, such as lighting, heat, noise, and interruptions, that can distract health professionals from their medical tasks.

So what is risk?



Risk v. Benefit



Risk1 v. Risk2



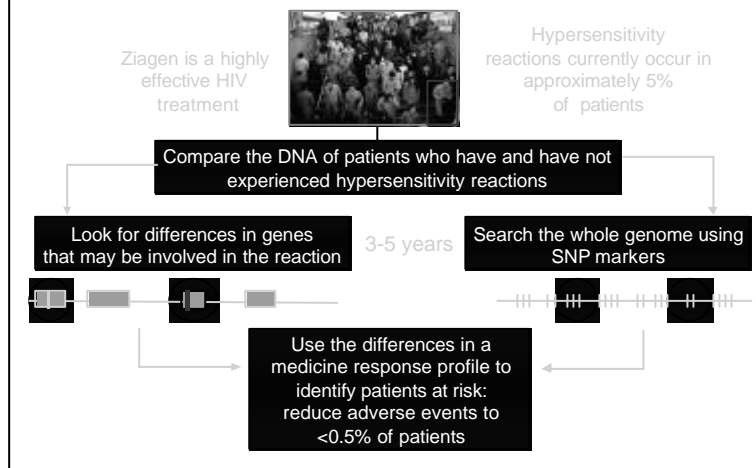
The risks of Common Voluntary Activities

Voluntary Risks	Deaths/Person/Year	(odds)
Smoking (20 cigarettes per day)	1 in	200
Drinking (1 bottle of wine per day)	1 in	13 300
Soccer	1 in	25 000
Car racing	1 in	10 000
Car driving (UK)	1 in	5 900
Motorcycling	1 in	50
Rock climbing	1 in	7 150
Taking contraceptive pills	1 in	50 000
Power boating	1 in	5 900
Canoeing	1 in	100 000
Horse racing	1 in	740
Amateur boxing	1 in	2 000 000
Professional boxing	1 in	14 300
Skiing	1 in	1 430 000
Pregnancy (UK)	1 in	4 380
Abortion (legal – less than 12 weeks)	1 in	50 000
Abortion (legal – more than 14 weeks)	1 in	5 900

Bases for risk assessment

- Industry – own & published data – health of populations
- Regulators – data plus political policy – health of populations (National / Regional)
- Medical professionals – experience – health of patient
- Public – opinions, frequently borrowed – my health

Pharmacogenetics to improve the risk:benefit ratio for Ziagen



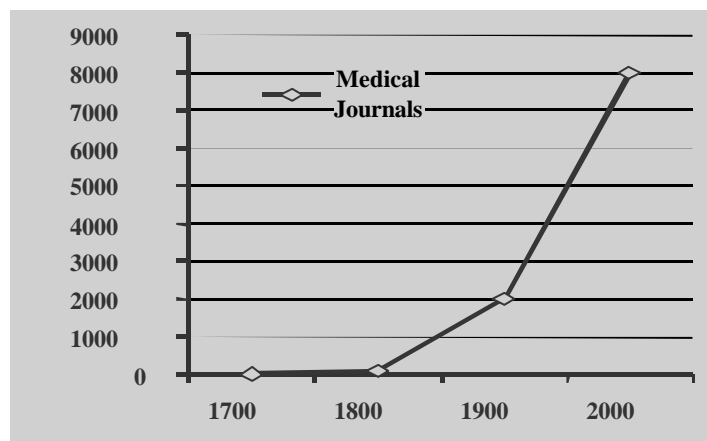
Risk as a consequence of complexity and information overload



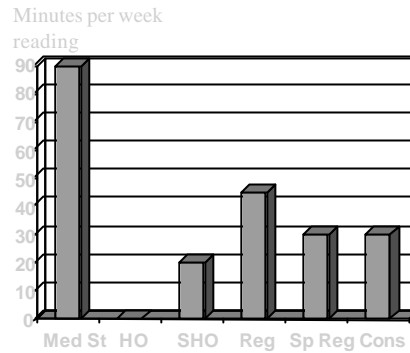
Peter Honig, FDA:

- Labeling changes and 'Dear Dr' Letters are ineffective ways of communicating risk with the intention of changing behavior
- Concept of 'labeling fatigue'
- Labeling and labeling changes \neq knowledge
- There is plenty of information and knowledge but this does not necessarily drive behaviour
- Active dissemination of information needed

Information Explosion



Reported time available for reading
information to support decision-making
(Oxford)



The Statistical Issue

The public believes that all
medicines should be safe....

“The granting of a product licence for
a new drug merely means that any
hazards unacceptable to the licensing
authority have not been identified. It
does not ensure that a medicine will
be safe in subsequent prescribing
practice”

W.H.W Inman

Number of patients required to be 95% certain
of detecting 1,2 & 3 cases of an adverse event

Incidence	1 case	2 cases	3cases
1:100	300	480	650
1:200	600	980	1300
1:1000	3000	4800	6500
1:2000	6000	9600	13000
1:10,000	30000	48000	65000

Selective Ignorance

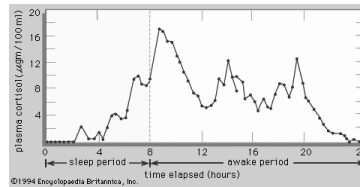
Circadian rhythms

- Many physiological and biochemical cycles
- In rodents, anticancer drugs have markedly different efficacies and toxicities when administered at different times of day (links to cell cycle)
- Shift workers (25% of population) – when do they medicate?
- BP at very low level at 4 am - ?too risky to treat (especially by sleep deprived doctor on night shift!)



Chronotherapy

- Blood pressure
- Asthma
- Cancer



Public Expectations

Product Withdrawals

Drug	Withdrawn	Indication	Company	Time on market (months)
Baycol	8/01	Cholesterol	Bayer	42
Lotronex	11/00	Irritable bowel	GlaxoSmithKline	9
Propulsid	7/00	Heartburn	Johnson & Johnson	84
Rezulin	3/00	Diabetes	Warner-Lambert	34
Rotoshield	11/99	Vaccine	American Home Products	15
Raxar	10/99	Antibiotic	GlaxoSmithKline	24
Trovan	6/99	Antibiotic	Pfizer	17
Tasmar	9/98	Parkinson's	Roche	7
Posicor	6/98	Hypertension	Roche	11
Duract	6/98	Analgesic	American Home Products	12
Redux	9/97	Diet Pill	American Home Products	16
Pondimin	9/97	Diet Pill	American Home Products	288

There is mistrust of those perceived to wield power




What does the media tell us?

- Scientists are basically evil
- The pharmaceutical industry is corrupt
- The Government is incompetent
- Someone is always to blame
- My rights are under constant threat



- Who praises the major advances in science and medicine?
- Who highlights the exciting possibilities from genetic modification or therapeutic cloning?

Herbals are “natural = good”



Tuesday, 9 April, 2002

Herb ineffective as anti-depressant

The popular herbal supplement, St John's wort, is an ineffective treatment for depression, a major study has found.

Wednesday, 6 February, 2002

Pregnancies prompt herb warning

A new warning about the effect of the herbal remedy St John's Wort on the contraceptive pill has been issued after two Swedish women had unwanted pregnancies

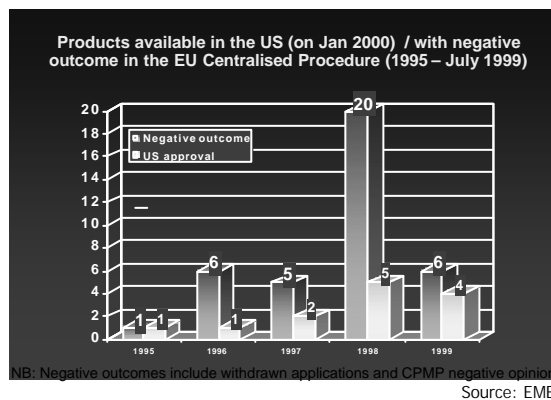
Key Issues for Patients

- More informed
 - Right information?
 - Whose role to inform?
- It is their life
 - What choices should they realistically be making?
- I-countability!
 - Current Healthcare delivery and analysis focuses on populations.

The Regulatory Angle



There are clear differences in outcome of review between US and EU



Recent examples of FDA action:

1. Accutane

- Objective: Zero tolerance of misuse; no pregnant woman to receive Accutane; FDA approved aggressive Risk Management programme by sponsor (Roche) as alternative to removing drug from market
- Mandatory registry of prescribing physicians and patients
- Limited number of Pharmacies able to dispense
- Requirement for documented negative pregnancy test before dispensing
- Medication Guide to accompany product and draw patient's attention to possible link to psychiatric disorders

Recent examples of FDA action:

2. Lotronex

- Objective: Drug used only in approved population; no constipated woman to receive Lotronex
- Second product to have a Medication Guide aimed at patients (Ziagen was first)
- Also labelling changes
- Also "Dear H/C Professional" letters
 - Prescribers
 - Pharmacists
- No agreement on what constituted an appropriate / viable Risk Management Strategy
 - Company withdrew product

Risk Management in Europe

- Debate less evident or well-developed
- Higher regulatory hurdles for establishing acceptable safety / efficacy ratio
- Emphasis on risk avoidance
- Precautionary Principle is evident and will increase (e.g. Polio Vaccine withdrawal)
- Referrals on "Public Health" grounds suffer from lack of clarity /agreement on what "Public Health" means
- Emphasis on cost may divert attention from discussion on risk management

Regulation of BSE

- Probability of contracting CJD from taking gelatine capsule tds x 1yr = <1: 100,000,000,000
 - Certification schemes introduced
- New tests for detection of BSE in carcasses in abattoirs:
 - Requirement to show new tests no worse than old in spite of potential major advantages

Looking to the Future



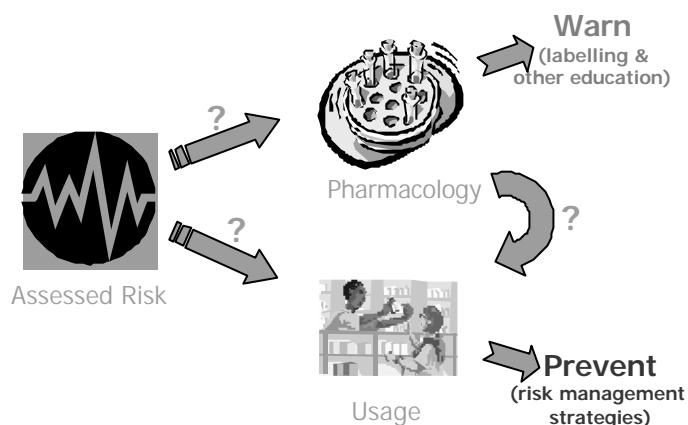
Concepts of Risk Management are still emerging

- Not all recent proposals are practical
- Little “prior art”
- Each case is different
- Regulators may “require” but
- Sponsors have to “design and propose”
- Effectiveness of RM should be measurable

All parties have responsibilities

- Regulators: Is advice consistent with information?
- Industry: Is all necessary information available?
- Healthcare Professional: Is the match between disease, patient, prevailing context and medication right?
- Patient: What can I realistically expect? Do I have the necessary information to make decisions?
- Governments: How do we communicate to the public?

There is a need to understand basis of risk and hence the appropriate response



On-line help?



QuackwatchSM

**Your Guide to Health Fraud,
Quackery, and Intelligent Decisions**

Operated by Stephen Barrett, M.D.
Questions related to consumer health answered by e-mail.
If you write, please mention how you found this Web site.

What should a Risk Management strategy do?

- Acknowledge that risks are real
 - Not possibilities to be played dealt with “if it happens”
- Identify emerging or potential safety issues
 - Unfavourable shift in risk/benefit ratio
 - Related to pharmacology or usage?
- Assess impact on usage
 - Appropriate populations, dosage, length of treatment, continuing benefit over alternative products
 - Suitability of packaging / delivery systems
- Define response of Sponsor
 - What triggers lead to what action
 - New studies, communication, education
 - Define ways of measuring effectiveness of response
- Be dynamic
 - Respond to changing knowledge
- Maintain balance
 - Explore new benefits as well as manage risk

Risk Management may go beyond the Corporate portals

- Multi-company research within Therapeutic areas or new technologies
- Collaborative efforts to define new monitoring systems
- Collaborative efforts to establish new education channels
 - E.g. Clinical Practice guidelines
- Willingness to participate in multi-product comparator trials
- Open approach to publication of “negative” results

Has the Drug Development paradigm changed?



What emphasis is placed on promoting innovation?

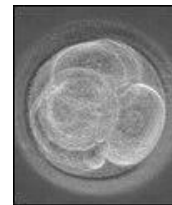
What do we need?

- Minimisation of risk
 - Where possible
- A more effective way of communicating new information
- Acclimatisation to risk
 - There are no absolutes in Safety
- Recognition of where the pendulum is today
 - Are we stifling innovation?



And you thought it was already complicated...

- Cell therapies
- Based on Stem cell research
- Plus engineered scaffolds
- Already regulatory differences
- Plus major public emotional element
- Plus uncertainty of outcomes



The Use of Models for Benefit-Risk Assessment

CMR International Workshop
Risk Management: The Role of Regulatory Strategies in
the Development of New Medicines

Filip Mussen
Director, Regulatory Affairs Europe
Merck Research Laboratories

25 April 2002



The use of models for benefit-risk assessment

Content of the presentation

- **Why would models for benefit-risk assessment be useful?**
- Which models are currently available?
- Which factors should be considered in benefit-risk assessment?
- How are benefit-risk conclusions expressed by regulators?
- The way forward: should there be more standardisation of benefit-risk assessment?

(Survey results will be discussed within each section)

Responses from regulatory authorities:
Responses from pharma companies:



Why would models for benefit-risk assessment be useful?

- λ Enhances consistency in expressing the benefit/risk 'ratio' of a product
- λ Enhances objectivity in recommendations/decisions on the benefit-risk of a product (by Registration Committees and in Marketing Authorization Applications)
- λ Increases transparency of regulatory decisions (approval and post-approval)
- λ Forces the assessor to focus on benefits and risks
- λ Ideally, could be used as a tool to compare products
- can be used as a tool for regulators and industry, but cannot substitute for the final decision-making



The use of models for benefit-risk assessment

Content of the presentation

- Why would models for benefit-risk assessment be useful?
- **Which models are currently available?**
- Which factors should be considered in benefit-risk assessment?
- How are benefit-risk conclusions expressed by regulators and industry?
- The way forward: should there be more standardisation of benefit-risk assessment?



Which models are currently available?

- **Currently there are no well-established, validated models (qualitative or quantitative)**
- **A few models are described in the literature:**
 - 'Principle of threes' (Edwards et al, 1996)
 - TURBO model (Amery, 1998)
 - Evidence-based benefit and risk concept (Beckmann, 1999)
- **<include responses to survey question 1>**



Which models are currently available?

1. **These three models were mainly developed for pharmacovigilance purposes - post-marketing re-assessment (the 'Principles of Threes' model and the TURBO model are described in the CIOMS IV report)**
2. **Other models have been developed to assess the benefit-risk based on one clinical trial, e.g.,**
 - 'Benefit-Less-Risk Analysis' (Chuang-Stein)
 - Mathematical model based on Numbers Needed to Treat & Numbers Needed to Harm (Schulzer & Mancini)



'Principle of threes' grading system (Edwards et al.)

	High	Medium	Low
Disease			
Seriousness			
Duration			
Incidence			
Level of improvement produced by the medicine			
Seriousness			
Duration			
Incidence			
Adverse effects of the medicine			
Seriousness			
Duration			
Incidence			



'Principle of threes' grading system (Edwards et al.)

Grading System for Disease

	High	Medium	Low
Seriousness	Fatal	Disabling	Inconvenient
Duration	Permanent	Persistent	Temporary
Incidence	Common	Frequent	Rare

Grading Systems for 'Level of improvement' and 'Adverse effects' have not been developed



'Principle of threes' grading system (Edwards et al.)

- **Adverse effects : consider the 3 most common and the 3 most serious adverse effects**
(justification is however lacking)
- **A modified quantitative model is described in the CIOMS IV Report**



Comments on the 'Principle of threes' grading system

- λ **The grading system is not well-defined and not very discriminating**
- λ **Incidence of disease should not be taken into account**
- λ **No clear rationale on which adverse effects should be taken into account**



The Turbo Model (Amery)

λ **Benefit factor 'B' = $B_0 + B_c$**

- B_0 = primary benefit (1-5)
- B_c = ancillary benefit (0-2)

Probability of benefit	Nearly always	3	3.5	4	4.5	5
	Frequent	2.5	3	3.5	4	4.5
	Common	2	2.5	3	3.5	4
	Not uncommon	1.5	2	2.5	3	3.5
	Rare	1	1.5	2	2.5	3
			Minor	Slight	Moderate	Market
Degree of benefit						

λ **Risk factor 'R' = $R_0 + R_c$**

- R_0 = risk associated with the medically most serious adverse effect (1-5)
- R_c = additional risk (0-2)

Estimated incidence	Frequent	3	3.5	4	4.5	5
	Common	2.5	3	3.5	4	4.5
	Not uncommon	2	2.5	3	3.5	4
	Rare	1.5	2	2.5	3	3.5
	Very Rare	1	1.5	2	2.5	3
			Minor	Slight	Moderate	Severe
Estimated severity						



The Turbo Model (Amery)

R-factor								
7	T = 1	T = 1	T = 2	T = 2	T = 3	T = 3	T = 4	
6	T = 1	T = 2	T = 2	T = 3	T = 3	T = 4	T = 5	
5	T = 2	T = 2	T = 3	T = 3	T = 4	T = 5	T = 5	
4	T = 2	T = 3	T = 3	T = 4	T = 5	T = 5	T = 6	
3	T = 3	T = 3	T = 4	T = 5	T = 5	T = 6	T = 6	
2	T = 3	T = 4	T = 5	T = 5	T = 6	T = 6	T = 7	
1	T = 4	T = 5	T = 5	T = 6	T = 6	T = 7	T = 7	
	1	2	3	4	5	6	7	B-factor



Comments on the TURBO model (Amery)

- ⌘ **The categories for quantifying the probability and degree of benefit are not well defined and inaccurate**
- ⌘ **Unclear what ancillary benefit actually represents**
- ⌘ **Risk is not necessarily driven by the medically most serious adverse effect (and the second most serious/frequent adverse effect)**
- ⌘ **The categories for quantifying the frequency and severity of risk are not well defined and inaccurate**
- ⌘ **The TURBO diagram is not accurate**



Weaknesses of the current models

- **Many parameters in the models are arbitrary and/or not well defined**
- **Models are not very sophisticated and allow only a very crude benefit-risk assessment**
- **Models have not been validated and broadly used in practice <include survey results Q2>**



Why are there not more models for benefit-risk assessment?

- ⌘ **Is benefit-risk assessment too sophisticated to capture in a model?**
- ⌘ **Is there no need for models?**
- ⌘ **Have insufficient efforts and resources been allocated to this area?**



The use of models for benefit-risk assessment

Content of the presentation

- Why would models for benefit-risk assessment be useful?
- Which models are currently available?
- **Which factors should be considered in benefit-risk assessment?**
- How are benefit-risk conclusions expressed by regulators?
- The way forward: should there be more standardisation of benefit-risk assessment?



Factors to consider in benefit-risk assessments

- **Benefit-risk must be considered separately for each indication and its corresponding dosage recommendations**
- **Benefit-risk can be (positively) influenced by establishing contraindications or precautions and other restrictions to the use of the drug (e.g., second-line indication, indication only for a restricted population)**



Factors to consider in benefit-risk assessments

Benefit <include survey results Q4)

- **Magnitude of the treatment effect (obtained from the results of the primary endpoints in the pivotal clinical trials)**
 - ⌘ Clinical relevance of the magnitude of the treatment effect
 - ⌘ Statistical significance of the treatment effect
 - ⌘ Relevance of the primary endpoints of the pivotal clinical trials
 - ⌘ Relevance of the studied population of the pivotal clinical trials
 - ⌘ Evidence for the efficacy in relevant subgroups in the pivotal clinical trials
 - ⌘ Statistical/design robustness of the pivotal clinical trials
 - ⌘ Confirmation of treatment effect by results of secondary endpoints and results of non-pivotal trials
- ⌘ **Anticipated patient compliance**



Factors to consider in benefit-risk assessments

Risk <include survey results Q4>

- 1 Overall incidence of adverse effects (from clinical trials)
- 1 Overall incidence of serious adverse effects (from clinical trials)
- 1 Discontinuation rate due to adverse effects (from clinical trials)
- 1 Incidence, seriousness and duration of specific adverse effects (from clinical trials and post-marketing surveillance)
- 1 Interactions with other drugs and with food
- 1 Safety in subgroups (e.g., age, race, sex)
- 1 Potential safety risks with off-label use
- 1 Generalizability of the safety profile to the general population



The use of models for benefit-risk assessment

Content of the presentation

- Why would models for benefit-risk assessment be useful?
- Which models are currently available?
- Which factors should be considered in benefit-risk assessment?
- How are benefit-risk conclusions expressed by regulators?
- The way forward: should there be more standardisation of benefit-risk assessment?



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

- **Objectives:**
 - To review the consistency of expression of the benefit-risk conclusions in EPAR's of new drugs approved through the EU centralized procedure
 - To find out which criteria are discussed most frequently and thus presumably considered as most important by the EU regulatory authorities, and to find out whether there are differences between certain categories of products in terms of the criteria discussed.



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

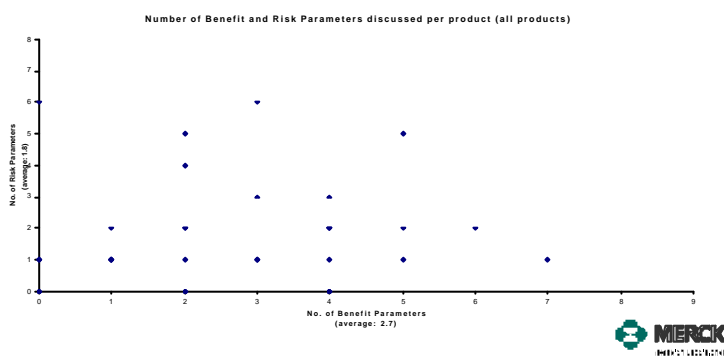
• Methods:

- Drugs selected: all NCE's approved both in the EU through the centralized procedure and in the US during 1998, 1999 and 2000 (33)
- The last section of the EPAR entitled 'Overall benefit/risk assessment' or 'Overall conclusions and benefit/risk assessment' was searched for predefined benefit (9) and risk (8) factors



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports - Overall Results



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

λ Results (benefit)

% that criteria was mentioned in the EPAR conclusions (EPAR core text):

- Magnitude of the treatment effect: 42.4% (100%)
- Clinical relevance of the magnitude of the treatment effect: 72.7% (100%)
- Statistical significance of the treatment effect: 12.1% (83.3%)
- Relevance of the primary endpoints: 27.3% (100%)
- Relevance of the studied population: 27.3% (100%)
- Evidence for efficacy in subgroups: 48.5% (100%)
- Statistical/design robustness of the pivotal clinical trials: 12.1% (50.0%)
- Confirmation of treatment effect by other results: 27.3% (83.3%)
- Anticipated compliance: 3.0% (3.0%)



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

λ Results (risk)

% that criteria was mentioned in the EPAR conclusions (EPAR core text):

- Overall incidence of adverse effects: 15.2% (50.0%)
- Overall incidence of serious adverse effects: 18.2% (83.3%)
- Discontinuation rate due to adverse effects: 18.2% (100%)
- Incidence, seriousness and duration of specific adverse effects: 78.8% (100%)
- Safety in subgroups: 15.2% (100%)
- Demonstrated interactions: 6.1% (100%)
- Potential safety risks with off-label use: 3.0% (0%)
- Generalizability of the safety profile: 24.2% (0%)



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

λ Conclusions (1):

- Limited consistency between products
- More emphasis on efficacy than safety
- Magnitude and clinical relevance of the treatment effect only discussed for respectively 42.4% and 72.7% of products
- Important safety topics are frequently missing (overall incidence of serious AE's, interactions, generalizability of the safety profile)
- The core text of the EPAR's covers most criteria



How are benefit-risk conclusions expressed by regulators in the EU?

Study to test the expression of benefit-risk conclusions for new drugs in European Public Assessment Reports

λ Conclusions (2):

- No obvious trend that certain criteria are linked to certain categories of products
- Possible reasons for these findings with regard to the concluding sections of EPAR's:
 - Lack of attention to this section?
 - Lack of guidance on how to write a benefit-risk conclusion?
 - Is it influenced by the audience to which it is aimed?
 - Does it reflect difficulties to make a benefit-risk conclusion?!



The use of models for benefit-risk assessment

Content of the presentation

- Why would models for benefit-risk assessment be useful?
- Which models are currently available?
- Which factors should be considered in benefit-risk assessment?
- How are benefit-risk conclusions expressed by regulators?
- **The way forward: should there be more standardisation of benefit-risk assessment?**



Should there be more standardisation of benefit-risk assessment ?

Include survey results Q3 and Q4



Minimizing Risk in the Development of New Medicines: A Delicate Balance

CMR International Workshop
Risk Management: The Role of Regulatory Strategies in
the Development of New Medicines

April 25, 2002

Michael D. Clayman, M.D.
Vice President, Global Regulatory Affairs
Eli Lilly and Company



What is Risk:

“The possibility of suffering harm or loss...
- American Heritage College Dictionary,
Third Edition, 2000

Risk in Drug Development is Multi- Dimensional

- For patients
 - May suffer harm
 - May not derive sufficient benefit

- For the company
 - May suffer the loss of a new drug candidate for either (1) or (2) above

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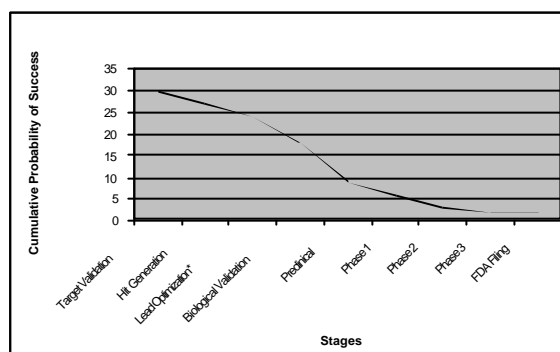
Considerations

- **Ethically physicians are bound by the Hippocratic oath:**
 - Primum non nocere (First, do no harm)
 - Benefit must outweigh possible harm
- **Business implications**
 - Reducing attrition rates
 - Lower attrition rates as a surrogate for lower risk
- **Only drugs with appropriate risk/benefit ratios will be successful**

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Cumulative Probability of Success

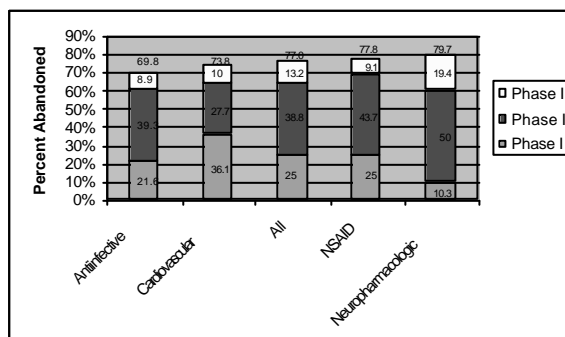


*Assumes two hits investigated per validated target.

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Attrition Rates During Clinical Phases by Therapeutic Category



For every 100 NMEs, two end up as drug (not all are profitable).

Models by McKinsey/Lehman

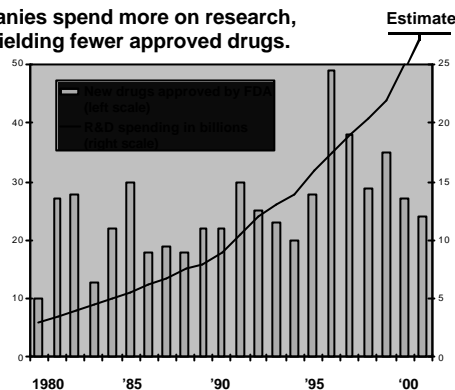
Source: DiMasi et al., Pharmacoeconomics 1995; 7(2): 152-169

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Widening Gap

As companies spend more on research, they're yielding fewer approved drugs.



Sources: Food and Drug Administration; PhRMA
Recreated from Wall Street Journal, April 18, 2002

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The Ideal: Omniscience

At time of target selection, we would know:

- Target is valid
- Screen will yield viable hit
- Hit can be developed into lead
- Lead can be optimized with right biopharm, ADME and tox profiles yielding clinical candidate
- Clinical candidate will demonstrate right balance of safety and efficacy yielding a marketing application
- Marketing application will be approved
- Approved drug will have the right balance of safety and efficacy, address an important unmet medical need and provide an acceptable return on investment

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In the Absence of Omniscience, We Seek 3 Things:

- (1) Pre-clinical and clinical data sets that are most predictive
- (2) Complete transparency
- (3) Best judgment and decision-making married to best process

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In the Absence of Omniscience, We Seek 3 Things:

(1) Pre-clinical and clinical data sets that are most predictive

- **More and better data earlier**

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Pre-clinical and Clinical Data Sets That Are Most Predictive

More and better data earlier

- **Tox, ADME, biopharm before candidate selection**
- **Hepatotoxicity - pre-clinical and clinical algorithms with decision-making thresholds**

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Pre-clinical and Clinical Data Sets That Are Most Predictive

More and better data earlier

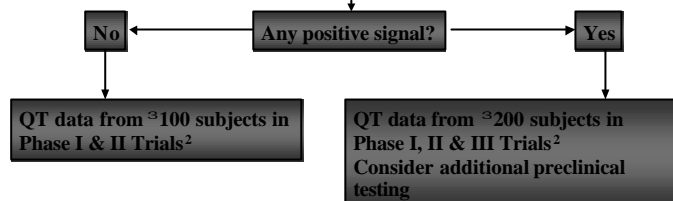
- **Tox, ADME, biopharm before candidate selection**
- **Hepatotoxicity - pre-clinical and clinical algorithms with decision-making thresholds**
- **QT prolongation - pre-clinical and clinical algorithms with decision-making thresholds; getting measurements right; spontaneous variability**

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Assessment of the Potential of a Compound to Prolong the QT Interval

Pharmacological/chemical class
In vitro I_{Kr} ion current assay (HERG Study¹)
Ventricular repolarization assay (Dog Purkinje Study)
Dog (or monkey) cardiovascular safety pharmacology study
Dog (or monkey) repeat-dose tox studies w/ quantitative QT assessment



- HERG = Human Ether-Related A Go Go Gene
- Determine if dose-concentration-effect relationship or if effect of age, gender, metabolism or drug interaction

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Pre-clinical and Clinical Data Sets That Are Most Predictive

More and better data earlier

- Tox, ADME, biopharm before candidate selection
- Hepatotoxicity - pre-clinical and clinical algorithms with decision-making thresholds
- QT prolongation - pre-clinical and clinical algorithms with decision-making thresholds; getting measurements right; spontaneous variability
- Risk management plans as part of new drug applications
- Automated signal detection software

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Pre-clinical and Clinical Data Sets That Are Most Predictive

More and better data earlier

- Genomics/pharmacogenomics
 - Technology is not exploratory/applications are
 - Many emerging examples of genotype/expression dictating drug response

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Pharmacogenomics: Bench to Bedside

Complex promoter and coding region β_2 -adrenergic receptor haplotypes alter receptor expression and predict *in vivo* responsiveness

Carole M. Drysdale^{1*}, Dennis W. McQuinn^{1*}, Catherine B. Smith¹, J. Chakraborty², Richard S. Johnson³, Krishnan Hanthavakar⁴, Kevin Arnold⁵, Susilberto Russo⁶, and Stephen B. Liggett^{1#}

Source: PNAS / September 12, 2000 / vol. 97 / no. 19

HERCEPTIN Label

Indications and Usage

... HERCEPTIN should only be used in patients whose tumors have HER2 protein overexpression. (See CLINICAL STUDIES: *HER2 protein overexpression* for information regarding HER2 protein testing and the relationship between the degree of overexpression and the treatment effect.)

Pharmacogenomic-guided drug development: regulatory perspective

LJ Lesko and J Woodcock

The Pharmacogenomics Journal (2002) 2, 20–24.

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Pre-clinical and Clinical Data Sets That Are Most Predictive

More and better data earlier

- Genomics/pharmacogenomics
 - Some challenges:
 - State of validation pre-clinically
 - Application to safety
 - Avenues moving forward
 - Biomarkers for earlier decision-making
 - SAR dictated by given pathway profiling
 - Target polymorphisms that inform the understanding of drug effect
 - DNA banking in clinical trials – enable future inquiry

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In the Absence of Omniscience, We Seek 3 Things:

(1) Pre-clinical and clinical data sets that are most predictive

- More and better data earlier
- The killer experiment
- The earlier the kill, the better

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The Killer Experiment

There is one sure road to failure that I have seen many wander down: some people become so afraid of failing that they are unable to do a critical experiment... Even though Merck has been bold in its strategies, the company has missed out on some major opportunities because people were unwilling to take that truth-telling step - to conduct the experiment that would show once and for all if what they had spent so many years studying would actually produce a new drug."
-Roy Vagelos, Harvard Business Review interview, 1994

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In the Absence of Omniscience, We Seek 3 Things:

(1) Pre-clinical and clinical data sets that are most predictive

- More and better data earlier
- The killer experiment
- The earlier the kill, the better

(2) Complete transparency

- Internal expectations
- External expectations

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Complete Transparency

- Better meet internal and external customer expectations
- Meeting customer expectations is at the heart of quality
- Hence a quality driven effort

How we do this at Lilly

- Robust implementation of the Draft Launch Label (aka Targeted Package Insert)
 - Developed cross-functionally very early (before candidate selection)
 - Insures right conversations and decisions are being made early enough by the right people

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Best Judgment and Decision-Making Married to Best Process

- **Portfolio management**
- **Deep drug development expertise**
- **Innovation without walls**
- **Organization that enables more rapid decision-making to insure highest priority projects are adequately resourced**

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In Closing

- **The approach of more robust data earlier +**
- **Transparency of customer expectations (draft launch label) +**
- **Experienced drug development decision-makers using portfolio management tools**

Has allowed a significant decrease in phase-specific attrition rates and improvement in productivity

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**“Knowing is not enough; we must apply.
Willing is not enough; we must do.”**

- Goethe

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POST MARKETING SURVEILLANCE: Risk Management Role

Mary A. Foulkes, Ph.D.
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and
Research
FDA

24 April, 2002
CMR Intl Workshop

WHY?

- **Signals of Public Health threats**
- **Identify need for preventive action**
 - **Labeling**
 - **Packaging**
 - **Indication**
 - **Target population**
- **Evaluate in face of changes**
- **Re-evaluate public health recommendations or licensing decisions**

WHAT?

- **Rare events missed in prior studies**
- **Improve quantification of known risks**
- **Unexpected/unanticipated risks**
- **Modest post-exposure increase in the relative risk of a non-rare event**
- **Long delayed outcome (e.g., vaginal cancer after exposure to DES)**

HOW?

- **PASSIVE**
 - Voluntary reporting
 - Retrospective & Observational
- **ACTIVE**
 - Systematic reporting
 - Prospective controlled designs
- **SENTINEL**
 - HMOs
- **SPECIAL**
 - Survey

WHERE?

- **MEDWATCH**
 - AERS
 - VAERS
 - CEARS
- **Blood & Blood components**
- **MAUDE**
- **Many, Many Others**

Hierarchy of Strength of Evidence

Anecdotal case reports
Case series without controls
Series with literature controls
Analyses using computer databases
"Case-Control" observational studies
Series based on historical control groups
Single randomized controlled clinical trials
Confirmed randomized controlled clinical trials

[Green SB, Byar DP. *Statistics in Medicine* 1984; 3: 361-70]

Exploratory Methods

- Cumulative sum (CUSUM) techniques
- Control charts
- Data mining
 - Bayesian neural network
 - Bayesian shrinkage estimators
- Time series modeling
- Visual presentation
- Other

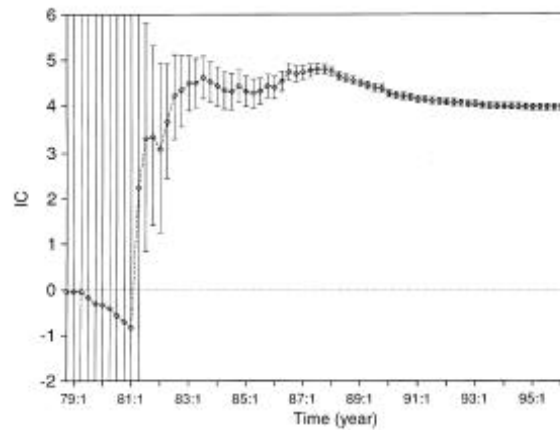


Fig. 1 The change in IC between 1979 to 1996 for the association captopril-coughing. The IC is plotted at quarterly intervals with 95% confidence limits shown

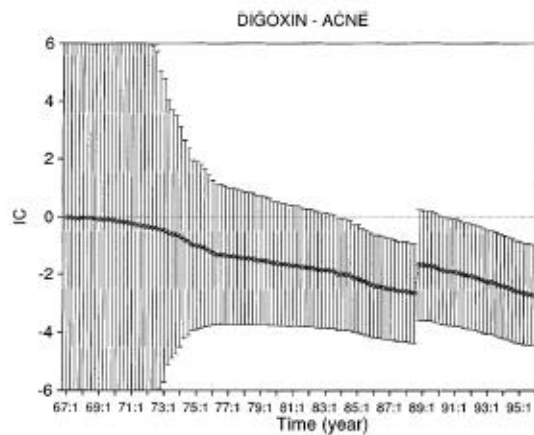
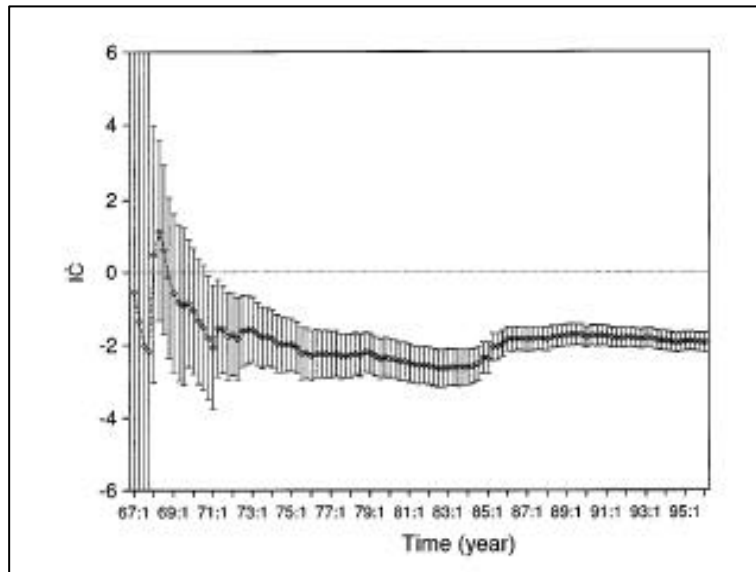


Fig. 2 The change in IC between 1967 to 1996 for the association digoxin-acne. The IC is plotted at quarterly intervals with 95% confidence limits shown

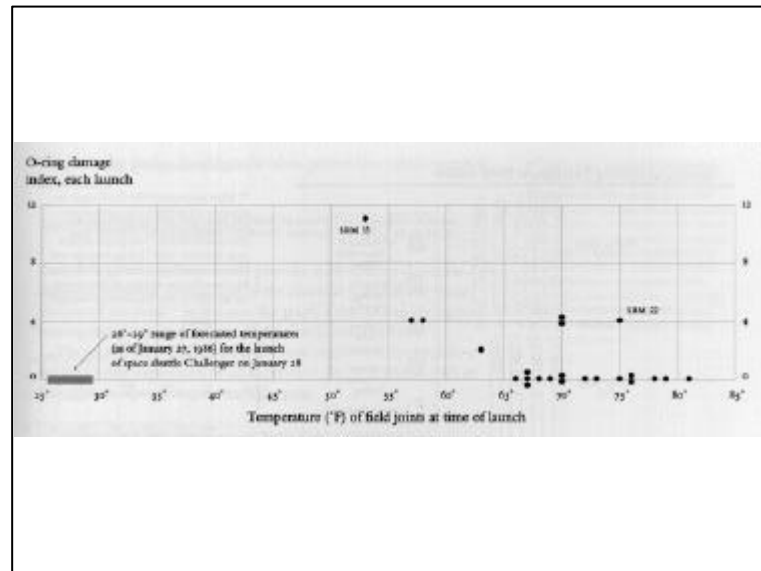
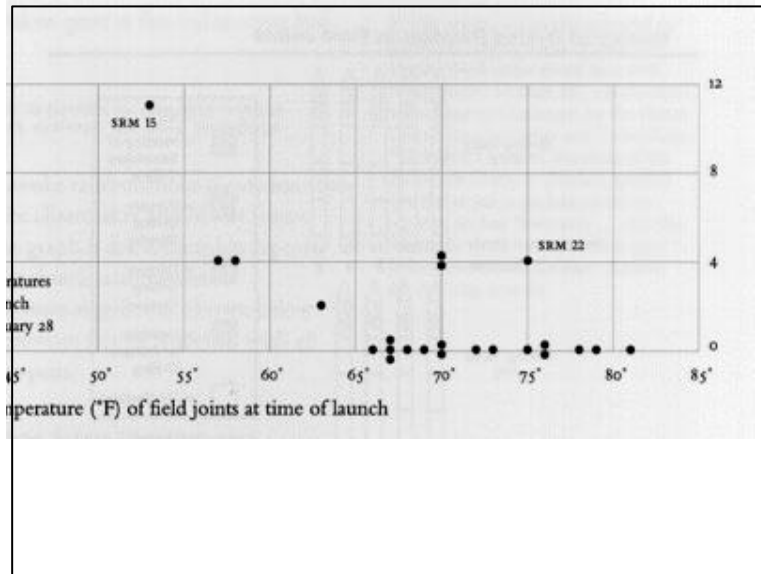


Analytic Complexity

- Sampling frame
- Release/roll-out
- Capture-recapture
- Matching
- Clusters (time/space)
- Record linkage
- Missing data

RETROSPECTIVE EXAMPLE

- 1986 Challenger launch
- Existing data on O-Rings properties at various temperatures
- Manufacturer recommended, unpersuasively, the night before, that NASA cancel the Challenger launch
- Tufte showed how the mfr presentation violated several principles of design, and then showed a more persuasive rearrangement of the same data



Hierarchy of Strength of Evidence

- Anecdotal case reports
- Case series without controls
- Series with literature controls
- Analyses using computer databases
- "Case-Control" observational studies
- Series based on historical control groups
- Single randomized controlled clinical trials
- Confirmed randomized controlled clinical trials

[Green SB, Byar DP. *Statistics in Medicine* 1984; 3: 361-70]

ANECDOTAL REPORT

- Device adverse event reporting comes to FDA through the Manufacturer and User Facility Device Experience (MAUDE) system
- Anecdotal report on an ultrasonic cleaning device used in dental offices that emitted electrical shocks and resulted in an office fire
- Investigation revealed missing ground wire

CASE SERIES EXAMPLE

- August '98 FDA approved RRV-TV w intuss'n as possible AE in label and in recommend of ACIP
- Between Oct'98 and June'99, VAERS reports of 9 cases
- Prompted data mining investigation of how soon VAERS would have detected this signal

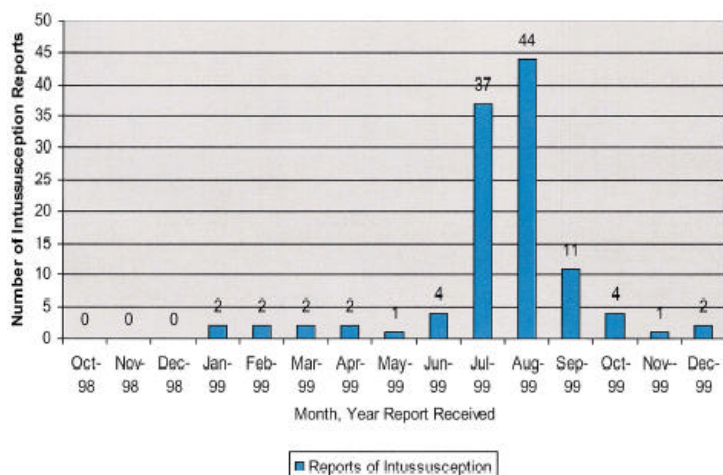
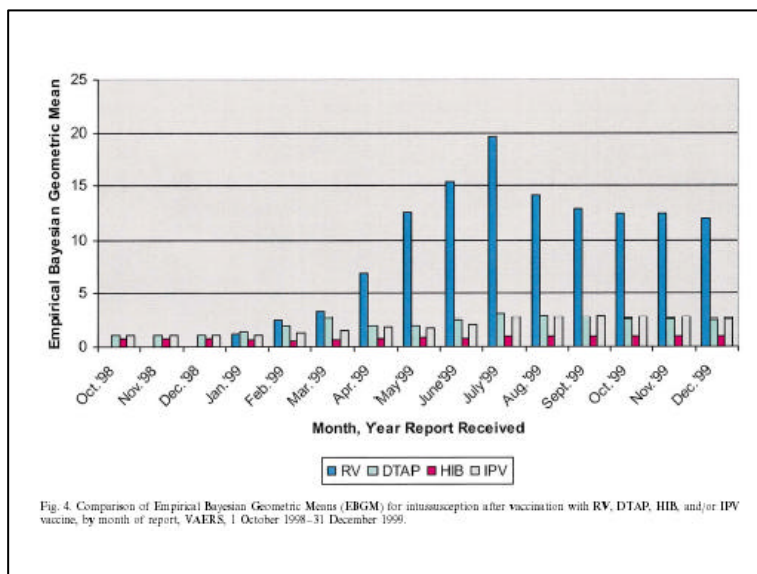


Fig. 1. Cases of intussusception after vaccination by month of report, VAERS, 1 October 1998-31 December 1999 (n = 112).



UK CASE SERIES

- Abnormal liver function tests observed in patients undergoing IV Ig therapy
- Suggestions from Sweden and Spain of association between IV Ig and acute hepatitis C

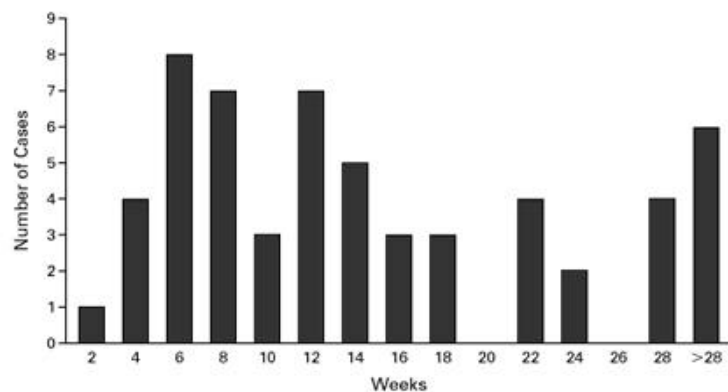
Acute Hepatitis C & Gammagard

Clinical Features	Batch 93F21AB11	Other Batches	Total
No. pts	34	12	46
Age	42.8 (6-77)	37.8 (23-52)	41.5
M/F	15/19	7/5	22/24
HCV RNA+	28/34 (82.4%)	0/9	

CASE SERIES EXAMPLE

- Approx 150,000 pts worldwide rec'd a humanized antibody against TNF- α
- Case series of 70 reported cases of TB after Infliximab (median 12 wks)
- Rate of TB higher than estimated background rate (6.2/100,000)
- Risk of TB with Infliximab therapy higher than other opportunistic infections
- Recommend screening for latent TB

Initiation of Infliximab to Dx of TB



COHORT STUDY

- Relation between vaccinations and first seizure
- Vaccine Safety Datalink - four large, regional HMOs
- ~700,000 children, '91 - '93
- Medical records abstraction
- Classification of seizure type
- Data on seizures w/o vaccination
- Neuological outcomes follow-up

COHORT STUDY

Days	DTP Vaccine		MMR Vaccine	
	#	Relative risk	#	Relative risk
Febrile seizures				
0	5	5.70(1.98-16.42)	0	-
1-7	9	1.16(0.53-2.56)	8	1.78(0.72-4.15)
8-14	10	1.12(0.53-2.33)	13	2.83(1.44-5.55)
15-30	18	1.43(0.82-2.50)	11	0.97(0.49-1.95)
Non-febrile seizures				
0-7	4	1.94(0.62-6.12)	1	-
8-14	2	0.77(0.16-3.67)	1	1.11(0.11-11.28)
15-30	4	1.05(0.32-3.37)	1	0.48(0.05-4.64)

CASE-CONTROL EXAMPLES

- Allergic reactions to Japanese encephalitis vaccine
- Intussusception after oral rotavirus vaccine
- Acute MI and neuronal serotonin re-uptake inhibitors
- Hemorrhagic stroke and phenylpropanolamine

Planned Follow-up Study

- Case-control study planned to examine the hypothesis that LYMERix® is associated with arthritis
 - arthritis cases confirmed by survey
 - two control groups identified from VAERS
 - arthritis cases reported following other vaccines
 - events other than arthritis reported following LYMERix®
 - conduct high resolution HLA typing and test for T-cell reactivity to OspA and LFA-1
 - probably only a very strong risk will be detectable

HISTORICAL CONTROL SERIES

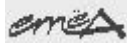
- Comparison of six statins introduced over a decade and the reports of rare fatal event
- Association of statin therapy with fatal rhabdomyolysis
- Caveats with historical controls

Rhabdomyolysis & Statins

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Cerivastatin
Year	87	91	91	93	96	97
Fatalities	19	3	14	0	6	31
mil pre-scripts	99	81	116	37	149	9.8
Rate per mil	0.19	0.04	0.12	0.0	0.04	3.16

CONCLUSIONS

- Invest in routine surveillance
- Devote resources to monitoring (data mining)
- Standard evaluations at change points or introduction of new recommendations
- Develop capabilities for emerging infections



CMR International Workshop:
The Role of Regulatory Strategies in the Development of New Medicines
25-26 April 2002, Cobham, Surrey, UK

Factors Influencing Risk Management in the EU

Thomas Lönngren
EMEA Executive Director



Factors Influencing Risk Management in EU

- **Legal and regulatory framework**
- **Organisation**
 - » **Procedure**
 - » **Responsibilities**
- **Competencies**
- **Scientific development**
- **The medicinal product and its use**
- **EMEA risk management strategy**



Legal and Regulatory Framework

- **Future proposals**
 - » **Access and authorisation mechanisms**
 - Conditional approvals – yearly review
 - Expedited review – fast track
 - » **Reinforced MAHs obligations to collect and report safety information**
 - » **No 5 yearly renewal – increased frequency of PSUR**
 - » **Pharmacovigilance enforcement and inspections**
 - » **Information?**



Organisation: Procedure and Responsibilities

- Scientific Advice
- Procedures for the authorisation of medicinal products
 - » Centralised Procedure
 - » National/Mutual Recognition Procedure
- Split responsibilities at EU level
- Review 2001: extending scope of centralised procedures to all new active substances
- EU co-ordination of pharmacovigilance activities



Competencies

- Expertise available within scientific committees
- Need to develop specific expert competencies, e.g. therapeutic teams at EMEA
- Expert groups for complex scientific areas: 'pockets of expertise'



Challenges from Scientific Developments

- Results of genome research
- New therapies
- Shift to more patient-orientated medicines
- Medicines for rare diseases and paediatrics



Medicinal Products and its Use

- **Difference in assessing risks from medicinal products compared to most other fields**
- **Normal condition of use**
- **Thalidomide – example of a risk management programme**



EMEA Risk Management Strategy

- **To provide a framework which allows to reduce as much as possible the risks associated with the placing on the market of new medicines**
- **Different aspects need to be considered:**
 - Risk Detection (tools)
 - Risk Assessment (expert advice)
 - Risk Minimisation (active post-authorisation surveillance)
 - Risk Communication (effective, transparent)



Final Remarks

- **Regulatory tools**
- **Competence**
- **Capability to operate the system and procedures by bringing together the right experts**

CMR International Workshop Risk Management

Thursday April 25 2002

A positive approach to risk management

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Our report - Supporting Innovation: Managing Risk



Why a report on risk?

- **Corporate Governance - The Turnbull report**
- **“Modernising Government” White Paper 1999**
- **Our analysis of NAO reports**



Analysis of NAO reports revealed

- Many projects and programmes
 - *over cost*
 - *over time*
 - *reduced performance*



Example - The British Library



What are the causes of these problems?

- laziness **X**
- lack of motivation **X**
- lack of intelligence **X**
- red tape **X ✓**
- failure to assess and manage risk **✓✓**



What is the auditor's perspective on risk

We are not against risk taking
provided it is well managed

Things will come out of the blue -
contingency planning

Public expectation



Risk Averse

or

Risk Ignorant ?



The Public Service Rabbit - 1



He doesn't know what risks
he's running!



The Public Service Rabbit - 2



He sees the risk!
He thinks the safest course is to
do nothing!



The Public Service Rabbit - 3



Poor risk assessment and
management - the result



Example Inadequate risk analysis and planning

The Passport
Agency



Example - Unrealistic business case

Dome



What public service often fails to do

Doesn't identify the key risks

Doesn't assess risk well

**Doesn't manage risk - too often
no contingency plans**



But progress is being made



Example - effective identification and management of risks

Electronic Tagging - Home Detention Curfew Scheme



A View of pharmaceutical industry

•*Might expect:*

- well aware of the risks associated with medical research
- leading edge in management of product risk to the public - thorough testing expected
- takes swift action when things go wrong - reputation, market share, public responsibility

But what other risks? Business risks, suppliers, overpricing, branding of products, relationship with key customers (NHS), contingency arrangements when things go wrong



Is the approach to risk sound?

- **Link risks to achieving objectives - analyse and manage the key risks**
- **Support and promote from the top**
- **Communicate the benefits**
- **Embed in management processes**
- **Manage the risks of working with others**
- **Harness opportunities for innovation**

