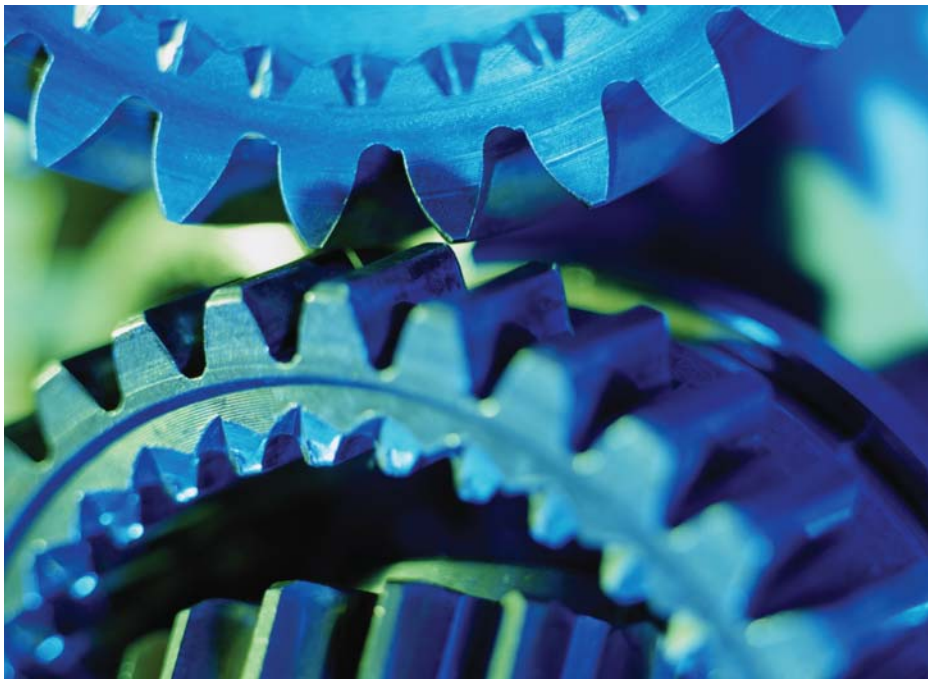
R&D Briefing

Building Quality into Regulatory Activities: What does it mean?



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Building quality into regulatory dossiers and the review process

A review of current Institute activities related to the monitoring and evaluation of quality measures adopted by companies and regulatory agencies as part of medicinal product registration.

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Institute for Regulatory Science

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Institute for Regulatory Science

The Institute for Regulatory Science is a not-for-profit division of Thomson Scientific. It works in the regulatory and policy arena and in close association with the research-based pharmaceutical industry and regulatory authorities around the world.

The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts (see back cover).

Further information on Institute Activities

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

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

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Building Quality into Regulatory Dossiers and the Review Process

A review of current Institute activities related to the monitoring and evaluation of quality measures adopted by companies and regulatory agencies as part of medicinal product registration.

Key points

In the world of medicines regulation, the term 'quality' is inextricably associated with data on the pharmaceutical characteristics of the medicinal product and the processes for chemical and manufacturing control (CMC). Increasingly, however, the term 'quality' is also being used in discussions of the regulatory process itself. What does it mean, in this context?

A definition of 'quality', as applied to regulation is elusive and it has been characterised as abstractly as "you know it when you see it" or, more pragmatically, as "knowing and meeting customer expectations".

The Institute for Regulatory Science held a workshop in 2004 on benchmarking regulatory procedures[1] which concluded that it is not enough to measure regulatory performance in terms of timelines and the speed of the review alone. The quality of the process, from the construction of the dossier to the ultimate regulatory decision must also be monitored and added to the equation.

The recommendations from the benchmarking workshop were followed up at the Institute workshop on 'Building quality into regulatory dossiers and the review process' which is the main focus of this briefing[2]. This in turn has led to two major projects which are also highlighted in this publication.

Scorecards: A project has been initiated to design and test a 'scorecard' system for obtaining feedback, in a harmonised format, following the review of a major application. One scorecard is designed to be completed by the agency and will provide the company with views on the quality of the dossier, with the objective of helping the sponsor understand the results of the review and learn from the outcome in order to implement improvements for future dossiers.

The second scorecard, on the agency review, will be completed by the company. Potentially a more sensitive issue, the objective is to encourage effective working relationships between industry and regulatory agencies by providing a means for an open exchange of views on the conduct of a review.

Survey of regulatory agencies: A major study has been undertaken among regulatory agencies to review the ways in which quality measures are being implemented. Although differences in approach and priorities were found, there were also clear similarities. For example, all the agencies work through a system of independent advisory committees and the greatest impact on quality was perceived to be through peer review and the implementation of standard operating procedures (SOPs) and assessment templates.

Through discussions in Syndicate Sessions, the Workshop also made recommendations on the elements of Good Practices that companies should address when assembling a dossier and that agencies should consider when looking at the quality of their review practices.

[1]Beyond Benchmarking: What are the key metrics that agencies and companies should use to measure performance? Institute Workshop, October 2004, Landsdown Park, Virginia, USA.
[2]Details on page 7 of this report.

Background

The Institute for Regulatory Science is currently involved in several activities related to quality as it applies to regulatory submissions and procedures, rather than the more conventional association with the quality assurance of the medicinal products themselves. Much of the Institute's work in this area can be traced back to the Workshop on Building Quality into Regulatory Dossiers and the Review Process, held in December 2004 in Surrey, UK.

> The quality of the regulatory review process is often judged solely by looking at the end point, but this might not give a true picture of the quality of the whole process.
>
> **Professor Rolf Bass**[1]

Recommendations from this Workshop related to monitoring and measuring the quality procedures adopted by companies and regulatory agencies and this briefing summarises the ways in which these have been followed up by the Institute and also provides highlights from the meeting.

> The goal of management, in the regulatory agencies, is to meet the obligations placed on them by government and to meet the expectations of stakeholders, whether industry or the public, for safe and effective medicines to be made available to patients. In order to achieve this, management systems must be in place with quality control measures built into all procedures.
>
> **Thomas Lonngren**[1]

Institute projects

Two major projects have been initiated using proposals from the Syndicate discussions at the Institute Workshop:

An evaluation of quality measures applied to the regulatory review process of major regulatory authorities: A study carried out for a Masters Degree by a pharmacy graduate, Andrea Mallia-Milanes, Maltese Ministry of Health, under the supervision of the Institute and the University of Cardiff, Wales (see page 6).

Scorecards: The development of a system of feed-back to assess agency performance and the company dossier following completion of a major application for a new medicinal product (see pages 4-5).

Other related Institute activities

Developing a model for benefit-risk assessment: The institute has held two Special Focus workshops for invited participants to study the technique of multi-criteria decision analysis (MCDA) and its application to the review of the benefits and risks associated with new medicines.

This is a method of looking at complex problems, of breaking the problem into more manageable pieces in order to allow data and judgments to be brought to bear on different aspects, and then of reassembling the pieces to present a coherent overall picture for decision-makers. The purpose of this tool is to serve as an aid to thinking and decision-making, but not to take the decision.

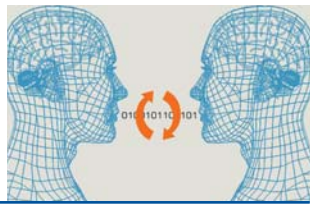
Regulation in the Emerging Markets: A major study has been undertaken which collected data and information on regulatory procedures and issues in countries, outside Europe, the US, Japan, Canada and Australia, that are becoming increasingly important as pharmaceutical markets and centres for pharmaceutical registration.

The study aimed to identify elements that represent 'good regulatory practices' for agencies with limited resources where the decision-making process depends to a greater or lesser extent on reviews carried out by more advanced agencies. The participating agencies welcomed the prospect of a further study on quality in regulatory processes and this is being followed up by the Institute.

> Decision-making is crucial to any organisation but never more so than in the regulatory agencies where the outcome of some twelve years' research and many millions of dollars investment depend on the decision of a handful of regulatory experts. Within companies, however, there is an equally important need to make good quality decisions throughout the development process.
>
> **Professor Stuart Walker**[1]

[1]Quotations from speakers at the Institute Workshop on Building Quality into Regulatory Dossiers and Review Processes, see page 7 for the programme and details on participants.

Ensuring and monitoring quality



The Institute Workshop on quality looked at the elements of Good Practices for companies when assembling a dossier and for agencies when carrying out a review. (Further considerations for preparing a quality dossier are also given on page 9).

Elements of a quality dossier

Content

- All the critical information in the appropriate detail
- Data mapped to the respective items in the label
- Negative data not obscured or hidden in any way
- Critical discussion of strengths and weaknesses in the supporting data

Insight

- Tells the 'history' of the application and the development of the label
- Indicates the key decision points in the development process

Navigation

- Navigable 'in both directions' (ability to find cross-references and return to the original place

Key elements when preparing dossiers

- Building quality into the dossier documentation from early in the R&D process
- Quality assurance as an integral part throughout the process: quality checks cannot be 'bolted on' later
- Implementing quality management systems with appropriate criteria-based audits
- Formalised steps ('milestones') in the process with decision points and criteria for proceeding
- A pre-submission review of the entire application by internal and external experts
- An assessment of the strengths and limitations of the dossier prior to filing

Measuring quality retrospectively

Assuming a direct relationship between the quality of an application and the speed and outcome of the review the following can be quantified and compared:

Number of Review cycles

- Comparisons against the same regulatory process since definitions of a single review cycle may differ

Label

- Differences between the final labeling (product information, SmPC), and the application proposal
- Whether the final label met expectations (target market and patient population)

Number of questions

A log of all questions and queries from the agency recording and learning from experience of:

- How many required additional data
- How many were navigational (the data was in the file but was not found by the reviewer)
- How many required additional studies
- How many issues could be addressed by agreeing to label changes

Quality reviews

A quality review results in general satisfaction, on the part of both sponsor and agency, with the way in which the review procedures have been conducted and the outcome of the application process. The key elements are:

Assessments that are:

- Carried out in depth taking account of all the salient data and information
- Evidence-based with respect to the recommendation on the outcome
- Reported in sufficient detail to allow peer review
- Consistent within the different sections of the application
- Consistent between applications for similar products

Assessors that are:

- Consistent in approach and attitude to sponsors
- Creative, analytical and innovative in relation to novel products and concepts
- Focused on problem-solving

Scorecards for monitoring quality

The Institute Workshop made recommendations that have led to a project to draw up and validate model 'scorecards' to report back following the review of a major application (new active substance or line extension). The elements agreed at the Workshop are summarised here.

Checklist for a Scorecard on Company Performance (Feedback from the regulatory agency)

- ✓ **Application format**
  The presentation and construction of the dossier, especially in electronic format
- ✓ **Summaries/Overviews**
  Accuracy, Relevance, Links to the supporting data
  Analysis of the safety issues, Risk management plans
- ✓ **Use of Scientific advice**
  Whether the applicant had followed the scientific advice or, if ignored, had given an explanation
- ✓ **Technical content**
  Adequacy of data to support the proposed label
  Whether official guidelines were followed
- ✓ **Response to questions**
  The way the company responded to issues raised during the review
  Completeness and timeliness of response
- ✓ **Communication**
  Value of interactions between the company and agency
- ✓ **Performance at hearings**
  Feedback on company performance at any appeal proceedings
- ✓ **Procedural operation**
  Company understanding of procedures and willingness to comply
- ✓ **Product datasheet**
  Whether realistic proposals were made for the Summary of Product Characteristics/Product Labeling
- ✓ **Overall assessment**
  Critical factors that led to the outcome of the review

Scorecards for monitoring quality

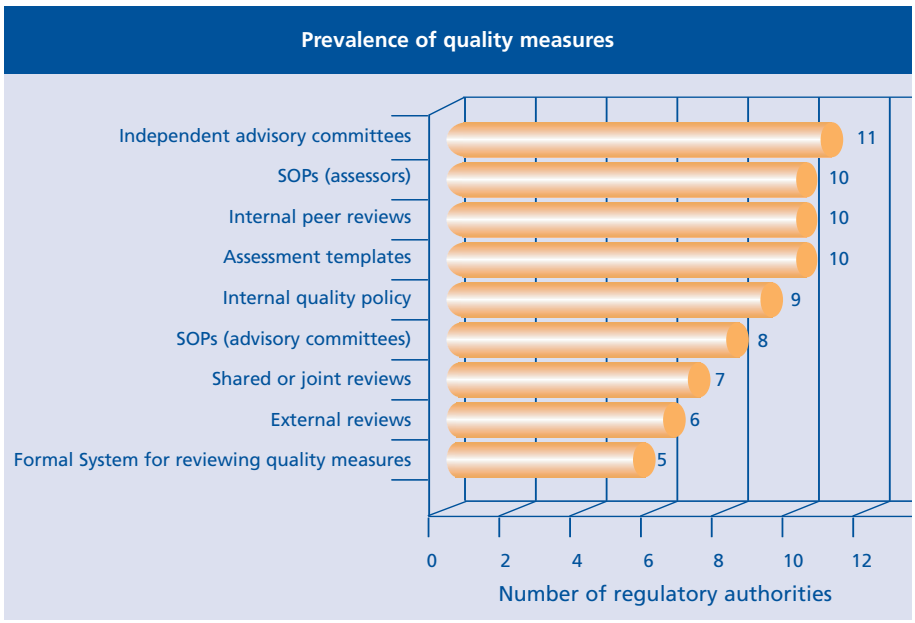
In developing the Scorecard project the Institute is aware of similar initiatives being carried outside elsewhere, for example a project by the European industry association EFPIA and the dossier assessment carried out by the European Medicines Agency (EMEA) on centralised procedure applications.

Checklist for a Scorecard on Agency Performance (Feedback from the company)

- ✓ **Scientific Advice**
  The extent of interaction between the agency and the applicant throughout the development process
- ✓ **Communication**
  How appropriate the agency's communication and responsiveness was during the review process
- ✓ **Consistency**
  Whether the agency followed its own guidelines and precedents when assessing the product
  How consistent the advice was in relation to previous experiences and precedents
- ✓ **Professional/scientific competence**
  Whether the agency experts had the appropriate knowledge and experience for the product under consideration
- ✓ **Procedures**
  How rigorously the agreed review procedures for applications had been followed
- ✓ **Questions**
  The usefulness and relevance of the questions asked during the review process and whether these highlighted valid issues or were they based on a misunderstanding or misinterpretation of the dossier
- ✓ **Product information**
  Whether final Summary of Product Characteristics/Product labeling was arrived at fairly and openly with requests for changes driven by science
- ✓ **Overall satisfaction**
  Whether the result of the review arrived at the outcome that the applicant had expected or whether there was a fundamental difference between the expectations and the conclusions of the agency

Quality survey among regulatory agencies

Quality is critical for ensuring that assessments and decisions are scientifically sound and that only effective and safe medicines reach the market. The survey carried out under the auspices of the Institute on Quality measures applied to the regulatory review process of major regulatory authorities confirmed that regulatory agencies are also introducing quality measures to ensure consistency, efficiency and predictability in the review process.



The Study

Eleven regulatory agencies were included in the study: EMEA, FDA (CDER), PMDA Japan, Canada, Australia and six national agencies in Europe.

The questionnaire covered many aspects of 'quality', in a broad interpretation, including training, transparency and communications as well as the specific quality measures shown in the figure opposite.

For this part of the study, agencies were given a list of quality-related activities and asked to record which they were currently implementing.

Continuous improvement

The study found that several continuous improvement activities are being undertaken by the eleven authorities to enhance the review and decision-making process. These include: training needs assessments, reviews of assessor and stakeholder feedback and internal tracking systems. Few authorities, however, carry out post-approval analysis in terms of cross-authority comparisons of the outcome of the review process and the collection of feedback from industry on the quality of the assessment.

Key measures for building quality into the review process

The study report discussed key measures that are critical for quality reviews and high-quality decision-making and the following list was proposed as one of the recommendations:

Key quality documentation: regularly updated and comprehensive quality policies, standard operating procedures and assessment templates.

Professional development of assessors: adequate and regular on-the-job training of assessors that focuses on, for example, improved work practices; latest developments; scientific and technological advancements; and knowledge and skills transfer.

Built-in quality controls: such as systematic management checks, structured approach to decision-making and robust internal tracking systems.

Internal reviews: a structured and integrated peer review system, as well as expert reviews by independent advisory committees.

Benchmarking and key performance indicators: such as regular use of quantitative indicators on processing times; response times; frequency and number of withdrawals; as well as the carrying out of benchmarking exercises that compare processes or outcomes.

Continual improvement activities: conducting internal quality audits, self-assessments, analyses of feedback from stakeholders, post-approval analysis with other authorities and industry, management reviews, and using the results to take corrective action or introduce improvements to the review process and decision-making.

An established setup and process that allows regular contact with industry: for example, to discuss development and review plans, clarify statutory requirements, provide scientific and regulatory advice, inform the applicant on how the review is progressing, and develop 'partnerships' and synergies between the two parties.

A transparent system that provides important review information to the public: for example open public hearings of advisory committee meetings, or the publication of the summary basis of approval and assessments following approval.

Workshop highlights

Workshop on Building quality into regulatory dossiers and the review process, December 2004, Surrey, UK

Session 1: Building Quality into the Application Dossier

Chairman: *Thomas Lönngren*, Executive Director, European Medicines Agency (EMEA)

Strengths and weaknesses in today's application data: Are companies meeting regulators' expectations? *Dr David Lyons*, Senior Medical Officer, Irish Medicines Board

Quality management in a Regulatory Affairs Department, *Dr Paul Huckle*, Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, UK

Critical Self Assessment: What companies can learn from analysing their own regulatory experience? *Dr Susan Forda*, Executive Director Regulatory Affairs, Europe, Eli Lilly & Co.

Session 2: Building Quality into the Regulatory Review Process

Chairman's Introduction, *Thomas Lönngren*

What companies expect from Regulatory Authorities, Dr Ronald J. Garutti, Group Vice President, Global Regulatory Affairs, Schering-Plough Research Institute, USA

Harmonising approaches to quality assurance: The European Experience, Dr Marijke Korteweg, Integrated Quality Management Advisor Directorate, EMEA

Perspectives from within the EU, Professor Rolf Bass, Head of Division, EU and International Business, BfArM, Germany

Session 3: Meeting Future Expectations

Chairman: *Professor Stuart Walker*, President and Founder, CMR International

Building Quality into Future PMDA Activities, *Dr Osamu Doi*, Senior Executive Director, Pharmaceuticals and Medical Device Agency, Japan

A future vision for quality reviews and decisions, *Moira Daniels*, Director of Global Regulatory Information and Intelligence, AstraZeneca, UK

Preparing for future technologies, *Dr David Jefferys*, Special Advisor-Healthcare Industries, Department of Health, UK

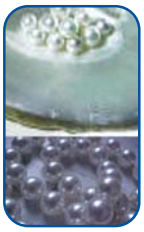
Session 4: Syndicate Discussions

- Proposed studies on building quality into regulatory dossiers and review
- Proposal for a 'Scorecard' assessment of dossiers and reviews

The quality of decisions and the decision-making process, *Professor Larry Phillips*, Professor of Decision Analysis, London School of Economics

Snapshots from the workshop presentations

European networking
With the expansion of the EU, in May 2004, there are currently 28 countries in the EU regulatory network – 25 EU Member States and three EEA countries, Norway, Iceland and Liechtenstein. Each member of the network can be likened to pearls that are valuable in their own right but when combined in a chain, they become a jewel of greater value. A chain, however, is only as strong as its weakest link, and to ensure consistency and quality of the network's deliverables, it is important that there are no weak links in the EU network.
Dr Marijka Korteweg



EU/EEA Medicines Network
linking loose pearls to a chain without any weak link

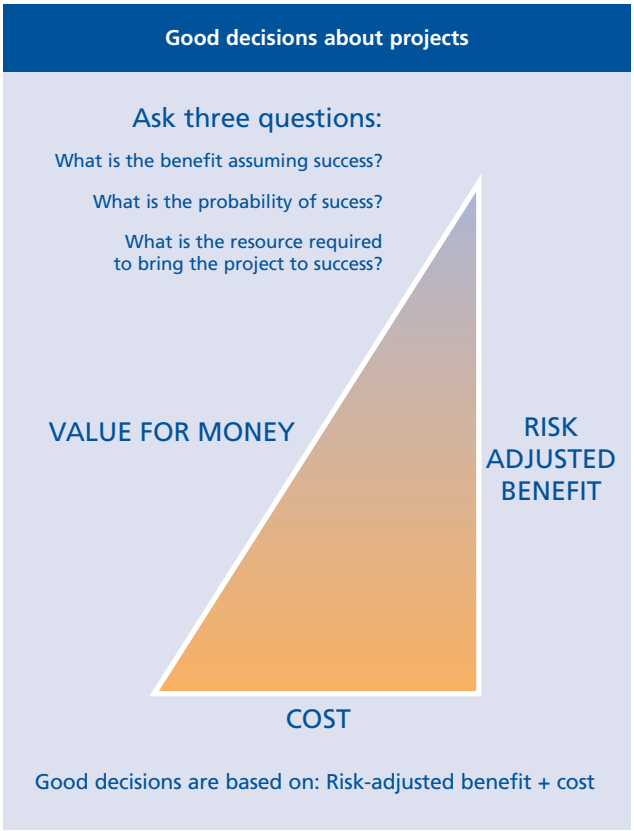
Japanese perspective
The PMDA is improving the quality and timeliness of its review processes and enhancing safety procedures, in the interests of patients. This is not only its responsibility to the Japanese people but also to patients at a global level. In order to respond to the expectations of the public, PMDA is committed to raising the standard of its operations in the field of science and technology in order to deliver timely and appropriate judgments on innovative new products.
Dr Osamu Doi

Quality of science
The quality of science is in danger of becoming a neglected area in the drive towards quality management of regulatory processes. Pharmaceutical legislation and codes of practice underpin and drive regulatory activities but there cannot be legislation and no codes exist on scientific quality. In the absence of measures to assess scientific quality, the quality of the final regulatory decision depends upon the personal judgement of individuals or groups of experts.
Professor Rolf Bass

Risk and benefit
Risk issues appear to assume more importance than benefit in the regulatory process and in public expectations. More work is needed to achieve the right balance and convey the message that medicines are not free from risk any more than other everyday activities such as driving a car and crossing the road.
Moira Daniels

Workshop highlights

The patient at the centre
One of the most significant developments is the focus on patient-centred healthcare. Systems were no longer being built around the healthcare professional but around the patient and 'empowered' and knowledgeable patients – a product of the Internet era – were making their voice heard and their needs known.
Dr David Jefferys



Quality of decisions
Contrary to expectations a quality decision and decision-making process should not be tested by looking at the outcomes and consequences. In an uncertain world, it is perfectly possible to take a good decision that has poor consequences and, equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes.

It is important to work with multifunctional teams to provide a diversity of opinion and improve the quality of decisions. Dissent and disagreement can be productive in formulating new courses of action not previously considered.
Professor Larry Phillips

Learning from experience
Whilst there is no substitute for practical experience in all aspects of compiling a quality dossier, most issues that arise and cause difficulties are unique to the particular molecule. The process of 'learning from experience' is also slowed down by the fact that most companies do not bring many medicines for the same indications to the market.
Dr Susan Forda

Communication
Communication is a key component for achieving safe and effective drug products.
- Public misconception of 'partnership' must not jeopardize communication.
- Sponsor/Regulator interchange does not compromise public health, rather it enriches product development.
- Interaction between sponsors and health authority staff is the only way to guarantee continued innovation.

Dr Ronald Garutti

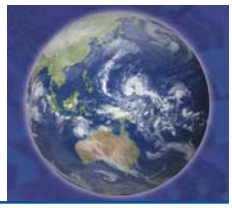
Avoiding potential pitfalls:
- Pay early attention to pharmacokinetic and pharmacodynamic results that might be indicators of pharmacogenetic factors;
- Follow the science and do not allow the marketing department to influence technical decisions;
- Do not defend or obliterate unexpected results –they happen.

David Lyons

A future vision for quality reviews and decisions
- Continual benefit/risk data: This is not a document but an ongoing evaluation of data on benefit and risk throughout the life cycle of the product.
- Generic electronic database information systems: A link into such systems that can provide the baseline and the benefit of comparative information.
- Shared, more predictable, transparent regulatory decisions: The ability to know that if you generate the agreed data there is a reasonable predictability of outcome.
- Significantly increased public confidence in new therapies: The achievement of patient ownership and participation to the extent that they feed data about their treatment and any adverse effects into the database.

Moira Daniels

Questions to ask when assembling a dossier



Quality of the message

- **PURPOSE**
  - Is the purpose of the development programme clearly stated?
  - How is the product differentiated from similar drugs and treatments?
- **CONTEXT**
  - Issues that influenced the development programme: Are these identified in the background?
  - Key elements of the development programme: Are these connected and cross-referenced?
  - Characteristics of the target disease: Have other treatments, demographics, economic impact been discussed?
- **LOGIC**
  - Has a logical, coherent picture of the drug been presented?
  - Are results interpreted in relation to the programme objectives?
  - Do the conclusions interpret the results clearly?
  - Are the conclusions consistent with the data? Are inconsistencies explained?
- **CONTENT**
  - Does the dossier meet regulatory agency expectations?
  - Is the size appropriate for the type of application?
  - Has compliance with GMP/GLP/GCP requirements been checked?
  - Are studies described in sufficient, but not excessive detail?

Delivery of the message

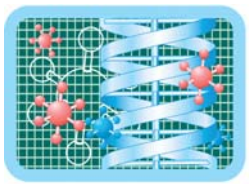
- **ORGANISATION**
  - Deductive layout: Does each section state content and conclusions?
  - Is there a logical data flow through the dossier?
  - Ease of navigation: Are headings, cross referencing, and numbering coherent?
  - Have summaries, tables of studies and appendices been used appropriately?
- **PRESENTATION**
  - Is the document appropriately displayed and readable throughout?,
  - Is the emphasis correct, highlighting critical parts of the dossier?
  - Have tables vs text been considered adequately?
    Are all the visuals clear?
- **LANGUAGE**
  - Have standard conventions for punctuation and grammar been used?
  - Editing: Have sentence construction and volcabulary been monitored?

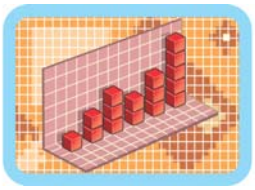
From the presentation by Dr Paul Huckle at the Workshop on
Building quality into regulatory dossiers and the review process

CMR International Institute for Regulatory Science

Assessing Regulatory Policy and Performance

Regulatory Science	Global Drug Development	Regulatory Processes	Patient Access to Medicines






2006 Agenda

New Technologies and Biomarkers	Asia's Role in Global Drug Development	Quality of Decision-making in Product Development and Review	Impact of Regulation on Access to Medicines in Emerging Markets

Past and future topics

Pharmacogenetics and pharmacogenomics Risk management: regulatory strategies and communication A new model for benefit-risk assessment	Integrated parallel development for the global market Declining submission rates for new medicines Acceptance of foreign data and implementation of the ICH E5 guideline	Performance metrics for regulatory processes Critical success factors in regulatory performance Building quality into regulation Post-approval commitments and conditional authorisations	The changing regulatory environment in the emerging markets Early patient access to medicines of therapeutic significance Initiating clinical trials in non-ICH environments

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