

Building quality into regulatory dossiers and the review process:

‘Knowing and meeting customer expectations’

**CMR INTERNATIONAL INSTITUTE WORKSHOP
2-3 December 2004, Woodlands Park Hotel
Cobham, Surrey, UK**

WORKSHOP REPORT

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Institute for Regulatory Science

BUILDING QUALITY INTO REGULATORY DOSSIERS AND THE REVIEW PROCESS: *'Knowing and meeting customer expectations'*

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WORKSHOP REPORT

Margaret Cone and Stuart Walker

SECTION 1: OVERVIEW

This was the fourth Workshop organised in 2004 by the Institute for Regulatory Science and rounded-off earlier discussions with an in-depth look at 'Quality' as it applies to compiling a regulatory submission and carrying out regulatory reviews.

At the Institute Workshops in May 2004 (global drug development)¹ and October 2004 (benchmarking the regulatory review process)², many references were made to the relationship between the quality of regulatory dossiers and successful review outcomes. This Workshop developed the subject further.

Built-in Quality

The Syndicate discussions, that are a regular feature of Institute Workshops, looked at proposals for studying the ways of building quality assurance into agencies' and companies' procedures. In the case of the regulatory agencies, the Syndicates made recommendations on proposals for a specific study on the current status and implementation of quality measures. For companies, the Syndicates made preliminary recommendations on the key elements for defining a 'quality' dossier and for monitoring the quality of submissions both during preparation and retrospectively.

Scorecard proposals

The *Benchmarking* workshop, October 2004, had arrived at specific recommendations for a 'Scorecard' system to facilitate feedback, at the end of a review, on the quality of the dossier and the way in which the review had been conducted. These proposals were developed further in the workshop on Quality with a proposal for a pilot study that will be considered by the Institute's Advisory Board, for inclusion in the work plan for 2005/2006.

Under this pilot study, two report forms would be drawn up and tested by participating authorities and companies:

Scorecard on the industry: for the reviewers to report their impressions of the quality of the dossier following the review of a new drug application;

Scorecard on the agency: for the company to report back on key aspects of the review process and their interaction with the authority during the review.

Synopsis of the Workshop Programme

The first two Sessions were chaired by **Thomas Lönngren**, EMEA Executive Director. Session 1 looked at 'Building quality into the application dossier' and **Dr David Lyons**, Irish Medicines Board, discussed his experience of the strengths and weaknesses of applications, contrasting 'avoidable' and the 'unavoidable' problems. Industry presentations by **Dr Paul Huckle**, GlaxoSmithKline, and **Dr Susan Forda**, Eli Lilly, looked at ways companies can implement quality management systems within regulatory affairs departments and the importance of analysing past experience in order to learn lessons from application history.

In Session 2 the focus was on 'Building quality into the regulatory review process'. **Dr Marijke Korteweg**, EMEA, described a major EU project to implement good regulatory review practices among accession states prior to the recent expansion of the EU. **Prof. Rolf Bass**, BfArM, Germany, then provided further experience from the twinning project between Germany and Poland. An industry viewpoint was provided by **Dr Ron Garutti**, Schering-Plough, who looked at companies' expectations for scientific integrity, communication, transparency and consistency in review processes.

Session 3, chaired by **Prof. Stuart Walker**, CMR International, looked towards future developments. **Dr Osamu Doi**, Senior Executive Director, PDMA, Japan, reported on the reforms and performance goals that are being implemented by the new Japanese agency. The regulatory implications of technological developments were discussed by **Dr David Jefferys**, UK Department of Health, especially against the background of the changing healthcare delivery environment. An industry vision for the future was presented by **Moira Daniels**, AstraZeneca, with a focus on earlier availability of new therapies to patients along with continual benefit- risk monitoring.

Finally, **Prof. Larry Phillips**, London School of Economics, gave a thought-provoking presentation on the philosophy, principles and practice of building quality into decision-making processes and how these apply in the pharmaceutical environment.

Workshop Report

This report is presented in three sections:

Section 1: Overview

Section 2: Outcome, summarising the main points and recommendations from the Syndicate discussions

Section 3: Meeting Summary, giving information on the individual presentations and the points in the discussion.

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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

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Workshop Organisation

Workshop organised by: Neil McAuslane, Margaret Cone and Stuart Walker, CMR International, Institute for Regulatory Science.

Report prepared by Margaret Cone

References:

1. CMR International Institute for Regulatory Science Workshop entitled '*Global Drug Development: Issues for the pharmaceutical industry and the regulatory authorities*', 26-27 May 2004, Tokyo, Japan
2. CMR International Institute for Regulatory Science Workshop entitled '*Beyond Benchmarking: What are the key performance metrics that agencies and companies should use to measure performance?*', 4-5 October 2004, Lansdowne Resort, Virginia, USA.

Full reports of the Workshops are available (to members of the Institute and regulatory agencies) via the Institute website: www.cmr.org/institute. R&D Briefings No 43 and 44 (open access) are also available on the Institute study, recommendations and presentations from the Global Drug Development Workshop.

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Workshop Report

SECTION 2: OUTCOME

Session 4 of the Workshop, during which the syndicate discussions took place, was chaired by **Professor Stuart Walker**, *President and Founder, CMR International*.

The Workshop participants formed three Syndicate groups to consider various aspects of the ways in which quality could be built into the regulatory review and submission process and make recommendations in relation to measuring and monitoring quality. The Chairpersons and Rapporteurs for the three groups were:

Syndicate 1	<i>Chair:</i>	Dr Robert Peterson , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
	<i>Rapporteur:</i>	Peter Bonne Eriksen , <i>Senior Vice President, Global Regulatory Affairs, Novo Nordisk A/S, Denmark</i>
Syndicate 2	<i>Chair:</i>	Professor Gunnar Alvan , <i>Director General, Medical Products Agency, Sweden</i>
	<i>Rapporteur:</i>	Professor Bernd-Günter Schulz , <i>Head of Global Regulatory Affairs, Schering AG, Germany</i>
Syndicate 3	<i>Chair:</i>	Dr Simon Larkin , <i>Director, Drug Development - Europe, Kyowa Hakko UK</i>
	<i>Rapporteur:</i>	Dr Leonie Hunt , <i>Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia</i>

The following report describes the specific tasks assigned to the Syndicates and the recommendations and comments arising from the discussions.

1. QUANTIFYING QUALITY MEASURES IN THE REGULATORY SUBMISSION AND REVIEW PROCESS

1.1 Building quality into the assessment and review process: Survey of regulatory agencies (Syndicate 1)

Objective: To comment, especially in relation to priority and emphasis, on items covered in the draft questionnaire for a proposed CMR International Institute study of regulatory agencies, and make recommendations on ways of optimising the outcome.

Background

In preparation for the Workshop, the CMR International Institute had prepared proposals for a study of the way in which regulatory authorities are building quality measures into the review process. Key questions from the proposed questionnaire were presented to the Workshop by Andrea Mallia-Milanes, from the Maltese regulatory agency who is studying for an MSc, on this topic, at Cardiff University.

Ms Mallia-Milanes outlined the key questions to be addressed in the study:

- What is quality and what are the reasons for introducing quality measures?
- What quality measures are in place and what impact do they have?
- How do authorities review the effectiveness of quality measures?
- What is the level of communication with industry during the review process and how transparent is the process to the general public?
- What human, financial and IT resources are available to the authorities to review dossiers and how are assessors trained?
- What are the barriers and new developments in this field?

The data would be assessed to compare the quality measures in place and differences in practice and approach, and to look at new developments in the field. It is hoped that the outcome of the survey, with anonymised data, will be used to promote further dialogue and discussion leading to the adoption of best practices.

Copies of the draft questionnaire were made available to Workshop participants and a summary of the main sections is given in *Box 1*.

Recommendation

The Workshop agreed that the study would provide a valuable resource in future discussions of quality measures and good review practices to be adopted by regulatory authorities. To achieve this goal, however, it is important that the questionnaire is completed at a sufficiently senior level within the agency

Box 1

Comments on the proposed Survey

- **Participation:** Although, for practical reasons, it may be necessary to limit the number of agencies participating in the survey, it was felt that, with respect to participation in the enlarged EU, all agencies should have the opportunity to see the questionnaire and be aware of the study that was being undertaken.
- **Scope:** The definition of the scope of the survey should be defined further as some of the questions need to differentiate between the procedures for new molecular entities, line extensions and generics.
- **Areas of greater focus:** It was suggested that the outcome of the survey would be strengthened if there were greater focus on:
 - *Decision-making:* The survey should look at the decision-making processes adopted by regulatory agencies, both the procedures and the philosophy of the elements that are taken into account.
 - *Scientific advice:* Any procedures for monitoring the quality of scientific advice should be included in the study.
 - *Interaction between agencies:* Greater detail is needed in questions concerning joint/shared reviews – a simple ‘yes/no’ response is unlikely to be adequate.
- **External Reviewers:** The need for quality assurance to be extended to external reviewers should not be overlooked, particularly in relation to the selection of experts, and how they are managed and integrated into the process.
- **Information Technology:** It is important that information on resources and training should cover preparedness of staff for handling electronic applications and the use of electronic templates, which may be backed by interactive electronic software to assist decision-making.

Building quality into the assessment and review process: Outline of questionnaire for authorities

1. Organisation profile:

Purpose: To provide an understanding of the organisational profile of the regulatory authority in particular, the number and professional background of assessors working in the assessment and registration section of medicinal products for human use.

2. Building quality into the assessment and registration process

Objective: To allow comparisons of quality measures used among different regulatory authorities and will provide an insight on the priorities of each authority on quality issues. Items include:

- *Defining quality,*
- *Measures in use to achieve quality,*
- *Key milestones in the assessment and registration process,*
- *‘Good Review Practice’ systems;*
- *Effectiveness of quality measures;*

3. Training and continuing education

Objective: To gather information on the ongoing training and continuing education of assessors working within the authority, including those employed on a full-time basis and those contracted for specific assessments

4. Assessor Input

Purpose: To gather information on the level of contact that assessors have in the authority with industry representatives, both during the development and assessment process.

5. Transparency

Objective: To gather data on the availability of information on the performance of regulatory authorities to the general public

- **Low priority:** The focus of the questionnaire should be on processes and it was felt that it was less important to collect information on:
 - Organisation profiles: and
 - Funding.

Note: Since the discussions at the Workshop, a modified proposal has been agreed to take account of the comments. A pilot study will be carried out among twelve regulatory agencies: Australia, Canada, EU (6 Member States and the EMEA), Japan, Switzerland and the USA. The order of questions in the survey has been changed with the previous Section 2 (*Building quality into the assessment and registration process*) moved to Section 1 and the questions on the *Organisation profile* being simplified and given lower priority.

1.2 Building quality into regulatory submissions: Good practices for companies (Syndicate 1)

Objective: To identify the priority measures and controls that companies should have in place in order to build quality into procedures for compiling regulatory submissions and to make recommendations in relation to proposals for a company survey to study current practices.

Recommendations

The characteristics of a 'quality' dossier and some key procedures for assuring quality during the preparation of a dossier were identified by the Syndicate. Metrics for monitoring the outcome of the review process and relating this to the quality of the dossier were also discussed.

It was recommended that these should be developed as the basis for codifying 'best practices' for further discussion by pharmaceutical companies. Whilst they could also be used to design an Institute survey to establish the current status of quality measures being implemented in the industry, it was felt that this should be given a lower priority than the survey of regulatory authorities (1.1 above).

The following proposals should therefore be referred to the Institute's Regulations Advisory Board for discussion and advice on follow-up action. Reference should also be made to the related items in the presentation on *Quality systems for multinational submissions* by Dr Paul Huckle¹.

Elements of a quality dossier

Content

- The dossier contains all the critical information in the appropriate detail;
- The data is well summarised;
- The relevant data are mapped to the respective items in the label;
- Negative data is not obscured or hidden in any way;
- There is critical discussion of strengths and weaknesses in the supporting data.

Navigation

- The dossier must be navigable 'in both directions' i.e., cross references must be easy to find with the ability to return to the original place. (This applies primarily to the electronic version).

Insight

- The dossier should tell the 'story' of the application and engage the reviewer's interest in the research project with insight into:
 - The historical development of the label;
 - How the application has changed and for what reasons;
 - The key decision points in the development process.

¹ See Section 3 page 5

Key elements in the process for preparing dossiers

Built-in quality

- Building quality into the processes for preparing the documentation for the dossier must start early in the R&D process;
- Quality assurance must be an integral part of the process throughout the compilation of the dossier and cannot rely on quality checks 'bolted on' to the end of the process;
- Quality management systems should be implemented, for example based on 'ISO' principles, with appropriate criteria-based audits;
- There should be formalised steps and 'milestones' in the process with well-defined decision points and criteria for proceeding.

Pre-submission review

- Procedures should be in place for the entire application to be reviewed and critiqued both by internal and external experts;
- A thorough assessment of the strengths and limitations of the dossier should be made before taking a decision on whether the application is ready for filing.

Measuring quality retrospectively

On the assumption that there should be a direct relationship between the quality of an application and the speed and outcome of the review, companies can record certain markers from the history of recent reviews. This should help to 'quantify' the comparative quality of the companies' dossiers in order to learn from past experience:

Number of Review cycles

- Comparisons should primarily be made against the same regulatory process since definitions of a single review cycle may differ:
 - In the EU centralised procedure there are almost always two cycles in the review process since a consolidated list of questions is routinely issued and the 'clock' is stopped during the review of the application.

Number of questions

A log should be kept of all questions and queries received during the regulatory review in order to identify recurring 'signals' of weakness in the documentation, for example:

- 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 to be carried out?
- How many issues could be addressed by agreeing to label changes?

Label

- Whether there were differences between the labeling (product information, SmPC), as finally agreed and the proposal in the application;
- Whether the final label met expectations, in relation to the target market and patient population intended for the product.

Note: There is some potential overlap between the suggestions outlined here for companies, themselves, to measure quality based on the outcome of the review and the proposals (described in section 2 below) for a 'scorecard' system where the agency feeds back information on similar elements, following a review.

The systems are not, however, mutually exclusive and could provide a useful means of comparing the company and regulatory perceptions of the quality of a dossier.

Post-approval history as an indicator of quality

This is a longer-term undertaking involving retrospective and prospective studies that could, potentially, link the quality of the development and submission process to regulatory outcomes, by examining:

- The number of *restrictive* changes required by authorities during the lifetime of the product, for example additional warnings in the labeling;
- The number of successful applications to relax warning in the labeling where the company felt that these were not justified;
- The relationship between post-marketing problems and data in the dossier:
 - An examination of whether there were signals that were missed at the pre-submission stage.

Risk management: inclusion in future studies

If a decision is made to carry out a quality-related study of regulatory submissions this should look specifically at risk management plans, in particular:

- To track how they are being addressed in the application;
- To assess the impact on the outcome of the review;
- To monitor the impact of the new EU requirements (October 2005) for risk management plans to form part of the review process.

General comments

Building a reputation for quality

It was felt that it is in a company's interest to establish a reputation for submitting good quality applications that are easy to navigate, understand and review. Although agencies normally apply strict queuing rules for initiating reviews, once picked up for assessment the assessor is likely to give priority to an application that they know, from experience, will be easy to assess.

2. PROPOSALS FOR A 'SCORECARD' SYSTEM

Syndicates 2 and 3 are asked to look at proposals for a 'scorecard' system for collecting feedback from regulatory agencies and companies, following the review of a major new application. The objective was to identify metrics that could be used for the quality of the application dossier and the way in which both company and agency had fulfilled their obligations during the review process.

The initial 'scorecard' proposal, along with other recommendations relating to quality were made during the Syndicate group discussions at the CMR International Institute 'Beyond Benchmarking' Workshop, held in the USA, 4-5 October 2004². A paper on these was provided as background to the Syndicate discussions and a presentation was made to the Workshop by Dr Neil McAuslane .

In the interests of clarity, the following report amalgamates the recommendations from the current Workshop and those from the October 2004 Workshop into a single proposal for a scorecard system.

Recommendation

The Workshop recommended that the CMR International Institute for Regulatory Science should consider, as part of its future work plan, undertaking a pilot study on the feasibility of introducing a 'Scorecard' system to collect feedback from companies and regulatory agencies, as part of the review procedure. The objective would be to monitor and improve:

- The quality of the regulatory dossier (Scorecard on the Industry)
- The quality of the regulatory review process (Scorecard on the Agency)

Draft proposals for the two scorecards are given on the next page.

² CMR International Institute for Regulatory Science Workshop entitled '*Beyond Benchmarking: What are the key performance metrics that agencies and companies should use to measure performance?*', 4-5 October 2004, Lansdowne Resort, Virginia, USA, full report available (to members of the Institute and regulatory agencies) via the Institute website: www.cmr.org/institute

SCORECARD ON THE INDUSTRY

<i>Item</i>	<i>Purpose and notes on the questionnaire</i>
Application format	<p>The presentation and construction of the dossier, especially in electronic format:</p> <ul style="list-style-type: none"> • Whether the required format was followed completely/partially/insufficiently • Whether the data were complete or deficient • Whether missing items were absent from the dossier or buried in the data
Summaries/Overviews	<p>Whether the reviewer feels that the company drew out and addressed the important issues, placing emphasis on the more critical areas.</p> <p>Overall rating (from above average to poor) for the summary/overview for each section (CMC, nonclinical and clinical) in the submission.</p> <p>The following to be rated 'fully' 'partially' or 'not at all'</p> <ul style="list-style-type: none"> • Accuracy: Whether the overviews reflect the supporting data • Relevance: The extent to which they addressed the major issues and highlighted them to assist the review • Links to other parts of the dossier <p>Safety issues:</p> <ul style="list-style-type: none"> • Whether appropriate analyses were performed to identify safety signals (yes/no) • Whether an appropriate risk/management plan was proposed in the case of safety signals being detected (yes/no)
Use of Scientific advice	<p>Whether the applicant had followed the scientific advice provided and integrated this into the development programme, study design and endpoints, GCP issues and analysis of results (yes/no).</p> <ul style="list-style-type: none"> • If advice was ignored, a rating of the justification for not following the guidance (satisfactory/unsatisfactory)
Technical content	<p>The extent to which the supporting data for each section of the application supported the proposed label (rated 'fully', 'partially' and 'insufficiently') for each section of the application</p> <ul style="list-style-type: none"> • Whether technical guidelines were followed and, if not, whether the justification was acceptable, not acceptable or missing
Response to questions	<p>The way in which the company responded to issues raised during the review and the speed with which they provided additional data to the reviewer:</p> <ul style="list-style-type: none"> • For each of the three sections the percentage of questions answered fully, partially or inadequately • The time taken to respond
Communication	<p>The extent and value of the communication between the two parties throughout the review and whether those involved understood, and provided, what was needed:</p> <p>Ratings on whether interactions were open and pleasant/ guarded/ unacceptable</p>
Performance at hearings	<p>Feedback on the performance of the applicant in terms of presentations to Advisory Committees, oral presentations or hearings, as part of the review process and how well the representations had addressed the issues and put forward the case:</p> <ul style="list-style-type: none"> • Overall rating: from above average to below average • Issues addressed: rating from fully to not at all • Outcome: Whether this was changed by the hearing (completely/partially/not at all)
Procedural operation	<p>Measures of how well the review procedures had been followed and operated, from the regulators perspective</p>

<i>Item</i>	<i>Purpose and notes on the questionnaire</i>
Labeling issues	Whether the agreed labeling/Summary of Product Characteristics, as submitted, was fully agreed/accepted with minor changes/subject to major changes <ul style="list-style-type: none"> • Rating given for the key sections of the label: Indications, Contraindications, Special precautions/warnings, presentation of adverse events
Overall assessment	Free text identifying three critical factors that led to the outcome of the review

SCORECARD ON THE AGENCY

<i>Item</i>	<i>Purpose and notes on the questionnaire</i>
Scientific Advice	Ratings on the extent of interaction between the agency that the applicant throughout the development process and degree of satisfaction in relation to: <ul style="list-style-type: none"> • The way in which advice was given • How appropriate it appeared to be • How amenable to being built into a development programme that could actually be conducted and delivered.
Communication	A rating of applicant's view of how appropriate the agency's communication and responsiveness was during the review process, including access to individuals in the agency
Consistency	A measure of how consistent the agency was in applying its own guidelines and procedures in the assessment of the dossier including: <ul style="list-style-type: none"> • Consistency in relation to previous advice given on similar issues or development programmes • Precedents set when reviewing similar products in the past • Comparison between previous experience different divisions of the agency (only applicable to larger agencies)
Professional/scientific competence	Whether the company felt that the individual agency had the appropriate knowledge and experience in relation to the therapeutic area under consideration (Rating with free text)
Procedures	Rating on the extent to which the agency had followed, rigorously, the procedures that they had laid down, when reviewing the particular application
Questions	Ratings on the usefulness and relevance of the questions asked during the process including: <ul style="list-style-type: none"> • Whether they were targeted on valid issues or were based on a misunderstanding or misinterpretation of the dossier • Whether any questions appeared entirely inappropriate and did not address a particular scientific deficiency in the data
Labeling	A rating of the key issues relating to the ultimate labeling decision and how it was reached including: <ul style="list-style-type: none"> • The extent that the decision was driven by science • The extent to which the decision-making process was, in the applicant's view, fair and open • Whether there was ample opportunity for discussion and negotiation between the applicant and the agency in order to decide optimal labelling • Whether the applicant put into a position of having to agree hurriedly on labelling to meet approaching timelines or cycle times
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 of the applicant and the conclusions of the agency

2.1 Scorecard on the Industry

Objectives:

- To help the sponsor understand the results of the review and to learn from the outcome in order to implement improvements for future dossiers.
- The questionnaire must be completed immediately at the end of the review by individual reviewers, relating to separate sections of the application;
- Completion of the scorecard should be coordinated by the review team leader in the agency

2.2 Scorecard on the Agency

Objectives:

- 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;
- To establish grounds for a longer-term dialogue
- To help empower regulators to commission improvements both locally and internationally.
- Results should be fed back to individuals involved in the review as well as managers at a senior level in the agency;
- In the longer term there may be a role for an overall analysis by an independent, respected third party.

2.3 General comments

Format

- The scorecards would need to be in the format of a brief questionnaire which should, ideally, be a maximum of two pages;
- They should be available as electronic documents supported by an interactive system to allow standard data to be entered and extracted easily, but with scope for additional free text comments;
- The core data should be common across regions, although regionally specific data would also need to be included.

Data

- The scoring systems should be designed to allow comparisons to be made within agencies and companies as well as between agencies and companies;
- Scores will necessarily be subjective but the system should be designed on the basis of 'best practice' for industry (see 1.2 above) and good review practice for regulatory agencies
- Whilst keeping the system simple, the data should be sufficiently detailed to allow specific areas to be analysed in depth.

Existing systems

Any pilot study undertaken by the Institute would need to take full account of existing procedures and other similar projects. This includes, in particular, the feedback on the quality of the dossier currently built into the EU centralised procedure and questionnaires being developed by EMEA/EFPIA.

Critical success factors

- A commitment to openness and honesty on the part of those filling in the scorecards;
- A commitment at a sufficiently senior level in the agency/company to both the timely completion of the scorecards and action in respect of the outcome.

The scorecard system cannot, and is not intended to, replace the need for a specific intervention during the review procedure should an acute problem arise.

2.4 Pilot Study

It was acknowledged that this is a long-term project and any initial study would only be on a pilot basis. It was suggested that the feasibility of the system could be tested by confining the questionnaire to one specific aspect of the submission and review process. In the case of the *Scorecard for Agencies* this could be the approval system, in order to allow a cross-agency comparison.

Should feedback be private or public?

An issue that needs to be resolved before undertaking the pilot project is the impact of *Freedom of Information* legislation on the willingness of the parties, particularly regulatory agencies, to participate in the study.

There needs to be further discussion on the merits, or otherwise, of the outcome of the scorecard system being available in the public domain, since this might be unavoidable under FOI procedures. There was discussion of whether this would inhibit the frankness and openness of those providing feedback or would be useful in the interests of reassuring the public about the transparency of the system.

3. Definitions of 'Quality'

All three Syndicates were asked to discuss, briefly, whether it was possible to draw up a definition of 'quality' as applied to regulatory submissions and the regulatory review. There was general agreement that the time and effort needed to agree a single definition was unlikely to be justified.

The key elements for a quality submission, were, however, identified in relation to 'Good practices for companies' (1.2 above) and a similar approach was suggested for defining quality in relation to the regulatory review:

Key elements for quality reviews

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 both within the different sections of the application and between applications for similar products.

Assessors that are

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

Resulting 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.



BUILDING QUALITY INTO REGULATORY DOSSIERS AND THE REVIEW PROCESS: 'Knowing and meeting customer expectation'

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SECTION 3: SUMMARY REPORT OF THE WORKSHOP PRESENTATIONS

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CHAIRMAN'S INTRODUCTION

Thomas Lönngren

Executive Director, European Medicines Agency (EMA)

In his opening remarks Thomas Lönngren drew a parallel between processes for preparing and reviewing regulatory applications and processes in other sectors of industry and public services that require quality management systems. The parameters that determine quality are similar, he suggested, starting with legislation, the implementation of the legislation and, at a more detailed level, the adoption of guidelines.

In the pharmaceutical sector, both regulators and industry work under the same framework of legislation and guidelines but the critical factor is the quality of the procedures that are set up in order to produce the application file and for the assessment of those files. Quality, in this respect, depends upon the level of scientific competence of all those involved and the level of resources, both human and financial, that can be committed to the processes. Mr Lönngren felt, however, that there was too great a preoccupation with timelines and the speed of the regulatory review process and he questioned whether this was such a critical issue when measuring quality.

The goal of management, in the regulatory agencies, is to meet the obligations placed on them by government and to meet the expectations of stakeholder, 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. At the EMA, he said, there had been a traditional model that separated operational management from quality management but they had now adopted a model of integrated quality management which brought together the rules for management and the rules for the quality system in the organisation. The next stage is to build risk management into the system.

Mr Lönngren hoped that the two days of the Workshop would provide an opportunity for high-level discussions on the kind of management systems that need to be in place and the rules that should be implemented in order to ensure a quality endpoint, whether the endpoint is an application dossier or a regulatory review.

STRENGTHS AND WEAKNESSES IN TODAY'S APPLICATION DATA

Dr David Lyons

Senior Medical Officer, Irish Medicines Board³

Dr David Lyons welcomed the topic he had been asked to address of improving the quality of regulatory submissions as he currently spends at least 80% of his time reading dossiers. Whilst it would be easy to launch into a stream of complaints about the negative aspects of the documentation, he acknowledged that the general quality of most submissions is good. In his presentation he gave examples of 'avoidable' errors in presenting data, the lessons that can be learnt from orphan medicines and other applications and problems that can be classified as 'unavoidable' because of the nature of the molecule that has been developed.

The Avoidable

Inaccurate claims

Dr Lyons first gave an example of a lack of accuracy of claims in relation to the data. He referred to an application for a Cox 2 inhibitor antiinflammatory where the draft product literature made the claim that the rate of perforations, ulcers or bleeds (PUBS) in patients treated with the drug was 'similar to placebo'. However, although data from double endoscopy studies showed that both

³ The presentation represents the personal views of the presenter

April 2005

placebo and Coxib were impressively better than the reference nonselective nonsteroidal antiinflammatory (naproxen) with less than 10% showing gastro-duodenal abnormalities compared with 72% for naproxen. On closer examination the rate of abnormalities for Coxib (9.5%) was almost 50% worse than the 6.45% rate for placebo, and the description 'similar to placebo' with regard to gastric abnormalities is clearly inaccurate. Although not representative of clinical reality, the data from double endoscopy studies may have contributed to an over-optimistic expectation of the gastric safety of Coxibs and consequent disappointment on the part of physicians and patients

Obscuring data

The second example was one where raw data that was relevant to the interpretation provided in the study report was 'buried' in the supporting data. It related to a study of a new product in patients with moderate to severe chronic obstructive pulmonary disease (COPD) that were previously stabilised on existing treatments (bronchodilators, inhaled steroids or systemic treatment). The analysis that was presented showed the improvement from baseline in forced expiratory volume (FEV₁) with the new treatment when compared with placebo, but failed to reveal the 'buried' information about deterioration in patients' FEV₁ during a placebo-only run-in phase prior to baseline. In fact, only those on the highest dose of the new treatment actually returned to their baseline FEV₁ and so most of the patients were worse off during the six-month study than they were on the conventional treatment before the study. Although these data were available in the dossier they were located in an obscure index and not presented in the company's main analyses.

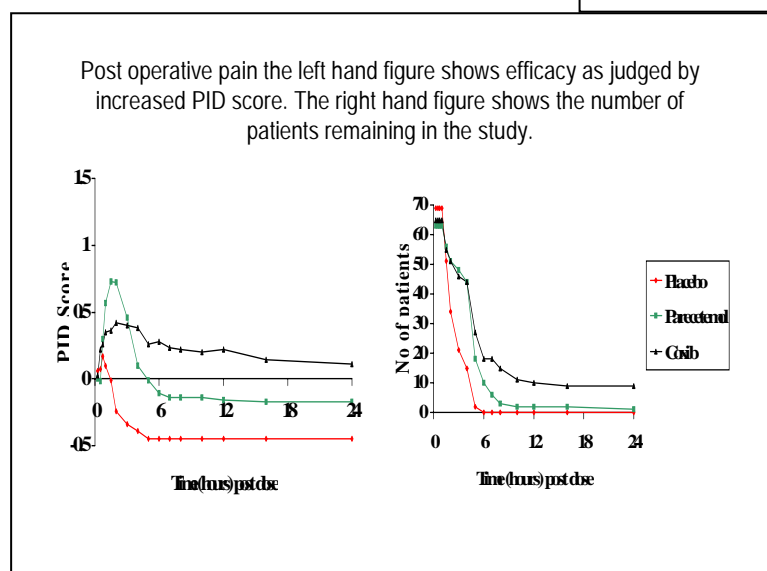
Lack of discussion

In his third example, Dr Lyons stressed the importance of acknowledging and discussing anomalies that occur in data. He showed data from a six-month study of COPD patients to illustrate that, in the normal course of the disease, the FEV can be expected to decline in patients on conventional treatment or placebo. In an application for a new treatment, however, data was presented in which the patients' FEV increased over six months, on both treatment and placebo. No comment of possible explanation was offered for this reverse in the normal biological trend, and Dr Lyons pointed out the negative impression that is left by such a lack of discussion of an obvious scientific anomaly.

Poor study design

The next example was a study of a new analgesic in post-operative pain (Figure 1). The graph on the left hand side was the one presented in the dossier to illustrate that the pain relief obtained over 24 hours with the test medication, although initially less than paracetamol was more sustained and significantly superior to placebo. A closer study of the data revealed, however, that this presentation of the results had not taken account of the number of patients remaining in the study over the 24-hour period. The study design was such that any patient asking for supplementary pain relief was automatically excluded from the study. The right-hand graph shows the by 4-5 hours no patients remain in the placebo group but this is not reflected in the way in which the efficacy data is presented. The difference in the area under the curve for the test drug and placebo is an 'illusion', Dr Lyons observed.

Figure 1



Orphan medicines

Dr Lyons discussed applications for orphan medicines in the context of the quality of dossiers since the medicines are scientifically interesting from a regulatory point of view. The special nature of the products, he suggested, means that they amplify some of the difficulties in making successful applications.

The failure rate for orphan drugs is currently approximately 37% which is higher than the average for non-orphan applications. Dr Lyons suggested that the failures could mainly be attributed to the drive to reach the required endpoint on a development plan that is, almost inevitably, sub-optimal because of small numbers of patients. Other factors are short studies with strange endpoints, patients admitted with major protocol violations and the involvement of small companies with limited resources.

Oncology drugs, however, pose particular problems. There is an understandable temptation on the part of the industry to file applications on the basis of Phase II non-controlled studies. If that path is taken it inevitably leads to the requirement to demonstrate 'outstanding anti-cancer activity' as described in the CPMP oncology guideline. Failure of such products, Dr Lyons suggested, reflects a regulatory issue rather than a scientific one. The guideline leaves it to the judgement of the authorities to determine what constitutes 'outstanding' activity and this can result in the very unwelcome situation of having to turn down applications for much-needed anti-cancer drugs which are clearly active, but not necessarily outstandingly so, because the criterion is not deemed to have been met.

Other potential pitfalls

Dr Lyons gave examples of other aspects of applications that can cause problems:

'Greedy' therapeutic indications: Where products are presented in therapeutic areas with a wide range of existing treatment options – for example the management of asthma, diabetes and organ transplantation – it is essential to test the product in the context of current medical management of each condition and in combination with existing established treatments for the relevant condition. The clinical development programme would probably need a combination of monotherapy and add-on studies. A clinical development for a candidate treatment which is based on 'first line' monotherapy studies is unlikely to displace an established treatment which may have been the cornerstone of the pharmacological management of a condition for decades; even if the supporting studies are sizable and well conducted. Faced with the situation where the grant of a marketing authorisation will potentially allow the wholesale replacement of a well established treatment for a common disease with a novel treatment regulators are likely to err on the side of caution.

Pharmacogenetics: Whilst the vision of 'personalised' medicines tailored to the genotype of the patient is probably many years away, the impact of genetic polymorphism is common and important as it can lead to unexpected responses – lack of efficacy or increased toxicity. Therefore, attention should always be paid to pharmacokinetics and pharmacogenetics in the early development of a medicine.

Presentation: Although use of the ICH Common Technical Document (CTD) format is now a requirement, Dr Lyons expressed the view that is not 'user friendly', with paragraphs and cross-references numbered to the fourth or fifth level. He asked those compiling applications to spare a thought for the reviewer and try to make the application as readable and navigable as possible, within the constraints of the CTD.

The (mainly) unavoidable

Dr Lyons presented some examples where good-quality applications had failed because the products were flawed and not through faults in the data or its presentation.

Antiviral agent

The first was an example of the impact of genetic polymorphism and related to an antiviral agent whose major metabolite, in certain patients, inhibited the metabolism of 5-fluorouracil leading to sustained increase in plasma levels. The drug was used for the treatment of herpes and shingles

infections in patients undergoing cancer chemotherapy and led to 18 deaths in Japanese patients being treated with 5FU.

The product had a valid place in the treatment of, for example HIV infection and organ transplantation but was withdrawn by the sponsor as the product did not meet the intended therapeutic target.

Antirheumatic

The second was an example of a high quality application with a good overall clinical development and excellent data presentation demonstrating a probable/possible new mechanism of anti-inflammatory action. It had foundered, however, because of differing views on the significance of proteinuria and potential nephrotoxicity. This was considered a common adverse effect of the molecule and not amenable to improvement or remedy on the part of the developing company

Treatment of Alzheimer's Disease

The third case study presented by Dr Lyons related to a new product for the treatment of Alzheimer's disease where the application failed due to a difficult risk/benefit problem and not as a result of development or presentational issues in the submission. The product was moderately effective but had potential for hepatotoxicity. The concern of the Irish Medicines Board was that enthusiasm for the product by patients and care workers might over-ride the need for caution in respect of toxic symptoms. The negative outcome was on the advice of a geriatrician and psychogeriatrician who advised that, in their opinion, the risk benefit was negative.

Conclusions

Dr Lyons concluded his presentation with some advice to sponsors:

- 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;
- Put accurate and factual data in the Summary of Product Characteristics (product labeling) preferably using numerical measures.

Finally, in the interests of improving the quality of review in the expanded EU, Dr Lyons encouraged companies to involve the new member states in the EU registration processes as soon as possible through visits and by nominations as Rapporteurs/Co-rapporteurs.

QUALITY MANAGEMENT IN A REGULATORY AFFAIRS DEPARTMENT

Dr Paul Huckle

Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline, UK

Dr Paul Huckle explained that he would be looking at the topic of building quality into the review process from initiation to the time of submission and would be considering, in particular:

- The practical considerations and details;
- The importance of engaging internal stakeholders in the process;
- Assessment techniques for testing the quality before submitting the dossier.

Initial report writing

A prerequisite of a quality submission is robust, good quality raw data from the clinical, pre-clinical and CMC (chemistry manufacturing and control) development programmes. This entails ensuring that the requirements of GCP, GMP and GLP have been met and that procedures are in place to ensure that data are transcribed accurately from the laboratory notebook and case report.

The question of authorship arises as the raw data is compiled into reports and summaries for the application and Dr Huckle referred to the on-going debate as to whether it is better for bench

scientists and clinical physicians to author and critique their own work or whether it is best to have scientific writers embedded in the regulatory or technical groups. This is the approach used by GSK. Drafts produced by the scientific writers then require review by the scientists responsible for the work and must be satisfied that it is an accurate technical representation of the work and conclusions.

Finally, each report needs senior management approval in terms of the way in which the submission is being compiled, its accuracy and its reflection

Compiling and publishing the dossier

Once the technical data is assembled a very robust procedure is needed to compile the dossier and ensure that it is complete when dispatched:

- Collation of study reports, summaries, references;
- Assembly of dossier components:
 - Implementation of the Common Technical Document (CTD) format entails many more subdivisions than previous formats;
- Validated production processes:
 - Robust procedures are needed to avoid incorrect versions and early drafts being incorporated into the final document
- Regional/national additions
 - For example, Certificates of a Pharmaceutical Product (CPPs) and GMP certificates for international markets.

Dr Huckle said that, when it comes to formatting the data for publishing, his organisation has specialists devoted to the work of developing document templates. Whilst 'not particularly exciting work' he emphasised the importance of presenting a good looking dossier that was clearly the product of a single development programme and did not give the impression of having been put together by 'a committee of scientists who never met'.

Although a significant number of dossiers are now written to CD many still need to be prepared as hard copy to meet the requirements of different agencies. The dispatch and safe delivery of the dossier, whatever media has been used is obviously critical and Dr Huckle noted, in particular, the logistical considerations when applying to a large number of member states, simultaneously, within the EU.

Internal stakeholders

In today's environment most companies operate development programmes projects using multifunctional project teams. In his company, Dr Huckle explained, this means that the regulatory affairs department is not only dealing with many different functions spread around the company, but also in different parts of the world. In a large company there is the 'luxury' of having not only scientists with a very deep knowledge of the specific project but also technical specialists with expertise that cuts across a number of dossiers. The challenge is to ensure that these expertises are built into multifunctional project and portfolio teams and for this the company has moved towards 'matrix' project teams to ensure that the review of the dossier includes a cross-cutting component in addition to the functional line or professional line view.

Other challenges in terms of putting together a good quality dossier in an international environment include:

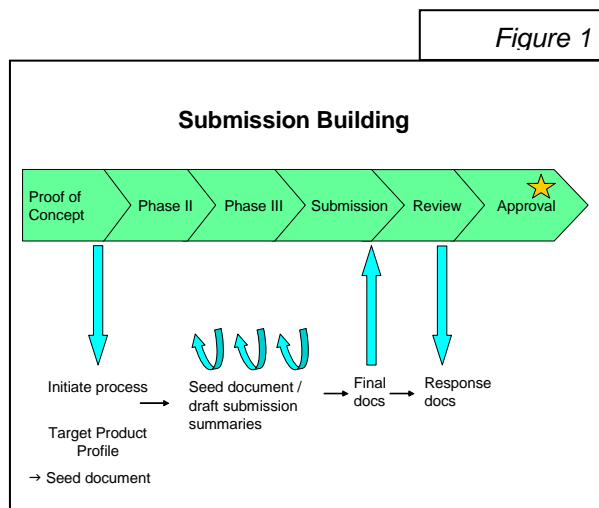
- *Geography*: It is not unknown to have the preclinical, clinical and quality aspects of the programme actually undertaken in separate and different regions;
- *Language*: This is not just a question of using the same language to compile the application but also to ensure that it makes sense in a linguistic way;
- *Time zones*: These can have both a positive and negative influence. There is the problem of having to wait for contacts in another time zone to be available to respond to queries but there are also advantages, using common publishing systems that allow 24 hr round-the-clock publishing to pull dossiers together more quickly.

Process

Dr Huckle suggested that the key to a successful process for compiling quality dossiers was to start early with drafting reports and summaries. This gives time to work on the texts and improve quality. A potential problem, however, is ensuring that the key messages remain consistent with the current target labelling. If drafting takes place over a long period it can happen, he suggested, that that people are still working on 'aspirational' labels when the data is actually pointing in a different direction.

Seed document

One of the techniques adopted to address this is the use of a so-called 'seed document' in which the key messages are recorded for the whole programme along with a log of how the programme has evolved. Dr Huckle explained that this document is created at the start of Phase II (see Figure 1) and maintained throughout the entire development process. The seed document also provides a useful tool for focusing senior management on the critical aspects when the time comes to review the dossier, internally, before submission for regulatory review.



Assessing quality prior to submission

Dr Huckle described the methodology that had been developed, in partnership with external organisations, to set objective criteria against which the quality of the dossier can be assessed before deciding that it is ready for submission to the authorities. Seven criteria have been identified relating to two aspects: The *quality* of the message (*criteria*: purpose, context, logic, content) and the *delivery* of the message (*criteria*: organisation, presentation, language).

Quality of message

Purpose:

- Does the documentation clearly state the purpose of the development programme that the sponsors are trying to deliver, in a way that the reviewer can understand?
- What must the product demonstrate in order to differentiate it from other drugs or treatments and position it in terms of the company target?

Context:

- Is there enough detail in the background to understand not just the issues identified in the dossier but how these have impacted on the product and development programme?
- Are there specific statements in relation to the disease, its treatment, therapeutic need, demographics and economic aspects that could aid the reviewer?
- Have appropriate connections been made between the elements of the development programme, e.g. in terms of cross-references, consistency of study designs, and evolution of understanding as the programme has evolved?

Logic

- Has a logical, coherent picture of the drug been presented in the dossier?
- Is there a clear statement of the purpose, objectives, measures, data, results, and conclusions with a logical flow throughout the scientific work?
- Do the conclusions interpret the results clearly and state the significance of individual pieces of work in relation to the rest of the programme?
- Do the discussions address not only the consistency of results but also any inconsistencies that may arise between studies?
- Are the conclusions still consistent when all the data are assembled?

Content:

- Does the content of the dossier address the regulatory agency expectations?
- Are the studies adequate both individually and making up the programme as a whole?
- Has compliance with GxP requirements been checked (GMP, GLP, GCP)?
- Is the size of the application correct in relation to the type of project (new chemical entity or minor line extension)? This will also reflect whether the level of detail is correct.

Delivery of message

Organisation:

- Is there a deductive layout? Each section should state, up front, what it contains and the conclusions that have been drawn from that piece of work;
- Is there a logical flow through the dossier? The data should be presented in a way that the reviewer will find natural, in terms of chronology.
- Has sufficient attention been paid to ease of navigation, headings, cross referencing, and numbering? Problems of cross-linking can best be addressed through use of electronic dossiers but much can be achieved through clear logical labelling of documents;
- Have summaries and tabulations been used appropriately with information removed from the body of the application to appendices, when suitable.

Presentation:

- Is the document appropriately displayed, with such basic considerations as appropriate size fonts, layout, readability and clear visuals and graphs?
- Have tables been used rather than text where this enables data to be presented more succinctly and with greater clarity?
- Is the emphasis correct so that the critical parts of the dossier are drawn quickly to the attention of the reviewer?

Language:

- Has the use of vocabulary and sentence construction been monitored to ensure that the documentation has a clear meaning, without ambiguity?
- Have standard conventions for punctuation and grammar been used?

'Sentence construction is often a challenge for highly paid scientists who create sentences that look like paragraphs and paragraphs that look like chapters'.

Independent review of dossier quality

Dr Huckle explained how the seven criteria are used to rate the quality of documentation, either for the complete dossier or by different internal reviewers reading through separate sections. This allows comparisons to be made between dossiers produced by different therapeutic teams across the company. By using a third party organisation, it has also been possible, anonymously, to compare the quality ratings for GSK submissions against other companies' submissions.

Figure 2

Internal comparison of dossiers					Comparison with other companies		
	A	B	C	D		Company Average	Industry Average
Purpose	●	●	●	●	Purpose	●	●
Context	●	●	●	●	Context	●	●
Logic	●	●	●	●	Logic	●	●
Content	●	●	●	●	Content	●	●
Organisation	●	●	●	●	Organisation	●	●
Presentation	●	●	●	●	Presentation	●	●
Language	●	●	●	●	Language	●	●

A scoring system of 1 (poor) to 5 (excellent) is used to rate each criterion but, for the purpose of his presentation, Dr Huckle used a 'traffic light' representation of low (red), medium (yellow) and high (green) scores as shown in *Figure 2*

Looking 'horizontally' at the inter-company comparison on the left-hand side, this identifies strengths and weaknesses across the company. Viewed vertically the matrix identifies strengths and weaknesses among the different development teams. In the example, the dossier prepared by team B looks good, with a slight weakness in presentation whereas the scores for D are low across most criteria, signalling a poor quality dossier and a team that needs some attention.

Dr Huckle pointed out that this is not done as an 'interesting academic exercise'. Assessing the dossier before submission provides an opportunity to go back and improve the documentation before the application is filed.

Post-review Quality Assessment

In addition to the quality assessment that is carried out routinely, prior to submission, Dr Huckle spoke briefly about the re-assessment that can be made after the regulatory review. The questions asked during the review can be correlated with internal comments on the way in which the data was presented. Agencies can also be asked for feedback on the application and this is sometimes provided spontaneously – both positive and negative. The most significant agency feedback, however, is the outcome of the review procedure, as a measure of whether the objectives have been achieved in terms of the agreed label.

Perhaps the greatest value of the pre- and post- assessments, Dr Huckle suggested, has been that they provide constructive and objective feedback to the teams that are putting dossiers together. The ultimate goal is to drive continual improvement within the organisation by going back and carrying out re-assessments routinely rather than taking a 'snapshot' of quality at one period in time and not pursuing the matter further.



CRITICAL SELF-ASSESSMENT:

What companies can learn from analysing their own regulatory experience

Dr Susan Forda

Executive Director Regulatory Affairs, Europe, Eli Lilly & Co.

Dr Susan Forda addressed the subject of monitoring and assessing the quality of regulatory submissions from the perspective of learning lessons from practical experience and from an objective review of past successes and failures. In order to provide such an analysis she had examined the marketing authorisations that had been filed by Eli Lilly, through the EU centralised procedure between 1995 and 2003, and subsequently reached approval.

The data set

In that period there were marketing approval applications for eight new molecules:

- 5 new chemical entities (NCEs) - classified as 'Part B' substances under the EU centralised procedure;
- 3 biotech molecules - classified as 'Part A' substances

The degree of innovation was as follows:

- one first in class: by mechanism of action and indication;
- two first in class: by mechanism of action;
- three first in class: by indication;
- one not first in class – a 'follow-on' product.

Measures for assessing the submission and review process

In order to provide an objective review of the submission and authorisation process Dr Forda had looked at the following aspects, in relation to the eight applications:

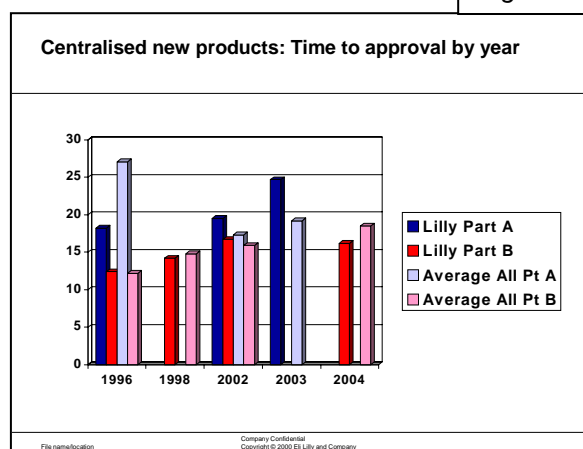
- Time to approval;
- Nature of submission (data package and whether it was simultaneous US/EU/Japan)
- Number of questions and major objections;
- Regulatory evaluation by the company, at time of filing
- Label language: how the Summary of Product Characteristics (SPC) is modified as a result of the review;
- Regulator feedback

Time to approval

Taking the average review time for products authorised in 2004 (up to September), Dr Forda had compared Eli Lilly's performance with other major multinational companies and found that the company had done well, being second in the 'league' with an average time of 16.2 months. The times for the other six companies studied ranged from 13.3 to 27.1 months and the average for all approvals in 2004 was 18.5 months.

Dr Forda had carried out a similar analysis of the company's approval times against the CPMP average, over the last nine years but, as shown in *Figure 1*, this had not shown any clear trends. As might be expected, the average time for Part A molecules was longer than for Part B products and the company had, generally, performed well against the average for the latter. For Part A molecules, however, the time to approval had increased over time, compared with the average.

Figure 1



Nature of submissions

Dr Forda had analysed the eight applications in the study in terms of different development and submission strategies in relation to approval times. With one exception, applications had been submitted almost simultaneously in the EU and US. The subsequent approval times were then very similar, except where a priority review had been agreed in the US, resulting in a much faster review time.

Comparisons between the EU/US review time and those for Japan could not be made since many of the submissions to Japan had lagged behind by several years and most had included additional studies or, in one case, been based on a separate Japanese development package. For the remainder of her presentation, therefore, Dr Forda had taken the Japanese review process out of the discussion.

Questions and major objections

The next correlation that Dr Forda had made was the number of questions and time to approval. Not unexpectedly, as shown in *Figure 2*, there was a direct relationship when the number of questions at day 120 of the EU centralised procedure was compared with approval times. However, Dr Forda reported the somewhat surprising fact that, as shown in *Figure 3* there was no similar correlation between approval times and the number of major issues that are still outstanding after the questions had been answered, at day 180 of the procedure.

Figure 2

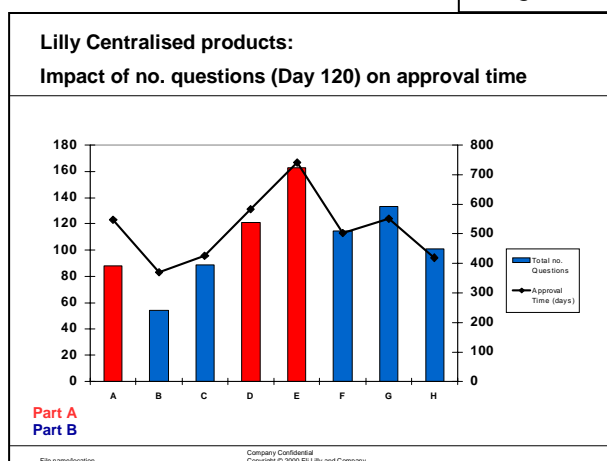
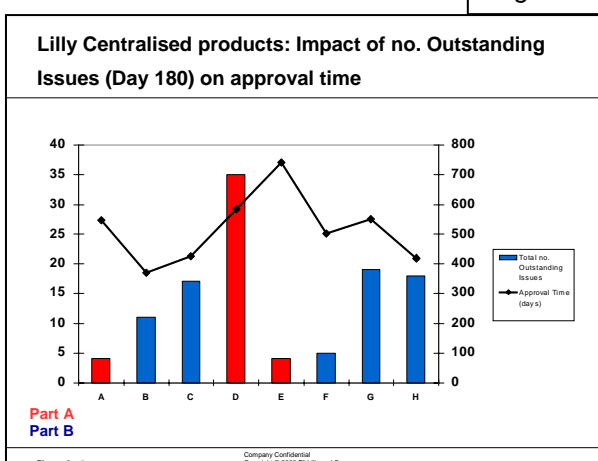


Figure 3



The company has a very rigorous way of monitoring CMC questions through a 'living manual' and Dr Forda commented that she had expected to show a steady decrease in the number of CMC questions, as a result of keeping this manual. However, when she had compared the number of questions at day 120 for compounds A through H (which also represented the sequence in time) this did not appear to be the case, and no consistent trend was discernable. When the number of questions on nonclinical data over time was studied there was, again, no clear downward trend and similar analyses for the clinical sections showed a noticeable increase in the number of questions, in recent years. Dr Forda, however, attributed this to a change in the attitude of the regulators rather than the company's failure to learn from previous experience.

Dr Forda had also studied the type of major objections, for each of the eight applications, at day 120 and day 180. As might be anticipated, there were considerably more issues raised on the nonclinical and clinical sections than the CMC section of the application. Nonetheless, she highlighted examples where there had not, apparently, been major CMC questions at day 120 but major CMC issues then appeared at day 180. The lesson to be learnt from this was the importance of understanding the terminology. Items grouped innocuously as 'other questions' in the list received at day 120 might not appear to be major issues, or the importance might not be fully understood, but they can reappear later as significant obstacles, if not addressed and resolved earlier.

Evaluation by the company

The major clinical objections to the eight applications had been analysed to determine whether they were 'predictable' on the basis of the company's own assessment of the data and in relation, for example, to scientific advice (see Table 1).

Dr Forda noted that for the majority the clinical objections were not the same when assessed by the FDA and EMEA. In only one of the four cases for which EU Scientific Advice had been sought was there a clear link between the advice and subsequent objections and there were four instances where the company's pre-submission assessment had 'anticipated' that problems might arise.

Lessons had been learnt from the types of clinical question, Dr Forda suggested, in that there was no repetition of specific questions from one product to the next but there was some evidence of 'themes'.

Table 1

Predictability of major objections				
Product	Shared by EU and FDA	Linked to EU Sci. Advice	Anticipated by company	Reflected in SPC
A	No	-	No	No
B	No	-	N/A	Yes
C	No	-	N/A	No
D	No	No	No	Yes
E	Somewhat	Yes	Yes	Yes
F	No	-	Yes	Yes
G	No	No	Yes	Yes
H	Slightly	No	Yes	No

For example, there had been

- No major clinical safety objections for acute-use products;
- Major clinical safety objections, relating to long-term, use raised for products for chronic indications;
- Major clinical efficacy objections, relating to efficacy in a sub-group of patients, raised in 4/8 cases.

Although such clinical objections were 'predicted' during development, none had precluded final approval of the product.

Impact on the label/SPC

As shown in *Table 1*, the SPC was affected following resolution of the clinical issues, in five out of the eight cases studied. The main changes were additional warnings and precautions or possibly a restriction on the indicated patient population.

Dr Forda also gave an example of a lesson Eli Lilly had learnt in terms of what may, and may not be expected in relation to the 'predictability' of the regulators attitude to labelling. The company has two products for the treatment of osteoporosis for which there is an EU guideline that recommends wording for indications to be included in the SPC: *'...is indicated for the treatment ...of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.'*

For the first of Eli Lilly's products they were asked to include an additional statement that 'An effect on extravertebral fractures has not been demonstrated'. When, two years later, they registered the second product, for which the effect *had* been shown they were not, however, allowed to include the phrase 'An effect on extravertebral fractures has been demonstrated'.

Regulator feedback

Dr Forda stressed the importance of obtaining feedback from regulators and noted that, for EU centralised applications, there is a page in the assessment report that provides a critique of the application. In addition, the company tries to obtain informal feedback on the quality of the application, which is sometimes forthcoming from the reviewers. Such comment is, however, invaluable to the process of self-improvement.

Not only is feedback on individual applications important but regulatory intelligence and communication with the agencies is also essential in times when, as seen recently in the EU, requirements and procedures have been in a state of constant change. Dr Forda cited an example of an application that had been seriously delayed by being caught up in a change of EU policy and guidance. Such eventualities make it hard to anticipate outcomes, timelines and labelling, which is a major goal of the internal evaluation of applications undertaken by the company.

Conclusions

There is no substitute for practical experience in all aspects of compiling a quality dossier, Dr Forda concluded, but this is particularly important for understanding procedures and managing the more 'bureaucratic' aspects of Commission decisions. In her own experience, however, the way that, for example, the FDA and EMEA have looked at data is subjective and learning lessons based on past experience can be misleading. Also, the review processes can be impacted by events in the external environment such as the concurrent review of a similar medicine.

She suggested that most issues that arise and cause difficulties are unique to the particular molecule and the process of 'learning from experience' is also slowed down by the fact that most companies do not bring too many medicines for the same indications to the market. The lessons from global development are that a single programme is rarely achieved and that compromises may be required to meet regional expectations.

Looking back at the eight cases under discussion, Dr Forda felt that one must ask the final question: Given that all the molecules were eventually approved, were there other ways that the outstanding issues could have been resolved at an earlier stage?

SESSION 1: POINTS FROM THE DISCUSSION

Pharmacogenetics: David Lyons was asked to clarify his position on pharmacogenetic testing. He replied that he believed that it was important to be realistic about the state of the science and its potential. Currently one cannot look at the way each individual metabolises a new medicine and nor are the required diagnostic agents available. On the other hand, there is much existing knowledge on well-known drugs that can, and should, be used to help understand the impact of different phenotypes on the efficacy and incidence of adverse effects for new medicines.

Quality of applications: Asked to give a 'global' rating of the quality of applications, Dr Lyons said that, of the 19 centralised procedure applications for which he had been *Rapporteur*, it was difficult to recall a really poor quality dossier. He suggested a global score of seven out of ten, with a range of 5-9.

Internal review: Asked if there was a danger that individual responsibility would be diluted by involving a large number of individuals in the company review, Paul Huckle acknowledged that there was a risk that potential problems would be left to be 'fixed' later as they would be picked up in the global review. It is important to have incentives for the development teams and GSK had found that the scoring system was a useful way of ensuring that standards do not slip.

In response to other questions on the internal review process he confirmed that:

- The results of the assessments are published on the company's internal website;
- The process has been applied primarily to new molecular entities and major clinical line extensions but there is no reason why it could not be used for all applications;

Risk benefit: Dr Huckle said that risk-benefit assessments are carried out throughout the whole development programme to ensure that they do not arrive at the end of the programme and find the project is 'fatally flawed' by some safety issue.

Scientific Advice: Asked whether some of the problems encountered during the review of applications could have been forestalled by better use of opportunities to obtain scientific advice, Susan Forda felt that, in most cases, the issues had been explored as thoroughly as the system allows. Advice had been sought before finalising the Phase III protocols when there was still opportunity for changes to be made.

EMA vs. FDA objections: Surprise was expressed at the lack of consistency between the concerns raised by EMA and FDA when presented with the same data. Some of the examples presented by Dr Forda had referred to procedures in the mid to late 1990s when there was less trans-Atlantic coordination and other factors might be procedural – the decision-making process and the fact that the US have a system of conditional approvals that is not (yet) possible in the EU.

EU/US Confidentiality agreement: Thomas Lönngren reported that, under the agreement signed between the FDA and EMA, there would be a benchmarking exercise to track and compare the decisions being made on similar applications.

'Anticipated' issues: Regulators were somewhat intrigued by the concept that companies identified potential problems in applications but still submitted the data for review Dr Forda suggested that it is extremely unlikely that an application for a 'first in class' medicine or novel mode of action would be reviewed without raising questions on the new science, however good the dossier. Dr Huckle added that the measure of concern to companies was the number of 'unanticipated' questions on sections of the dossier that were felt to be straightforward.

SESSION 2: CHAIRMAN'S INTRODUCTION

Thomas Lönngren

Executive Director, European Medicines Agency (EMA)

Opening the Session on quality of the regulatory review, Thomas Lönngren provided an update on activities at EMA to improve the centralised procedure. He referred to the 'Roadmap' that was launched in 2004¹ and the related discussions with all the stakeholders. 2005, he said, will be an important year because of the implementation of the revised pharmaceutical legislation and, in particular new procedures for fast track applications and for conditional approvals.

At the same time various actions will be undertaken to help improve the quality of the centralised procedure and these were also mentioned in the 'Roadmap'. There would be changes in the procedures for giving scientific advice focusing on providing more depth in the advice and covering broader aspects of lifecycle but also looking at quality assurance in relation to the advice that is given. Mr Lönngren reported that he was currently heading a group at the EMA, which included the Chairman of the Committee for Human Medicinal Products (CHMP) and members of the Scientific Advice Group in order to develop this. Discussions with stakeholders were scheduled for early in 2005.

Another development in the centralised procedure, related to quality assurance, is a proposal for a new type of *Rapporteur*, in recognition of the need to have a peer review and critical analysis of the *Rapporteur's* report. Marijke Korteweg would, he noted, cover other aspects of developing quality management systems in her presentation. Improving quality assurance throughout the EU network of regulatory agencies was a major undertaking in which all the links in the network need to participate.

Mr Lönngren also referred to the internal audits that had been initiated by the EMA. The functioning of the CHMP and other scientific committees are now audited regularly. He looked forward to the outcome of the Workshop discussions since to topics touch upon many of the issues currently under discussion for bringing about improvements in the centralised procedure.

WHAT COMPANIES EXPECT FROM REGULATORY AUTHORITIES

Dr Ronald J. Garutti

Group Vice President, Global Regulatory Affairs, Schering-Plough Research Institute, USA

A common mission

Before addressing the main theme of his presentation on industry expectations, Dr Ron Garutti looked at some of the factors that drive those expectations. He looked first at extracts from the mission statements of industry, as set out by global pharmaceutical companies and their trade associations (*Box 1*) and extracts from those of the major regulatory authorities (*Box 2*). He noted that, although there are obviously differences in overall mission of the commercially-based industry and the government regulators the underlying philosophy was the same in relation to improving the public health and ensuring access to safe, effective and innovative medicines.

Box 1

Pharmaceutical Industry: Mission

- Provide society with superior products and services by developing innovations and solutions that improve the quality of life and satisfy customer needs....
- Provide innovation and value in the provision of products and services to improve human health and quality of life.
- Provide innovative new medicines, improve human health and enhance people's lives.
- Provide innovative proprietary products and high-quality service. Focus on bettering health through improved healthcare.

Box 2

Health Authorities: Mission

EMEA:

- ... providing high quality evaluation of medicinal products, to advise on research and development programmes ...
- Developing efficient and transparent procedures to allow timely access by users to innovative medicines
- Controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network

FDA:

- Assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, ...
- ... speeding innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

PMDA:

- ..working expeditiously to improve the safety and efficacy of pharmaceuticals. . . .
- . . . employ the latest specialized knowledge and wisdom to provide consistent services ranging from guidance and advice

From mission statement of PDMA, Japan, Dr Garutti highlighted, in particular, the use of the word 'wisdom', in respect of the services provided by the agency. He noted the aptness dictionary definition of 'wisdom': *the accumulated knowledge and experience needed to make sensible decisions and judgments.*

Industry drivers

Dr Garutti discussed the factors, in today's environment, that influence companies' expectations. The success of the pharmaceutical industry is founded on innovation but the costs associated with that innovation are extremely high and continue to rise. Political and societal pressures mean that there is a constant demand for innovative new medicines but there is also a reluctance to pay a realistic price. At the same time, within the industry, there is intense competition and the race to be 'first to market' in a new class of medicines is an important driver of company strategy. There is also the necessity to differentiate new molecules from existing therapies and the constant pressure to find the 'blockbuster' drugs that 'will fuel the enormously expensive R&D engine'.

In order to expedite the development process, the phases of traditional development are being compressed or conducted in parallel. As a result, attrition rates are increasing with the high failure rates occurring not only in the early phases of development but also in late clinical phases. When a drug makes it through the convoluted development process, Dr Garutti said, it is a very precious commodity and companies are understandably looking to maximise its value. As a result, we are seeing more emphasis of life cycle management with applications for new indications and the development of new dosage forms in order to enhance the incremental benefit of the product and extend its 'life'.

Global dynamics

Notwithstanding the changes brought about by ICH and other harmonisation initiatives the global pharmaceutical industry has to navigate an increasingly complicated regulatory environment in order to satisfy the requirements of multiple health authorities. Dr Garutti referred to the EU clinical trials directive and the on-going differences over requirements for comparator products for clinical trials.

He also touched on the financial implication for the industry of parallel importing and counterfeiting and the impact of impending patent expiries that would lead to a revenue loss of some 112 billion dollars by 2008. In order to absorb or balance such losses against revenue, it has been calculated that over 100 NCEs will need to be approved by 2008 but, as Dr Garutti pointed out, the output of successful applications has recently fallen to an all-time low. Recent high-profile safety concerns over SSRI antidepressants and COX-2 antirheumatics had also diminished customer tolerance for risk and made the need to establish a clear benefit-risk profile a primary requisite.

Key Industry Expectations

Against this background of increasing pressure for innovation, cost containment and greater safety, coupled with increasing costs and more challenging requirements for clinical development, Dr Garutti stressed the need for a supportive regulatory environment. He enumerated the industry expectations under five headings:

- Science-based oversight
- Communication
- Timeliness
- Transparency
- Consistency

Science-Based Oversight

The pharmaceutical industry is science-based, Dr Garutti said, and there is therefore an expectation that regulatory decision-making will be based on sound science that is free from political expediency or partially informed public pressure. Scientific advances are occurring at the rapid speed and regulatory decision-making needs to be flexible enough to incorporate the application of new technologies. All stakeholders, including scientists from academia and investigators, should be brought into the debate on how to apply these new technologies to the development process

Science-Based Oversight

- Political pressure and public opinion should not take precedence over science.
- Adoption of innovation in regulatory decision-making is predicated on a strong scientific foundation.
- Scientific knowledge is evolving; regulatory processes should be adaptive to change.
- Scientific expertise resides in many sectors; consideration of those experts is crucial.

Communication

- Key component to achieve mission of 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 HA staff is the only way to guarantee continued innovation.

Communication

This is essential to any collaboration involving human beings and it is no less vital to the success of the regulatory process. The opportunities for companies to meet reviewers are greatly appreciated by companies, Dr Garutti stressed, and the agencies also benefit when the outcome is a better quality application and a greater likelihood of the first cycle approval. He expressed concern that there is a public misconception that 'partnership' between industry and regulatory agencies is unhealthy whereas, in fact, it works in favour of the public health by promoting a more efficient development process that helps to ensure that the innovative medicines reach patients more efficiently.

Timeliness

Dr Garutti reiterated the time-intensive and competitive nature of the industry and the importance of speed to market. A timely and predictable review is essential, not only as the endpoint of development but throughout the process. He gave the example of the importance of rapid feedback on trial protocols in order that companies can reserve their place on the ethics committee calendar and start the process of patient recruitment. Equally important is timely feedback, during development that alerts the sponsor to potential problems relating, for example, to labeling.

Timeliness

Pre-specified time frames for health authority advice are critical component for each stage of product development and life cycle management.

- Protocol review / advice
 - Ethics board approval; patient recruitment; study conduct
- Early alerts during dossier review
 - Minimizes multiple review cycles
- Labeling / trademark review
 - Approval; pricing; launch

Transparency

The efforts being made by all health authorities to improve transparency are welcomed and appreciated by the industry, Dr Garutti said. It is much easier to work within a system that is open and clearly explained. Of particular importance to industry are the opportunities to be involved in consultations on technical guidelines, new legislation and issues affecting regulatory policy. The establishment of open and transparent committee procedures and arrangements for hearings provide the opportunity to bring extra advisers and expertise to contribute to the debate.

Consistency

- Advice must be reliable and science-based not arbitrary.
- Best practices should apply across all sectors within health authority.
- Application of policies should not differ between:
 - Review teams
 - Therapeutic divisions
 - Centers
 - Health authorities

Consistency

Dr Garutti suggested that there was room for improvement in the area of consistency in the interpretation of scientific data and application of development guidelines. Greater consistency in the acceptance of global data at regional level was particularly important. He called for the application of best practices both within and between health authorities.

Transparency

- Written policies provide clarity on local requirements.
- Stakeholder involvement during policy development critical to successful implementation.
- Minimizes “hidden” agendas – academic curiosity vs. regulatory requirement.
- Allows for open expression of expectations.

Health Authority Initiatives

Dr Garutti concluded by highlighting some recent initiative from health authorities that had been welcomed by industry:

Japan: The establishment of PDMA bringing the systems for providing advice and reviewing applications under one administration, and including a transparent appeal system;

EU: The EMEA Roadmap 2010 with its promise of top quality scientific assessments and recognition that protection and promotion of the public health is compatible with encouraging and facilitating scientific innovation;

US: The FDA Critical Path initiativeⁱⁱ with its emphasis on utilising new scientific knowledge to improve the drug development process and its willingness to consider new biomarkers and surrogates and their integration into novel trial designs.

HARMONISING APPROACHES TO QUALITY ASSURANCE: *The European Experience*

Dr Marijke Korteweg

Integrated Quality Management Advisor Directorate, EMEA

Dr Marijke Korteweg contrasted the way in which the regulation of medicines operated in Europe compared to the systems in the USA and Japan. The EMEA, she said, is ‘virtual’ regulatory agency that works through a network connecting all the national agencies in the European Union and European Economic Area (EEA). Whether considering the centralised process, where the EMEA is at the hub, or the mutual recognition procedure, the same partners are involved in working together and in trying to build quality into their procedures, both pre- and post- authorisation.

With the expansion of the EU, in May 2004, there are currently 28 countries in the network – 25 EU Member States and three EEA countries, Norway, Iceland and Liechtenstein. Dr Korteweg likened each member of the network 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.

GRP and Benchmarking

The basis for ensuring the consistency and quality of the deliverables, said Dr Korteweg, is the implementation of Good Regulatory Practices (GRP). Within the EU the definition of GRP (which covers veterinary as well as human medicines) is as shown below.

A quality system to ensure that users of medicinal products, the applicants and the regulators are satisfied with the scientific advice, opinions, the establishment of Maximum Residue Levels, inspection and assessment reports and related documents, taking into consideration legal requirements and guidance in order to protect and promote human and animal health.

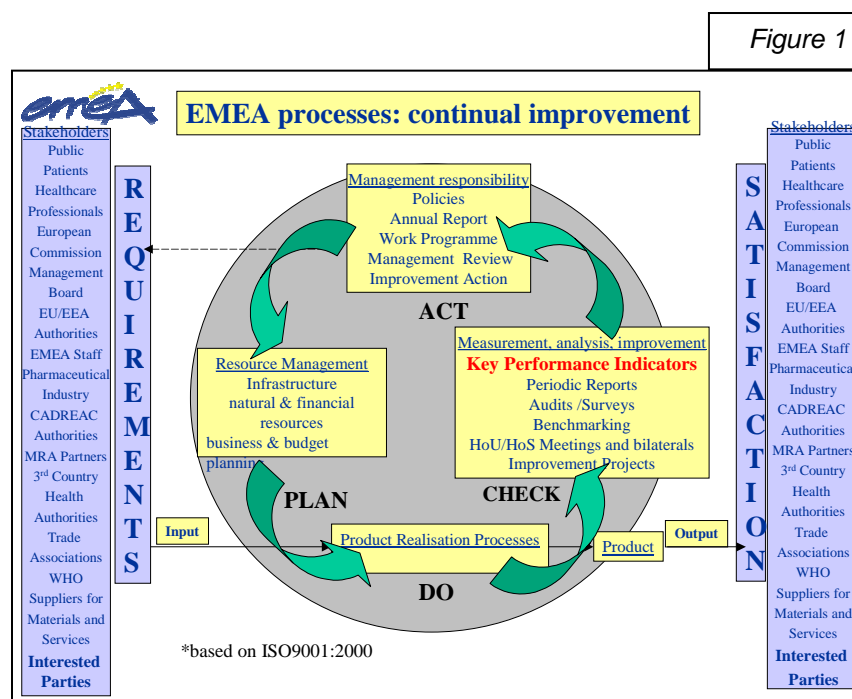
Building a medicines network in Europe, based on GRP, implies the need to address not only the core tasks foreseen in the regulatory framework but also to address management and logistics. This has led to the need for benchmarking to compare the way that different systems work and identify best practices that are cost effective, efficient and workable, within the assigned budgets.

Dr Korteweg stressed the difference between the benchmarking process and audits and inspections. Unlike the latter, benchmarking does not focus on non-compliance and non-conformities but tries to reveal strengths and innovative approaches. The EU benchmarking system was initiated to facilitate the accession of new EU member states and help them implement quality management systems (QMS) but, as Dr Korteweg explained later, has now been extended to all members.

Quality systems

Those who are familiar with quality management systems, said Dr Korteweg, will know that whatever model is followed (e.g., European Foundation for Quality Management – EFQM- or Baldrige National Quality Program – BNQP - in the US or the International Standards Organization - ISO) the objectives of continuous improvement are the same and the indicators used to measure and compare performance pertain to the same key elements and equivalent standards.

The EMEA has chosen to adopt and adapt the ISO 9001 model for its quality management system because it is an international 'language' that allows comparisons to be made not only within the EU but also with the FDA and Japanese authorities, although they follow different systems. This model (Figure 1) shows that there are regulatory requirements and stakeholders to be satisfied.



The stake holders, from sponsors to patients, may have different, and sometimes potentially conflicting, expectations of the agency but all share the common requirement that products must be evaluated in a quality way. In order to achieve this, Dr Korteweg stressed the need for the agency to have an *integrated* quality management system that looks at risk management, financial aspects, process enhancements, safety and quality.

The EMEA is not, of course alone in implementing such a system and Dr Korteweg quoted from the Gold Sheet Vol. 37 No 10 October 2003:

In conjunction with the international effort, domestically under the umbrella of its pharmaceutical quality initiative, FDA is striving to design an integrated, agency-wide, risk-based quality management system.

PERF Benchmarking Project

Dr Korteweg explained that the current benchmarking project for quality management systems has its origins in the Pan-European Regulatory Forum (PERF) that was established in 1999 to facilitate the transposition of EU technical regulations and laws into the legislation of the EU accession countries.

With respect to QMS, the EMEA wanted to measure the maturity level of the national systems and therefore recommended that each participating National Competent Authority should purchase ISO 9004:2000 in order to understand the questions in the questionnaire that was developed. This ISO standard contains a self-assessment questionnaire that is closely similar to those of the EFQM and BNQP systems, and addresses the same principles. The authorities were also advised to procure the ISO 19011:2001 Guidelines for quality and/or environmental management systems auditing as guidance for the benchmarking exercise. The methodology for auditing and benchmarking are essentially the same, Dr Korteweg noted, although the objectives are different.

In the third phase of PERF the participating agencies were given a 'reference' questionnaire based on ISO 9004:2000 to assess the organisation's overall management system and interfaces with operational areas, such as assessment, post marketing surveillance, inspections, control laboratories and ministries of health. This was designated the 'mother' questionnaire and Dr Korteweg explained that, in January 2003, two tailor-made 'offspring' self-assessment questionnaires were agreed on the specific activities of application assessment and post-marketing surveillance.

Following completion of the questionnaires there were benchmarking visits to the agencies by teams composed of EU national agencies, accession countries and EMEA. Seventeen agencies in central Europe were visited to assess the maturity level of their management systems.

Extension to EU Benchmarking

The PERF project was considered so successful that the European Commission decided that it should be continued in the future and extended to the 28 EU/EEA countries and the 42 agencies in those countries that regulate medicines (both human and veterinary). Moreover, in revising and updating the review questionnaire, account was taken of the recommendations of the G10 Lisbon meetingⁱⁱⁱ to support a stronger European-based pharmaceutical industry, for the benefit of the patient.

The European Commission has designated the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the German Paul-Ehrlich Institut (PEI) to take the lead for the EU Benchmarking project for human medicines, whilst the Irish Medicines Board was assigned the project for veterinary medicines. The decision has since been made, however, that it is more efficient and cost effective to merge the two systems. There will, therefore, be a single self-assessment questionnaire, Dr Korteweg explained, but different examples will be used to illustrate the way in which the questions should be addressed.

Objective

The aim of the EU benchmarking system is to contribute to the development of the world-class regulatory system for medicinal products based on the network of agencies operating the best practice standards

The current situation is that a Steering Committee consisting of delegates from MHRA, PEI, BfArM, the Italian, Finish and Czech Medicines Agencies, as well as EMEA, have developed a questionnaire. This is based on the series of PERF III questionnaires ('mother and offspring') and the G10 key performance indicators, and applies to Agencies involved in medicines for human use. Similarly, Ireland together with Hungary and the EMEA has started tailoring the questionnaire for use by Agencies concerned with medicinal products for veterinary use.

On the 4 and 25 October 2004, fifty-three assessors from 23 countries were trained to use the single self assessment questionnaire that goes from the top layer of managerial questions down to the operational 'layers'. Again, Dr Korteweg stressed that the training that this provides for assessors, in methodology and interpretation of the questions, is as important as the criteria addressed in those questions.

Figure 2

Extract from ISO 9004		
A.2 Performance maturity levels		
The performance maturity levels used in this self-assessment approach are shown in Table A.1		
Table A.1- Performance maturity levels		
Maturity level	Performance level	Guidance
1	No formal approach	No systematic approach evident, no results, poor results or unpredictable results
2	Reactive approach	Problem- or corrective-based systematic approach, minimum data on improvement results available
3	Stable formal system approach	Systematic, process-based approach, early stage of systematic improvements, data available on conformance to objectives and existence of improvement trends
4	Continual improvement emphasized	Improvement process in use, good results and sustained improvement trends
5	Best-in-class performance	Strongly integrated improvement process, best-in-class benchmarked results demonstrated

Rating system

Dr Korteweg explained that the rating system used for 'performance maturity levels' would be the same as those set out in ISO 9004 (Figure 2). This is also the same as the system used to rate agencies in 2003, under the PERF benchmarking project and allows comparisons to be made with results from future visits of the 'peer review teams'.

She provided examples of the type of key performance indicator (KPI) that are included in the questionnaire and noted that each KPI has one or more specific/sub-performance indicator (SPI) to strengthen the value of the KPI. The performance indicators are constantly reviewed and updated since, Dr Korteweg stressed, the benchmarking system itself, like the systems it measures, is subject to continual improvement.

Example of a Key performance indicator

KP1 Objectives or targets are set for the different processes of the organisation, and they are reported publicly

[This is followed by a number of examples, e.g., publication of work programme and activity reports on the website.]

SP1 Top management demonstrates its leadership, commitment and involvement to the delivery of objectives

[Examples]

SP2 Management ensures the use of systematic and documented methods to assess the organisation's performance, and puts in place any necessary improvement measures

Examples

Use of quantitative data to establish performance targets, and monitor and improve targets;

Performed audits, Quality Management reviews KPIs and SPIs are first tools

Internal audit system assures management that the system is working effectively or provides opportunities for improvement.

A further example from the operational level of the questionnaire was:

KP6 The full range of high level, internationally recognised, regulatory and scientific expertise to fulfil the chosen regulatory functions is available within the organisation and from appropriate external sources

Dr Korteweg explained that this KPI had been formulated in this way because the EU partnership includes smaller countries that may not have the full range of scientific expertise and they may choose to specialise in a specific area. The expectation is that, for that scientific area, the full range of regulatory functions will be available to do the job well.

Summary and conclusions

In today's environment, Dr Korteweg said, with the heavy workload on agencies it is not possible to carry out quality 'control', in terms of repeating assessments and therefore systems need to be built to ensure that quality is built into the assessment process. This is the objective of the benchmarking project.

Training is an essential part of the process but the training seminars arranged for participants are, in themselves, part of the learning process for all involved and contribute to the process of continuous improvement. The benchmarking methodology and the capability to translate questions for use in the assessed environment are crucial for the success of the undertaking, but, equally, if there is a difference in interpretation and rating of these questions 'you end up with apples and pears and cannot compare anything' Dr Korteweg commented.

Summarising, Dr Korteweg emphasised the importance of an integrated management system from managerial to operational level. This leads to continual improvement of the processes needed for the regulatory tasks by analysing the related risks and determining the relevant performance indicators. The ultimate result is greater efficiency, effectiveness, and consistency of output. Thus integrated (quality) management also plays a vital role in medicinal product development

PERSPECTIVES FROM WITHIN THE EU: Germany and Poland

Professor Rolf Bass

Head of Division, EU and International Business, BfArM, Germany

In his presentation, Professor Rolf Bass provided observations based on his experience of the regulatory procedures and practices in both Germany, a founder member of the EU, and Poland, one of the Central and Eastern European countries (CEEs) that joined the EU in May 2004. As part of the process for assisting countries to prepare for accession, several 'twinning' projects had been undertaken between established and prospective EU members. Professor Bass had been the special adviser for the twinning programme between Germany and Poland.

Awareness of the need for quality

The fact that the quality of regulatory processes is a subject for discussion at all is a major step forward, Professor Bass suggested. Until recently 'quality' was a subject discussed only in the context of the quality control of products but it is now accepted that the regulatory world has become so complex that it must, itself, be the subject of quality assurance procedures. It is also accepted that there is concern among the public at large about the lack of transparency of regulatory procedures and a feeling that the information disseminated may be biased and incomplete. These issues need to be addressed and Professor Bass welcomed the EMEA initiatives to promote and harmonise the implementation of quality management systems (QMS) not only among the accession countries but also throughout the expanded EU.

He, however, cautioned against becoming so pre-occupied with the implementation of transparent and good quality procedures throughout the network that the quality of the science is overlooked. Science is heavily involved in the regulatory process and there is also a need for

quality management of that science. There had, indeed, been notable recent examples where problems had arisen that could be attributed to science rather than procedures. Professor Bass stressed the importance of learning from successes in other regulated areas and suggested that good manufacturing practice was an example where good quality science as well as procedures had come together effectively.

Spectrum of quality assurance

Professor Bass noted that Germany and Poland run regulatory agencies with a similar spectrum of activities in that they cover both medicinal products and medical devices. The ways that the control systems operate in the two countries are similar but not identical and when looking at quality many different areas need to be considered:

- Input: the dossiers submitted
- Structures and responsibilities
- Interlinking, Co-operation and networking
- Administrative/regulatory procedures
- Scientific assessment
- Use of Advisory Committees
- Decision pathways/bodies
- Scientific/regulatory reporting
- Peer review and appeal opportunities
- Decisions and reasoning

The quality of the regulatory review process is often judged solely by looking at the end point, he suggested, and this might not give a true picture of the quality of the whole process.

The dossier

Professor Bass referred to comments earlier in the Workshop that the standard of regulatory submissions was generally good^{iv} and he agreed with this opinion. The old adage of 'garbage in garbage out' applies to applications and a good quality regulatory assessment cannot be expected from a bad quality submission that is poorly constructed with scientific information missing or hidden. He questioned, however, whether the converse could be guaranteed; whether a good quality application ('no garbage in') would necessarily mean a good quality review and felt that there is currently no answer to this, without further study.

Structures and responsibilities

The ease with which quality can be built into the regulatory process through quality management systems depends, to a large extent, on the complexity of the administrative structures that are already in place. Professor Bass compared the structures and responsibilities in Germany and Poland (*Box 1*).

Germany is a federation of 16 Länder (provinces) and the responsibility for the regulation of medicinal products and devices falls within both the Federal and decentralised sectors:

Legislation: Federal Ministry of Health

Marketing Authorisations: Higher federal authorities (BfArM, PEI, BVL) within the portfolio of the relevant Federal Ministries

EU Context: Implementation of legislation and contribution to the EU marketing authorisation systems at both Federal and Länder level (inspections)

Inspections: Federal and Länder authorities

Box 1

Structures and Responsibilities: Germany

- Marketing Authorisation: BfArM, PEI, BVL
- GMP: Länder (coordinated by ZLG), PEI, BfArM
- GLP: Federal GLP Coordination, "Länder"
- Environment: Federal Environment Protection Agency, BfArM, PEI, BVL
- GCP: BfArM, PEI, "Länder"

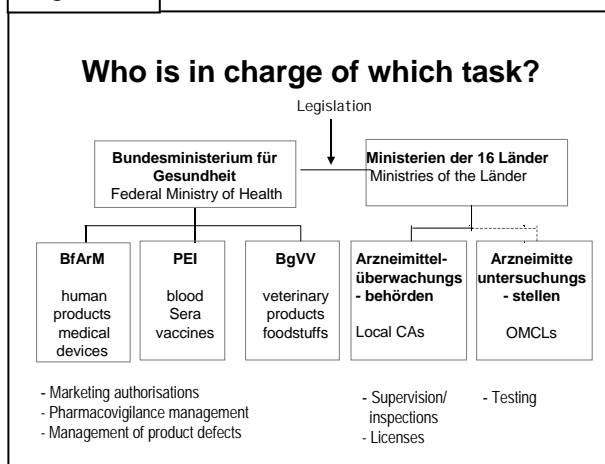
Structures and Responsibilities: Poland

- Marketing Authorisation: MoH (URPL)
- GMP: GIF (of the MoH)
- GLP: Office for chemical substances (of the MoH)
- GCP: URPL (of the MoH)

Abbreviations: See glossary, page 23

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Figure 1



At the Länder level: there are 16 MoH, 39 inspectorates and 11 control laboratories (OMCLs) that all have responsibilities that impact on the outcome of the review of applications and add to the complex nature of the administration. The whole structure is shown in *Figure 1*.

Whilst this structure may not be conducive to overall quality management as envisaged by EMEA, Professor Bass emphasised that quality management, when applied to each of the 'boxes', individually, contributes to the total quality picture.

In Poland, the advantage is that there is one federal Ministry of Health that is responsible for all the operations included in the quality management system.

The disadvantage of the system is that there is a lack of continuity as a result of frequent personnel and organisational changes. Ultimate responsibility rests at Ministerial level and is impacted by elections and changes within the government. At a practical level, Professor Bass explained, this also means that all communications with companies, from questions about the dossier to authorisation letters, have to be personally signed by the Minister. He provided an illustration of the chaos and backlog that ensues if the Minister is unable to deal with such correspondence for a while.

In neither Germany nor Poland has networking been achieved, at national level, to the extent that might be desired, Professor Bass suggested, but when all's said and done quality does not depend on structures and responsibilities, it come down to the individuals concerned. He expressed confidence that, given the opportunity to build quality into their processes, the people involved would do so.

The elements that build quality

Professor Bass reviewed some of the elements that build a picture of overall quality, starting with the essentials for a regulatory submission:

GxP: The reassurance that the scientific data included in the application has been generated in conformity with current codes of practice – GMP, GCP, GLP;

Application quality: Correctly and clearly assembled, data that meets high scientific standards and follows scientific advice and guidelines, reporting that is transparent and conclusions that are justified.

He expressed concern that the evaluation of the quality of a dossier, especially at the initial validation stage, can be reduced to a process of 'ticking boxes', which provides a quantitative, but not a qualitative check.

Regulatory processes

Professor Bass reviewed the following elements of quality management within the agencies, comparing Germany and Poland:

Mission statement: A statement of the vision for BfArM is in draft but not yet finalised. The Paul-Erich-Institut (biological products) and the Polish agency have finalised mission statements.

Workflow for procedures: For BfArM a system for describing and analysing the current status was originally established using *Visio* but was found to be relatively superficial and a more comprehensive system is being set up by a contract organisation. In Poland there was no definition of the workflow this has been drawn up by contactors who are upgrading IT systems, since they needed the workflow analysis for their tasks.

Standard Operating Procedures: There are a very large number of SOPs for the German system, which are important elements for quality management but require to be coordinated for a TQM. Poland has SOPs for core activities, especially related to European procedures and inspections but these are far from comprehensive.

Restructuring: This is under development for BfArM, but awaiting a consolidated, detailed and updated workflow. For the PEI restructuring has not been deemed necessary. In Poland a new head of the agency had recently taken office and a major reorganization is planned.

Supervision of manufacturers

Professor Bass cited the inspectorate in Germany as an example where 'total quality management' (TQM) has been achieved for inspection of GMP and GCP at regional level, through the Länder, as co-ordinated by the central co-ordination unit (ZLG). In Poland good progress has been made, through the twinning initiative, although TQM has yet to be achieved.

Conclusion

In his concluding remarks, Professor Bass returned to his premise that the quality of science is in danger of becoming a neglected area in the drive towards quality management of regulatory processes. Pharmaceutical legislation underpins and drives regulatory activities but there cannot be legislation on scientific quality. Whilst other activities are covered by good practice codes – and he cited peer review systems for publishing, benchmarking, running regulatory authorities and even controlling aeroplane safety – no such codes exist to control the quality of science. The final regulatory review needs to take account of the whole development process but, 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.

Glossary

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)

BgVV: Federal Institute for Consumers Health Protection and Veterinary Medicine

BVL: Federal Office of Consumer Protection and Food Safety

OMCL: Official Medicines Control Laboratory

PEI: Paul-Ehrlich-Institut

URPL: Office for the Registration of Medicinal Products, Medical Devices and Biocides (Poland)

ZLG: Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten (Central Authority of the Länder for Health Protection with regard to Medical Products and Medical Devices)

SESSION 2: POINTS FROM THE DISCUSSION

Dialogue between industry and agencies: In the aftermath of the safety concerns over COX-2 antirheumatics there had been criticism of the close relationships between companies and authorities. Dr Garutti stressed the importance of avoiding an over-reaction and allowing the pendulum to swing back to a situation where agency staff are isolated from interaction and communication with industry scientists. Dialogue between the parties, that results in a better product is in the best interests of the patient.

R&D vs. promotional costs: Challenged on the amount that companies spend on advertising and promotion – which was claimed to exceed the R&D budget - Dr Garutti pointed out that such figures include all post-marketing costs and not only promotional activities. This includes Phase IV studies and providing information services for healthcare professionals. Surveys have shown, he said, that the pharmaceutical industry is one of the largest providers of medical information to physicians.

Review times: The time taken for the regulatory review represents a relatively small part of the total development time for a new molecular entity. Dr Garutti was asked if it was worthwhile for regulators to spend time and efforts on trying to shorten review times and whether those resources

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would not be better used finding ways to reduce the shorten the development process. He replied that the development and review should be viewed as a continuum and each part needs to be examined to look for timesavings. He acknowledged that it was incumbent on industry to submit good quality applications in order to shorten review times and the number of review cycles. Thomas Lönngren expressed the view that the regulatory focus should be on improved scientific advice leading to more efficient development of medicines rather than reducing review time, which might not be compatible with maintaining the quality of assessments.

Centres of excellence: Agencies can now choose to specialise in specific areas where they have scientific expertise and Marijke Korteweg was asked whether such designations would be made on the basis of the agencies self-assessment or on an outside assessment. She confirmed that self-assessments would be followed up by a visit from a peer review team consisting of three assessors from other Member States and a member from EMEA.

Transparency of the self-assessment process: Asked whether the latest revised version of the self-assessment questionnaire would be made available to industry and whether there would be an opportunity for comment, Dr Korteweg was unable, at this stage to provide an official view as the meeting of Heads of Agencies had taken place earlier that week. Her personal view was that there should be full transparency as part of the learning and continual improvement process.

New EU members as Rapporteurs: Companies were being encouraged to nominate accession states as Rapporteurs and Rolf Bass was asked whether the Polish agency was yet well positioned to take on that responsibility. He replied that the main obstacle would be the fact that the agency is currently overloaded with organisational changes and the need to update some 13,000 existing products. From the point of view of scientific ability and expertise, however, the agency could certainly take on the role, in one of its chosen fields.



CHAIRMAN'S INTRODUCTION

Professor Stuart Walker

President and Founder, CMR International

Introducing the Session on *Meeting Future Expectations*, Professor Stuart Walker said that the discussions would first turn to developments outside Europe and the US that had been the focus of the earlier presentations on the quality of dossiers and the review process. The new agency in Japan, PMDA, had just been inaugurated at the time of the CMR International Institute Workshop on Global Drug Development in Tokyo, May 2004^v and this meeting would be brought up to date with current developments and plans for the future of regulation in Japan. The Workshop in Tokyo had initiated a debate on the future of drug development and regulation with some far-reaching recommendations for a 'new paradigm'. This theme would be developed further with a discussion on possibilities for changing in the way in which products are reviewed, whilst ensuring that the quality of regulatory procedures is maintained. Regulatory change may, however, be brought about by the changing nature of therapeutic products themselves. Innovative new technologies were resulting in a merging of the classic concept of a medicine and a device and the convergence of pharmaceutical, diagnostic and health technology research would also be discussed.

Professor Walker also chaired and introduced Session 4 of the Workshop in which there were Syndicate discussions on building quality into regulatory procedures⁴. He said that the Syndicates and the recommendations for further action that they produce had become an important feature of Institute Workshops and he believed that the current presentations would provide valuable material to fuel the Syndicate discussions.

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. The final presentation of the Workshop would therefore look at the decision-making process, not only in regulatory agencies but also within companies that, equally, need to make good quality decisions throughout the development process.

BUILDING QUALITY INTO FUTURE PMDA ACTIVITIES

Dr Osamu Doi

Senior Executive Director, Pharmaceuticals and Medical Device Agency, Japan

The patients' interests come first, Dr Doi stated in his opening remarks, and to meet these interests it is the mission of the new Pharmaceuticals and Medical Devices Agency (PMDA) to deliver innovative new drugs and medical devices that contribute to a better quality of life and therapy, and deliver them to patients faster.

The new PMDA

The PMDA was established in April 2004 and is designated as an 'independent administrative agency' which means that it is an independent administrative agency but remains under the supervision of the government.

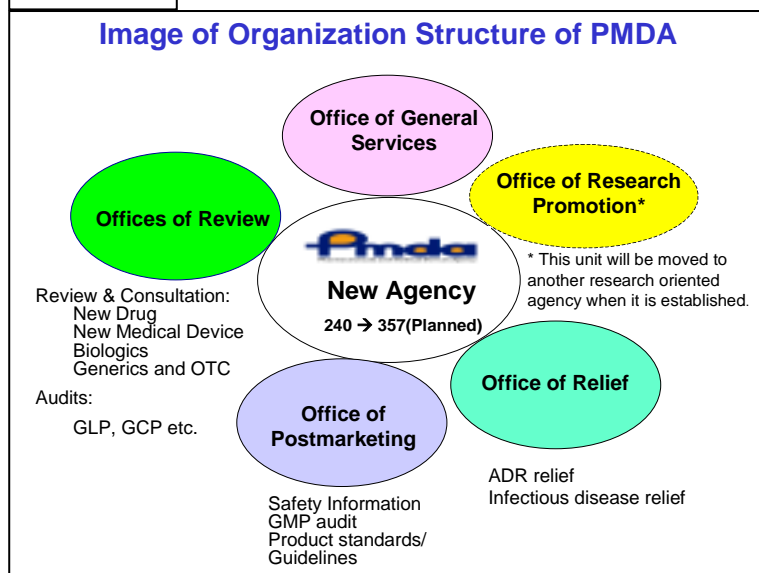
Dr Doi explained that a five-year medium-term plan for the agency's activities has been established as well as an annual plan that sets performance goals for the year. The progress towards these goals is monitored by the *Independent Administrative Agency Evaluation Committee* which carries out regular evaluations of progress.

⁴ The outcome and recommendations from the Syndicate discussions are given in Section 2 of this report

The PMDA is financed in part by industry user fees for the review of applications, consultations and audits and by an annual appropriation from the national government budget. In addition, industry contributes to the funding of postmarketing surveillance and relief activities (compensation for victims of serious adverse drug reactions).

Taking over the functions of the former PMDEC (Pharmaceuticals and Medical Devices Evaluation Center) the PMDA has been organised in five sections, as shown in *Figure 1*.

Figure 1



One of the targets under the five-year mid-term management plan is to increase staff levels from 240 (before PMDA was established) to 375. Adding to the staff resources and expertise within the organisation, Dr Doi said, would enable PMDA to improve the quality of its services by building more quality assurance into the review process and postmarketing surveillance (PMS) as well as increasing transparency and making the processes more productive.

Applications to carry out clinical trials are now made directly to PMDA, he reported, and consultations on clinical trials and applications can be held with the reviewers in charge of

the applications.

The only activities that remain the responsibility of the Ministry for Health, Labor and Welfare (MHLW), Dr Doi noted, are the final approval and issue of the authorisation.

New and improved procedures

Dr Doi reported on the new developments that have already started or can be expected to commence in 2005:

- A system of priority review will be introduced for medicines and devices for the treatment of serious diseases for which no other comparable therapy is available;
- A fast track consultation system is also planned for products with a high medical need;
- An appeal system has been established to resolve any issues or complaints from industry in relation to the review or PMS activities;

These developments will contribute to achieving the mid-term objectives set for the Agency (Box 1).

Dr Doi referred to the target for improving regulatory review times:

- 80% of new drug applications (NDAs) to be approved within 12 months (currently 50% in 12 months)
- 50% of priority review products to be approved in 6 months

Box 1

PMDA mid-term objectives and plans

Accelerate the Review Process -

Benefits for patients, benefits for companies:

- To shorten target review times for NDA/PMA* in order to have more effective and safer pharmaceuticals and medical devices accessible in a timely manner;
- To introduce a priority pre-NDA/PMA clinical trial consultation system in order to reduce the time to reach NDA/PMA submission.

Premarket Review and Postmarketing Vigilance Systems Working Closely Together

- The review process cannot be accelerated without risk management policy ensuring postmarketing safety monitoring (since any new drug or device has a potential unknown risk)

Safety assurance for general public

- To develop new proactive system with health professionals for thorough training in appropriate use at clinical site, not limited to passive ADR/AE monitoring.

Public benefit from new technologies:

Optimizing guidance provision and review for new technologies

- To strengthen review resources and enhance knowledge base to provide appropriate guidance for new technology products (e.g., biotech and genomic) consistently from pre-NDA/PMA level to NDA/PMA review level.

*PMA= Pre-Market Approval (Medical Devices)

Dr Doi stressed that, in order to meet these targets and reduce the application review times, industry would also need to play their part by improving the quality of dossiers. PMDA will also endeavour to reduce the backlog of applications that are currently a barrier to expediting the processing of good quality NDAs.

He noted that there was a further target for the second mid-term plan; that the overall elapsed review time (authority time plus applicant response time) should be at the same level as the US/European agencies.

Box 2

PMDA Safety Goals

Prevention of ADR/AE risks through proper use of pharmaceuticals and medical devices. Reinforcement of risk management system to promptly respond to occurrence of ADRs/AEs:

- Scientific vigilance
- Data mining method
- Establish sentinel medical institution network (PMDA to act as hub for "Sentinel Sites"- monitoring for new drugs/medical devices and intensive information provision)
- Premarket review and postmarketing vigilance systems working closely together

New postmarketing measures/services will be provided for greater accessibility of safety data for the companies concerned and will allow feedback information for safer design of new drugs/medical devices:

- Feedback information to health professionals and companies (access to database, information on dosage and use instruction, etc.)
- Feedback to patients, and the public (information via e-mail, consultation, etc.)

Postmarketing surveillance

Dr Doi then explained the changes to the postmarketing surveillance system now that it is under the auspices of PDMA. All information on adverse reactions will be reported by companies to the PMDA via secure electronic transmission to a central database. The data is analysed by external experts and those within PMDA and the results are reported to MHLW. Any action taken by the Ministry, including urgent action, will be based on information and advice from the PMDA.

Dr Doi also noted that PMDA is also responsible for monitoring the promotion of medicines and for providing advice on the appropriate use of medicines and medical devices. The latter will be provided to medical institutions manufacturers and patients.

PMDA has been set safety goals for the prevention of adverse events through the proper use of pharmaceuticals and medical devices as summarised in *Box 2*.

Dr Doi outlined the benefits to industry that could be expected from the revised PMS system:

- Strengthened expertise and resources for more scientifically sound decisions on vigilance and risk management;
- Reduced burden on companies for providing general safety information through the broader educational and safety information provided to health professionals and patients
- Improved guidance provision mechanisms for companies, e.g. on labelling and postmarketing studies;
- Integrated ADR/AE report database across products and companies that is accessible freely to each company with appropriate safeguards for confidential information;
- Proactive information feedback to companies:
 - ADR/AE reports submitted by health professionals to PMDA forwarded to manufacturers;
 - Information exchange with foreign agencies

Conclusions

In conclusion, Dr Doi gave his vision for the future. He believed that the simultaneous worldwide introduction of new products should be encouraged by facilitating global clinical trials and working towards coordinated review and approval. He looked forward to even closer cooperation between PMDA and its global counterparts in the EU and USA. PMDA is hoping to start conducting parallel clinical trial consultations with FDA in the near future.

The PMDA, he said, is improving the quality and timeliness of its review processes and enhancing its safety procedures, in the interests of patients. This is not only its responsibility to the

Japanese people but also, at global level, to patients around the world. Japan has an important contribution to make in the field of new medical product development. In order to respond to the expectations of the public, Dr Doi re-asserted PMDA's commitment 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.

A FUTURE VISION FOR QUALITY REVIEWS AND DECISIONS

Moira Daniels*

Director of Global Regulatory Information and Intelligence, AstraZeneca, UK

Describing the regulatory review as being just the end phase of a much longer development process Moira Daniels challenged the industry not to keep focusing on shorter review times but to seek ways to reduce the whole development cycle time, in order to bring new products to market earlier.

The challenges

Among the major challenges facing industry, she said, is the fact that many fewer drugs are being discovered and brought to market. The technology to identify new candidate molecules is there, but a scan of hundreds of thousands of potential candidates may be needed in order to identify a single molecule with the appropriate profile. The question, said Ms Daniels, is whether the product can then survive the development process.

It is becoming more critical to make good decisions earlier in the process. The cost of development is escalating but is this, she asked, because of regulatory requirements or because industry is trying to show a differential improvement in the quality of their drugs over the other products already on the market?

Industry needs to become better at demonstrating the value of its medicines to both patients and payers in the context of the health-care system, Ms Daniels suggested, and not just in isolation on given products. The pharmaceutical industry has failed in 'promotional' efforts with regard to its own image and in communicating to patients and carers about its contribution to improvement in public health.

Box 1

'As is'

- 'Snapshot' review approach
- Not very predictable decisions
- Risk issues seem more important than benefit
- Drug product, not therapy, focus
- Non-transparent processes during assessment and development
- Media and public questions judgement of Industry and regulators

Box 2

'To be'

Principles

- Continual assessment removing the development/real world usage silos
- Assessment starts at Phase 0
- Benefit as well as risk focus, driving appropriate successful usage of new therapies (avoiding failures)
- Diagnostics, devices, communication tools part of the data base
- Much larger real-world clinical data sets
- Transparency of data throughout development

Current reality and future vision

Ms Daniels contrasted the development and review scenario (Box 1) with a vision of changes in philosophy and practice that might be brought about (Box 2).

Currently, the focus is on a 'snapshot' review of the project with everything riding on a decision made in 180 days at the end of the development process. We need to move away from this end-stage review, she said, and the feeling that 'partnership' between the regulators and the regulated is 'a dirty word'. A way needs to be found of involving regulatory agencies at an earlier stage in order to achieve more predictable decisions.

Risk issues appear to assume more importance than benefit in the regulatory process and in public expectations.

*Paper prepared jointly with Dr George Butler, Vice President, Customer Partnerships, AstraZeneca Pharmaceuticals

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.

Ms Daniels also felt that there is currently too much focus on the product and not the therapy. There should be less preoccupation with clinical endpoints in isolation and new medicines should be viewed, from a patient perspective, in relation to the whole spectrum of treatment and, in particular, quality-of-life issues.

Another current issue is that processes are not yet sufficiently transparent to provide the public with the reassurance they seek about the quality of research and regulation. Notwithstanding the development of IT systems there remain problems of communication and transparency with the result that the judgement of both industry and agencies are constantly being challenged by the public and the media.

Ms Daniels discussed the principles for a future scenario based on the concept of a continuous assessment of new medicines and a move away from the current paradigm in which there is a sudden shift from a very controlled environment of selected patients in clinical studies to the diverse patient population of the real world. In the days before global development and the massive international launch of a new product, registration would take place in a step-wise sequence with the opportunity to learn from market experience. Whilst not wishing to step backwards, the sudden introduction of a product to the global market needs to be balanced by an ongoing review process that starts at 'Phase 0'.

Ms Daniels noted the introduction of the clinical trials directive in the EU as a step towards earlier assessment, but expressed concern about the potential disconnect between the process for clinical trial approval and the later assessment of the products from those trials. A dialogue needs to start earlier in the process, she suggested, and the procedures will need to take account of the clinical trial databases in which most of the industry will shortly be participating.

Improved communications will be needed to ensure that arguments about the benefits of therapies reach the target audience of patients and users and engage them in the development process. This, in future, will include the increased combination of devices and diagnostic agents with pharmaceuticals. Other issues to be addressed in the future scenario include the need for much larger real-world clinical data sets that are not financially crippling for the industry.

A new paradigm

Mapping out the changes needed to reach a new drug development paradigm, Ms Daniels returned to the importance, from the beginning of the process, of looking at the project from a therapeutic rather than a product perspective. A major step would be to look at the similar programmes across industry and take account of research being carried out elsewhere, which could lead to collaboration on the development and validation biomarkers and surrogate endpoints.

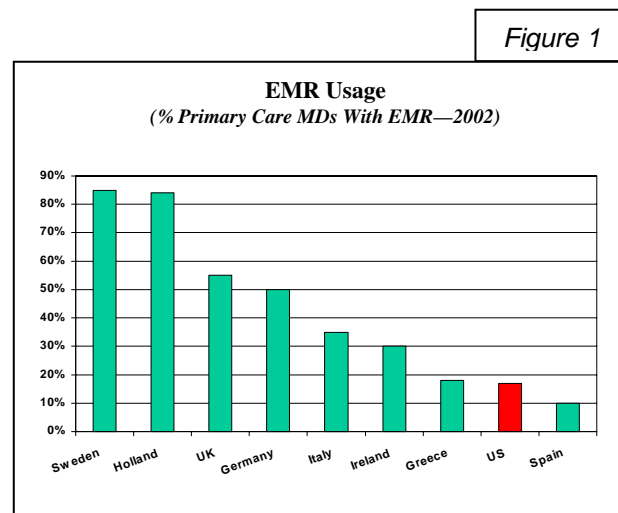
Academia could be involved from the outset instead of bringing them in at the last stage to act as experts and similarly the purchasers and users are currently only brought in at the 'last five minutes of the day of development time'. Purchasers, whether public or private sector need to buy into the concept of new products at an early stage and understand the benefits in terms of the overall health economic picture.

New therapy testing

Ms Daniels explained that the vision for the future, which she was proposing, was one where there was a continual data flow with an open and transparent exchange of information between the company and agencies, in order to build quality in during the testing process and not at the end. The chemistry and pharmacy package is often completed relatively early in the development process and could be given regulatory clearance when ready, rather than waiting for the end-point review. By involving the health authorities from an early stage, she suggested, they will become very knowledgeable about the therapy and development decisions, and science rather than bureaucracy might be re-established in regulatory decisions.

Patient records

Ms Daniels discussed the use of patient record databases as an invaluable source of information that could be tapped to improve drug development and evaluation. Industry would like to be able to extract data from electronic medical records (EMRs) in order to carry out wider data mining of patient records and provide access very much larger safety data sets. The UK and other countries are undertaking initiatives to set up EMRs but coverage is variable. Data from 2002 is given in *Figure 1* which shows that the countries with relatively small populations, Sweden and the Netherlands have high coverage whereas the biggest pharmaceutical market, the USA, has only 15% coverage.



Release for sale.

Pivotal to the vision for the future that Ms Daniels was presenting is the concept that many, if not all new products could be ready for release for sale, under controlled conditions, without the need for a confirmatory Phase III study since such confirmatory data may be better gathered from the real world and would benefit or enrich studies with large populations.. Once proof of concept and safety is established the product should be released for use in therapy without the need to prove comparative efficacy. Such release would carry legally enforceable conditions about benefit/risk of data and the theoretical conclusions that need to be met in order to continue to sell the product.

During sale

Early release for sale would need to be coupled with the facility to develop massive observational benefit risk databases for which the link into EMRs would be essential. The 'contract' would include a review of both benefit and risk that would be reflected in modifications to the product information (SPC in the EU). Ms Daniels contrasted the current system for the periodic safety update report (PSUR) where the accompanying regulatory guidance is focused almost exclusively on risk and not on a re-evaluation of medical benefit.

Conclusions

Summarising, Ms Daniels highlighted the key elements of the future vision she had presented 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 patient ownership and participation to the extent that they feed data about their treatment and any adverse effects into the database.

PREPARING FOR FUTURE TECHNOLOGIES

Dr David Jefferys

*Special Advisor-Healthcare Industries, Department of Health, UK**

Dr David Jefferys referred to recent criticisms of the concept of partnerships between industry and regulatory agencies but stressed that 'partnership' should be regarded in a positive rather than negative light. He referred to the Healthcare Industries Task Force (HITF), with which he had recently been involved, and its discussions on partnership between the medical devices and wider health-care industry. This had culminated in a report, published by the UK Department of Health shortly before the Workshop, entitled *Better health through partnership*^{vi}.

Box 1

Evolution of Pharmaco-Therapeutics

- Herbal preparations
- Chemical agents
- Molecular modelling
- Biotechnology
- Genomics, proteomics
- Nano technology

Looking back to look forward

Quoting the saying 'if you want to predict the future you have to understand thoroughly the past' Dr Jefferys reviewed the evolution of medicines (Box 1) and the regulations to control those medicines (Box 2).

Although herbal and chemical medicines are still much in evidence, he said, the biotechnological revolution and recent development in genomics, proteomics and nano-technology are set to raise many questions not only in relation to regulation but also in their impact on the whole healthcare delivery system. Meanwhile,

medicines regulations have progressed from the early preoccupation with quality and the use of toxic substances (mercury and arsenic) to the current systems that have evolved mainly from the procedures established in the 1960 following the thalidomide tragedy.

Dr Jefferys pointed to the major changes that had been seen in medicines regulations and regulatory practices over the past 40 years - international harmonisation, the EU centralised procedure, the progress in postmarketing surveillance and scientific advice, to name but a few. Nonetheless, they remained based on the same paradigms and principles and this, he suggested, may need to change.

The recent trend of mergers between agencies that regulate medicines and devices was, he believed, in anticipation of very major changes in technology, the increasing integration of medicines, diagnostics and novel delivery systems and the fundamental changes in health care delivery that must follow.

Box 2

Evolution of Medicines Regulations

- Pharmacopoeias (1341)
- Poisons and therapeutic substance legislation
- Consumer protection, federal trade legislation
- 1960s post thalidomide medicines regulation

Parallel Developments

Dr Jefferys outlined some of the current developments occurring in parallel that would, he predicted, have a cumulative impact on future attitudes and practices in health care delivery:

- **Health technology assessment:** reviews of the comparative cost-benefit of products, not only by national agencies and purchasers but also by consumer lobby groups;
- **Evidence based medicine:** adding a new dimension to the assessment of new products;
- **Patient safety initiatives:** a growing movement that started in Australia and is now very powerful in the US and UK, that has been taken up as a priority area by the World Health Organization and will be a major theme for the EU in the second half of 2005.
- **Competitiveness agenda:** known in Europe as 'the Lisbon agenda' and recognising the need to have a successful and competitive industry in order to advance health care through innovative new products.

* Since the Workshop Dr Jefferys has left the Department of Health and is Senior Adviser on Strategic Global Regulatory Affairs and Product Development, Eisai Co Ltd

New models of healthcare delivery

Box 3

Changes in healthcare Delivery Purchaser/provider split

- Payment by results
- Service frameworks
- Patient centred healthcare
- Expert/empowered patients
- Early health agenda
- Establishment of large healthcare databases

Dr Jefferys outlined some changes in healthcare delivery that might be anticipated (Box 3) and questioned whether industry was taking these into account in planning for the future. He envisaged that there would be an increasing split between purchasers and providers of health care with the purchaser, as the customers, wishing to become increasingly involved in the agenda for new product development. Within national health service frameworks the emphasis is, increasingly, on integrated health care and looking at whole disease entities rather than treatments in isolation.

One of the most significant developments, Dr Jefferys suggested, was 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.

The 'early health agenda' with an emphasis on prevention and early diagnosis of disease would also have an impact and Dr Jefferys noted that some companies were already becoming engaged in this. A major change is that treasury departments are beginning to regard expenditure on health care as an investment for the future and not merely in terms of costs and outlay.

Finally, there are many opportunities offered by the development of large databases of patient and healthcare information. As noted earlier in the Workshop^{vii} this is particularly the case in the UK but Dr Jefferys pointed out that many other countries are following a similar path. Such information offers significant opportunities for research that could influence the development of new therapies.

New Challenges

Dr Jefferys reviewed some of the technological developments that are and can, in future, be expected to provide new challenges to research and regulation.

Gene therapy: There had been a 'false dawn' with few products coming to fruition but the area is still one of active research and development.

Human tissue engineering: There are some 20 products on the European market, some representing highly advanced technology, and the full potential has probably not yet been realised. They pose a problem, however, because this is an area that is not currently regulated. In the US there is no legislation and regulation in the EU has been postponed.

Advanced cell therapy: The cell therapy products that have been developed may not be of the type envisioned when they were included in Annex A to Council Regulation (EEC) No 2309/93 in 1994 (products that must be processed through the Centralised Procedure)

Nano-biotechnology: There is a close link between advanced cell therapy and the application of nano-technology, for example the introduction of nano-particles into cells that transport them to the site of action for the treatment of cancer. The applicability of current legislation to the new technology is unclear and discussions within the EU were scheduled for later in December 2004.

Pharmacogenomics/genetics: As the potential for developing 'personalised medicines' advances, there are regulatory and economic issues that need to be addressed. Such products are characterised by the convergence of *in vitro* diagnostic (IVDs) and medicinal products.

The manifestations of change brought about by the convergence of new and different technologies include complex drug/device combination products and new targeted delivery systems. These are not, Dr Jefferys commented, such simple regulatory issues as, for example, the introduction of the insulin pen, but extremely sophisticated items that require specialised expertise to assess and raise questions of whether they are classified as drugs or devices.

The emergence of new treatment options and the development of new technologies are expected to have a profound impact on healthcare delivery systems and strengthened partnership between the healthcare industries and healthcare providers will be needed. We are already seeing

the emergence of a 'life science sector' Dr Jefferys observed, or what some are calling an 'advance health-care technology sector'. Some of the barriers that have traditionally existed between medicines, devices, bioengineering and tissue engineering products are beginning to break down and the consequences of this need to be addressed.

Impact of future technologies

Referring back to the report of the UK HITF, Dr Jefferys stressed the need to consider both the public health and economic consequences of future technologies.

One area of concern is how to encourage appropriate innovation and he noted that the UK is traditionally a country where new products are authorised relatively rapidly but the uptake of such products is slow. One of the objectives of the National Institute for Clinical Excellence (NICE) is to encourage the uptake of new medicines and ensure that funds are available through the NHS. A major thrust of the HITF report, Dr Jefferys said, is to set up an innovation 'network' with centres of excellence and to revamp the device evaluation process.

One of the objectives is to use partnership between the purchasers, the health service and the devices industry to meet the expectations. If quality is defined as 'meeting customer expectations' the new advanced healthcare industry must become more aware of, and more responsive to, the needs of the customers.

An important future issue is how to educate and train healthcare providers. This is perhaps more relevant in the healthcare technology sector, Dr Jefferys suggested, but there are echoes of this in the pharmaceuticals sector, through the patient safety movement. A related theme from the HITF report is the need for improved communications particularly to educate the public to better understand risk and benefit. Greater investment is needed and these discussions need to be brought into the education programme to increase awareness that all interventions have risks attached to them.

A new regulatory paradigm

Dr Jefferys concluded by returning to the question of whether the regulatory paradigm, developed from the model established in the 1960s will still be valid in ten years time. If fundamental changes are to be brought about, he cautioned, they will not be achieved rapidly and work must start now on the regulatory regimes envisaged as necessary in 2015. The convergence of medicines and device technology will produce a new generation of healthcare products that fit into a new spectrum of healthcare management. This will mean changes in the structure of the companies that produce them and the establishment of a new regulatory framework that maintains appropriate levels of quality and control whilst ensuring the new generation of therapies achieve their maximum potential.

SESSION 3: POINTS FROM THE DISCUSSION

Application backlog and review times: Dr Doi stressed that one of the objectives of recruiting additional PMDA staff would be to reduce the backlog of applications and prevent backlogs from building in future. Applicants would also be expected to answer questions promptly and within a deadline of six months after which the application would be withdrawn. There would be more attention, in future, to differentiating regulatory time and the company component when calculating the overall review times.

Fast track consultations: Dr Doi confirmed that it was not necessary for companies to have affiliates or agents in Japan in order to benefit from the new facilities for consultations on applications designated for accelerated review.

Review after Phase II: It was noted that there is already a precedent for the authorisation of products on the basis of Phase II data, as proposed in Moira Daniel's presentation. The FDA accelerated approval process allows this for products that fulfil unmet medical need and for orphan medicines.

Electronic medical records: The point was made that, even though there is only 15% EMR coverage in the US, this still represents many millions of records that could provide a valuable resource for identifying rare events in primary care. In a further comment there was strong support for the use of EMRs to collect information on adverse drug reactions and it was suggested that this might be a better investment than the current postmarketing surveillance schemes based on spontaneous reporting.

Horizon scanning: Gene therapy was an example where predictions of a major therapeutic breakthrough had been misplaced. Dr David Jefferys stressed the importance of effective horizon scanning to alert both regulators and healthcare providers to important future developments that might be 'disruptive' to regulatory and health service procedures.

THE QUALITY OF DECISIONS AND THE DECISION-MAKING PROCESS

Professor Larry Phillips

Professor of Decision Analysis, London School of Economics

Professor Larry Phillips introduced his topic by commenting that many people find it hard to believe that there can be a 'science of decision-making'. There is, he affirmed, such a science and it is based on a very coherent theory about how to make better decisions

He pointed out, however, that 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, he suggested, 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.

Elements of a quality decision

There are three questions that must be asked, Professor Phillips explained, in order to make good decisions about any project:

- What is the benefit of this project assuming the project is successful?
- What is the probability of success?
- What is the resource required to bring the project to success?

This concept can be represented diagrammatically by the right-angle triangle shown in *Figure 1*. The steeper the angle of the hypotenuse, the better the decision to proceed with the project.

Professor Phillips noted that this is not a controversial model and yet the vast majority of organisations with which he works do not apply this simple test. They do not divide the risk adjusted benefit by the cost to achieve an index – a single number representing the slope of the triangle - to indicate how good the decision is.

He provided a case study from a pharmaceutical company in the US. An analysis had been made of 121 projects, both current (41) and proposed (41), and the triangles were set out in order of the decline in the slope.

Figure 1

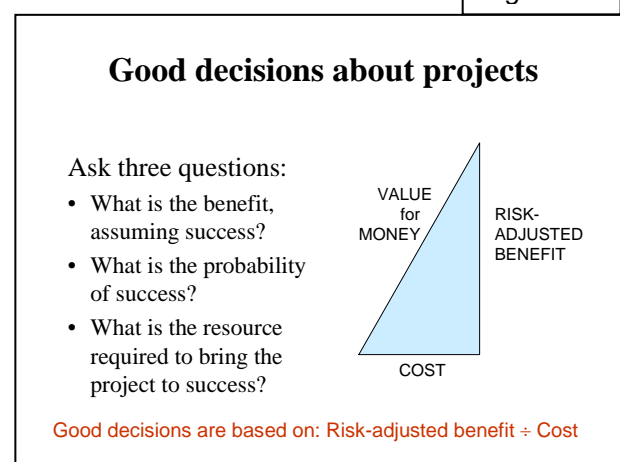
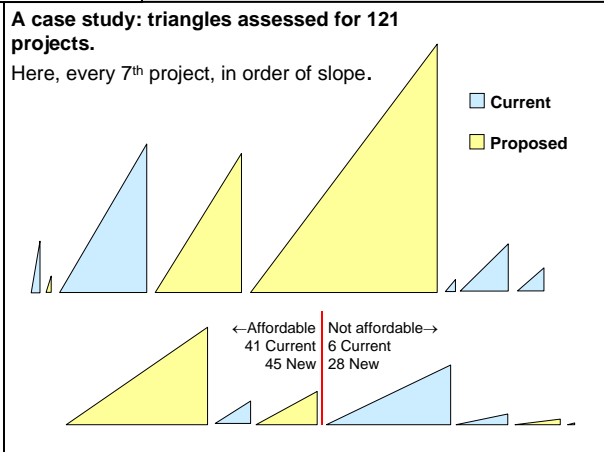


Figure 2



A sample (every seventh project) is illustrated in *Figure 2*. When the cut-off, to differentiate affordable from non-affordable projects, was set it was found that six of the current projects and 28 new ones fell outside the affordable budget, suggesting that some bad decisions were being made.

This, Professor Phillips noted, was typical of his findings when working not only with the pharmaceutical industry but also with other industries and the public and private sectors. The result is that a lot of money is being spent that is reaping some benefit but that many more attractive projects are not being undertaken.

Bad decisions are made about projects (see box) when the benefits that will accrue from a project cannot be judged and quantified.

Decision quality

Professor Phillips referenced the publication *Smart Decisions*^{viii} that is based on extensive research among different types of companies, carried out at Stanford University. This identifies six features that characterise good quality decisions, as shown in *Figure 3* and he expanded on each of these.

A 'good' frame for a decision

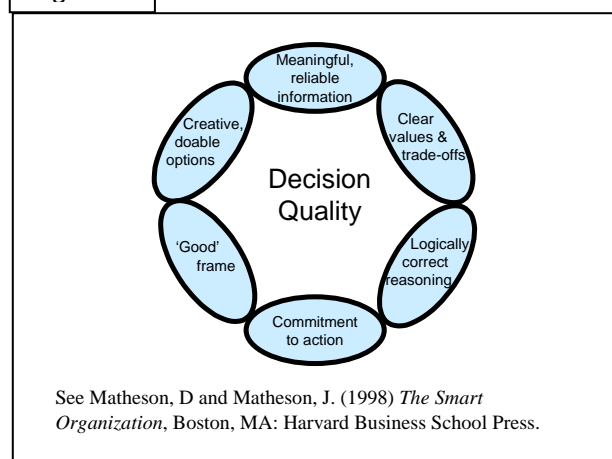
Consistent with the organisation's mission and strategic direction: There needs to be a general 'pull' in the same direction within the company, avoiding maverick options that are not consistent with the organisation's strategic intent (which is often the case with licensed-in products in the pharmaceutical industry).

Bad decisions about projects

- If you can't judge what benefit will accrue, why are you doing the project?
- If you can't assess the chances the project will be a success, why are you doing it?
- If you don't know how much the project will cost, why are you doing it?

Good project decisions require a reasonable answer to all three questions!

Figure 3



Informed by other areas in the organisation: 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.

Takes account of relevant external factors: The project will be undertaken within a political, social, economic, technological and legal environment that can all have an impact when judging whether a project is worthwhile.

Explicit about assumptions: The criteria for measuring the value of a project and for judging probabilities for success need to be consistent across the portfolio.

Creative, achievable options *Not just 'go-no go'*: Options should not be viewed in 'black and white' terms as there are many shades of grey in the alternative ways forward with, for example, a promising new compound

What would you do with additional resource? It is worth exploring the ideas that can be generated if the project team is allowed to open up the discussions and consider the direction they would take without budgetary constraints.

SWOT analysis: The options should be developed to grasp the **S**trengths, fix the **W**eaknesses, seize the **O**pportunities and stave off the **T**hreats.

Strategic factors: It is important to have multifunctional groups that can appraise the options on a strategic level without going into great detail of 'how and why' that are matters to be addressed at a technical and operational level.

Meaningful reliable information

Probabilities of technical and market success: Information about both of these is required but past successes cannot merely be counted up as a means of providing this. Base rates for success rates at different stages of drug development exist in, for example CMR data and such data should be referenced in determining probabilities.

Costs: The total forward cost for each option is needed and this does not include costs that have already been spent, (The costs at the bottom of the 'triangle' are forward costs).

Unknowns: The unknowns, and even the 'unknown unknowns' need to be explored, particularly with research teams where there may be assumptions that people are not willing to bring to the surface.

Consider alternative scenarios: It is important to consider the different events that might happen in the future in order to improve the quality of probability judgements, and this includes probabilities of failure as well as success.

Clear values and trade-offs.

Benefit criteria: This is the degree to which an option meets the different and often conflicting objectives of the organisation. In the case of the pharmaceutical industry this might be that the option:

- Creates commercial value
- Addresses unmet medical need
- Impacts current business
- Provides future potential

Trade-offs: How many units on one criterion are equivalent to units on another criterion? The issue here is, for example, how much is the organisation willing to trade in future potential for a little immediate loss in net present value. Making trade-offs on conflicting objectives leads to a more balanced portfolio than will result if decisions are driven by a single criterion of, say, commercial considerations or unmet medical need.

Logically correct reasoning

Information overload: The rule of the 'magic number 7 ± 2 ' illustrates a person's limited ability to process large amounts of information and very complex situations. Problems need to be taken apart in order to make judgments on the pieces whilst computers can be used to assemble the pieces again.

A role for models to combine information: Models are needed to enable information to be collated and reduced to a single number to denote the overall benefit of the project. Multiplying that by a probability and dividing it by the cost provides the model's basis for prioritising the options.

Computers to provide instant sensitivity analyses: This enables changes to be made in ratings and trade-offs to see what the consequences are of imprecision in the inputs and differences of opinion amongst key players.

Commitment to action

Shared understanding: Consensus is not necessarily required but there should be an understanding of why the parties disagree.

Sense of common purpose: Developing this in a team is essential to achieving commitment to the way forward but it is also important to maintain diversity. Members of the team can be following different paths while still working in the same general direction.

Figure 4

The PROACT process

- **Problem:** Frame the issues
- **Objectives:** Clarify objectives and criteria
- **Alternatives:** Develop courses of action
- **Consequences:** Identify consequences
- **Trade-offs:** Manage conflicting objectives
- **Uncertainty:** Consider alternative futures
- **Risk Tolerance:** Judge acceptable risk
- **Linked decisions:** Assess impacts

See Hammond, J. S., Keeney, R. L., & Raiffa, H. (1999). *Smart Choices: A Practical Guide to Making Better Decisions*. Boston, MA: Harvard University Press.

The PROACT decision-making process

Having reviewed the six elements of good quality decisions, Professor Philips then turned to the decision making process itself. He referred to the 'PROACT' process described in the book *Smart Choices*^{ix}

The acronym (*see Figure 4*) refers first to problems and framing the issues, which were discussed earlier. The second step in the process is being clear about objectives and the third is developing alternative courses of action. This is followed by the need to think of the consequences of the decisions and, as before, trade-offs as a way of managing conflicting objectives.

As shown in *Figure 4* there are an additional three pieces that fit the jigsaw – but not the acronym. Alternative futures need to be considered in order to assess uncertainty, and risk tolerance must be taken into account. Linked decisions are also a factor as the consequences of, for example, committing resources to one project might limit the resources available for another. The opportunity costs must be considered and the impact assessed.

Summary

In conclusion Professor Phillips summarised the key elements of quality decisions:

Decisions that are taken by accountable managers who, after engaging the key players, have:

- established an appropriate frame for the decision;
- ensured that the multiple objectives are aligned to the organisation's strategic direction;
- considered several courses of action;
- anticipated possible consequences;
- judged the relative values of the consequences, and the trade-offs among the objectives;
- assessed the probabilities of achieving the objectives;
- used modelling to put the elements together; and
- conducted extensive sensitivity analyses to develop insights about the issues and gain confidence in the best way forward.

POINTS FROM THE DISCUSSION

Size of the triangles: Asked about the relative size of the triangles, Larry Phillips replied that the differences related to the different costs represented on the x-axis, but the different areas were not significant in terms of the quality of decision-making. It was, however, important when comparing slopes across different projects in a portfolio to ensure that the same units were used for all costs and the same units (not necessarily the same units as the costs) for all benefits.

Collective wisdom: A committee, faced with decisions on benefit-risks may be faced with a minimum of 10 benefit and 10 risk factors which is of concern if the '7±2' limit applies when trying to cope with numerous pieces of information. Professor Phillips pointed to the importance of bringing together a group to deal with such decisions and referred to the philosophy that groups of people can be wiser than even the best individual^x.

Continuous review: It was suggested that the reason that projects with a poor 'slope' are being pursued by companies is that the assessment is carried out as a 'snapshot' at one point in time and Professor Phillips agreed that the assessment should be carried out on a continuous basis.

Quantifying benefit: Whereas risk can be quantified by the seriousness of the outcome and the probability of the adverse event occurring, it is hard to derive a similar metric for benefit. Professor Phillips referred to the technique of Multi-Criteria Decision Analysis (MCDA) that allows seemingly different and incomparable factors to be quantified in a single numerical metric that represents added value. (A model based on MCDA was discussed at a CMR International Institute Workshop on benefit-risk assessment in 2004^{xi})

ⁱ Discussion paper on 'The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future, published by the EMEA, March 2004, available from the EMEA website:

<http://www.emea.eu.int/pdfs/general/direct/directory/3416303en.pdf>

ⁱⁱ Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, published by the US Department of Health and Human Services and the FDA, March 2004, www.fda.gov

ⁱⁱⁱ G10 Medicines Report of 07 May 2002 and the 01 July 2003, Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Region: *A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient - A Call for Action*, COM (2003) 383 final.

^{iv} Presentation by Dr David Lyons, see Section 3 page 1

^v CMR International Institute Workshop on Global Drug Development 26-27 May 2004, Tokyo, Japan. Workshop Report (members only) available via the institute website: <http://www.cmr.org/institute>.

^{vi} Better Health through partnership: A programme for action, Department of Health, Healthcare Industries Task Force (HITF), November 2004 available via:

http://www.advisorybodies.doh.gov.uk/hitf/hitf_final_report_nov2004.pdf

^{vii} Presentation by Moira Daniels, Section 3 page 29

^{viii} Matheson, D and Matheson, J. (1998) *The Smart Organization*, Boston, MA: Harvard Business School Press.

^{ix} Hammond, J. S., Keeney, R. L., & Raiffa, H. (1999). *Smart Choices: A Practical Guide to Making Better Decisions*. Boston, MA: Harvard University Press.

^x James Surowiecki, *The Wisdom of Crowds*, London: Little, Brown, 2004; United States: Doubleday, 2004.

^{xi} CMR International Institute Workshop on The Development of a Model for Benefit-Risk Assessment of Medicines Based on Multi-Criteria Decision Analysis, 29-30 March 2004, London School of Economics. Report available (to members only) on the Institute website: www.cmr.org/institute