Beyond Benchmarking:

What are the key metrics that agencies and companies should use to measure performance?

CMR INTERNATIONAL INSTITUTE WORKSHOP
4-5 October 2004, Virginia, Washington area, USA

WORKSHOP REPORT

Margaret Cone
Stuart Walker

February 2005

CMR International

Institute for Regulatory Science

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SECTION 1: OVERVIEW

Monitoring performance

Why participate in benchmarking exercises?

This question was asked and answered at the CMR International Institute Workshop in October 2004 when regulatory experts from government agencies and pharmaceutical companies met to discuss metrics for monitoring regulatory performance.

In a series of presentations regulators and industry speakers discussed the motivation for undertaking studies that are often time- and resource-consuming. Whilst motivations may differ between companies and agencies it was apparent that both have a common goal of ensuring that new medicines are made available to the patient in the most efficient and cost effective manner.

It was also evident from the presentations and discussions, however, that it is not enough to measure performance in terms of timelines and the speed of the review alone. The quality of the process, from the construction of the dossier to the ultimate regulatory decision must also be monitored and added to the equation.

'Score card' proposal

This focus on quality was followed up in the Syndicate Sessions and led to proposals that the CMR International Institute for Regulatory Science should initiate a project to elaborate a system for collecting feedback after a regulatory review using:

Scorecards on the Industry: Completed by the agency on the quality of the dossier, the robustness of the data and way in which the company interacted during the review process;

Scorecards on the Agency: Completed by the company on the openness, fairness and consistency of their interactions and communication with the agency before and during the review, including scientific advice, questions and negotiation of the final label.

It was agreed that this proposal and other recommendations from the Syndicates should be explored further at the upcoming Institute workshop, in December 2004, on 'Building Quality into regulatory dossiers and the review process'[1].

CMR Institute Benchmarking Study

Participants at the Workshop were in a unique position to receive, at first hand, the initial reports of a major six-year study 'Benchmarking the regulatory review process' that had recently been completed by the Institute. Five regulatory agencies, FDA, EMEA, Health Canada, the Australian TGA and Swissmedic had worked together with the Institute to provide data on new drug applications submitted in the years 1997 to 2002 and tracked through to July 2003.

The methodology and study results were presented, in the opening Session, by Dr Neil McAuslane, CMR International Institute, and were the focus of the subsequent Syndicate discussions.

Regulatory response

The six regulatory agencies in the study were all represented among the speakers at the meeting and provided insights into their objectives in participating. They also discussed their on-going priorities which included: the implementation of Good review management principles (GRMP) in the US (*Dr Sandy Kweder, FDA*); responding to stakeholder expectations for a timely, transparent, predictable and consistent review process (*Dr Robert Peterson, Health Canada*); continuing the benchmarking study on quality management systems undertaken in preparation for EU expansion (*Dr Bo Aronsson, EMEA*); encouraging earlier inclusion of Australia in the global submission process for new drugs (*Dr Leonie Hunt, TGA*,); learning from the practices of larger agencies –positive and negative - as highlighted in the study (*Professor Samuel Vožeh, Swissmedic*).

Regulatory Performance of Industry

The final Session included discussions on measuring and benchmarking the regulatory performance of industry. The presentation by Dr John Jenkins, FDA, underlined the need to focus on quality and suggested it was time to turn attention from agency to industry procedures. 'We could have a perfect regulatory process', he said, 'but this will not result in an approval if the application you submit is not up to standard'.

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 subsequent questions and answers that they generated.

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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

[1] CMR International Institute Workshop on Building quality into regulatory submissions and the review process: '*Knowing and meeting customer expectations'*, 2-3 December 2004, Woodlands Park Hotel, Cobham Surrey, see www.cmr.org/institute

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SECTION 2: OUTCOME

Session 2 of the Workshop, during which the syndicate discussions took place, was chaired by **Dr David Jefferys,** *Senior Adviser on Healthcare Industries to the Department of Health, UK*.

There were four Syndicates that addressed two topics:

Topic A: *How can we maximise the potential of the current metrics used for measuring the regulatory review process*

Syndicate 1: *Chair:* **Dr Bryan Garber**, Head, Risk Management Unit, Senior Medical Advisor Bureau, Therapeutic Products Directorate, Health Canada

Rapporteur: **Dr Pat Porter**, Vice President Drug Regulatory Affairs, GE Healthcare, UK

Syndicate 2: *Chair:* **Dr Tim Franson,** Vice President of Global Regulatory Affairs Eli Lilly, USA

Rapporteur: **Professor Thomas Kühler**, Director of Operations, Medical Products Agency, Sweden

Topic B: *What new measures should be included in the future to monitor regulatory performance?*

Syndicate 3: *Chair:* **Dr Murray Lumpkin**, Principal Associate Commissioner, FDA

Rapporteur: **Dr Paul Huckle**, Senior VP, European and International Regulatory Affairs, GlaxoSmithKline, UK

Syndicate 4: *Chair***: Dr Ed Harrigan,** Senior Vice President**,** Worldwide Regulatory Affairs, Pfizer Inc., USA

Rapporteur: **Dr Stewart Geary**, Deputy Director, Corporate Regulatory Compliance and Quality Assurance Headquarters, Eisai Co. Ltd, Japan

SUMMARY OF THE SYNDICATE DISCUSSIONS

The Syndicate discussions were held against the background of the CMR International Institute Benchmarking Study on the regulatory procedures in the USA, EU (Centralised Procedure), Canada, Australia and Switzerland under which metrics for new drug application had been collected for submissions made from 1997 to 2002, tracked through to July 2003[1]. The Syndicates were asked to discuss maximising the benefits to be gained from continuing and, perhaps, extending the current benchmarking study, and also to make recommendations for future studies of metrics related to regulatory performance.

There was consensus that any future studies should focus on measuring quality in the submission and review procedures. A 'score card' system was proposed for collecting feedback on the quality of the dossier and the way in which the review had been conducted, for major new applications. These and other proposals from the Syndicates relating to quality studies are summarised below and it was agreed that these should be fed into the CMR Institute Workshop on 'Building Quality into Regulatory Submissions and the Review Process', 2-3 December 2004, Cobham Surrey UK, for further discussion.

The recommendations from the Syndicates on carrying out further studies under the current benchmarking study on regulatory performance are also summarised here. These underlined the continuing interest in overall timelines and in monitoring the components of the regulatory process responsible for hold-ups and delays in the registration process.

1. MEASURING QUALITY AND PERFORMANCE IN THE FUTURE

1.1 Proposal for a 'Score card' System

Rationale

Future metrics need to address both applicants' and agencies' performance in order to see both sides of the equation. Assuming that the current studies that are focussed on time lines and review cycle times will continue, it was proposed that the focus for developing future studies should be on quality metrics for the submission and review processes.

Two model 'scorecards' were proposed. The 'Scorecard on the Industry' is for agencies to feed back their assessment of the quality of a company's submission and the robustness of the data. The 'Scorecard on the Agency' is for companies to report their views on the agency performance, in terms of the quality of service before and during the review.

Draft Scorecards

SCORECARD ON THE INDUSTRY

- **Expert reports**
- **Application content**
  - Justification of label
- **Appropriate emphasis**
- **Submission tools**
  - Usefulness
  - Applicability to agency preferences
- **Scientific advice**
  - Integration
  - Study design/endpoints/ analysis/GCP
- ***Responsiveness***
  - Acceptance of issues
  - Speed of response
- ***Communication***
- ***Procedural operation***
- ***Performance at Advisory Committee/hearings***
- ***Company vs. industry measure***

Notes

Expert reports: The quality of the expert reports in the submission and the extent to which they addressed the major issues and highlighted them to assist the review.

Application content: The extent to which the applicant was able to demonstrate that the proposed label could be justified in relation to the development programme.

Appropriate emphasis: Whether the reviewer feels that the company drew out and addressed the important issues, placing emphasis on the more critical areas.

Submission tools: The presentation of the dossier, especially in electronic format, and whether it was constructed in such a way that it was useful and amenable to the search engines and search tools used by the agency.

Scientific Advice: The extent to which 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. If advice was ignored, was there adequate justification for not following the guidance that had been given?

Whereas the left-hand column refers to the actual application, the right-hand sets out metrics, some of them subjective, related to the way in which the applicant interacted with the agency during the review process.

Responsiveness: 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.

Communication: The extent and value of the communication between the two parties throughout the review and whether those involved understood, and provided, what was needed.

Procedural operations: Measures of how well the review procedures had been followed and operated, from the regulators perspective.

Representations: 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.

Company versus industry: An assessment of the company's performance both in relation to other applications from the same company and also in comparison to other companies that have made similar applications to the agency.

SCORECARD ON THE AGENCY

- **Relevance of questions**
- **Consistency**
  - Guidelines
  - Previous advice
  - Precedence
  - Procedures
  - Inter divisional / inter agency
- **Scientific advice/ interactions throughout development**
- **Labelling**
  - Science
  - Fairness
  - Procedure for agreement
- **Communication**
  - Appropriateness
  - Responsiveness
  - Access to individuals
- **Professional/scientific competence**
- **Procedural operation**
- **Discussion of different expectations**

Notes

Relevance of questions: A rating of whether questions were targeted on valid issues or were based on a misunderstanding or misinterpretation of the dossier, including the view that certain questions were entirely inappropriate and did not address a particular scientific deficiency in the data.

Consistency: A measure of how consistent the agency was in applying its own guidelines and procedures in the assessment of the dossier and also consistency in relation to previous advice given on similar issues or development programmes and other precedents set when reviewing similar products in the past. In the larger agencies consistency could be assessed in terms of comparison between different divisions of the agency, as well as being a means of measuring consistency between agencies.

Scientific Advice: A measure of the extent of interaction between the agency and the applicant throughout the development process and the way in which advice was given, how appropriate it appeared to be and how amenable to being built into a development programme that could actually be conducted and delivered.

Labeling: Key metrics relating to the extent to which the ultimate labelling decision was driven by science and whether the fairness of the decision and openness of the process was recognised by the applicant. This includes consideration of whether there was ample opportunity for discussion and negotiation between the applicant and the agency in order to decide optimal labelling or whether the applicant was put into a position of having to agree hurriedly on labelling to meet approaching timelines or cycle times.

Communication: The applicant's view of how appropriate the agency's communication and responsiveness was during the review process, including access to individuals in the agency.

Professional/Scientific competence: A metric relating to whether the company felt that the individual agency had the appropriate knowledge and experience in relation to the therapeutic area under consideration.

Procedural operations: The extent to which the agency had followed, rigorously, the procedures that they had laid down, when reviewing the particular application.

Discussion of different expectations: 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 that of the agency.

Implementation

It was acknowledged that the collection of the scorecard data would need to be more than a 'tick-box' exercise on a feedback form although an initial questionnaire would be a practical approach. This would, however, need to be followed up by some formal discussion between the parties to determine why certain items were given high or low ratings and on the items that call for a 'perception' rather than a specific rating.

Key issues for implementation were identified as:

- The ability of parties to be fully forthcoming:
  - Whether companies would feel comfortable criticising agencies and disclosing true concerns when they may have concerns about prejudicing future applications.
- Who should talk to whom?
  - Whether post-review discussions should take place between the individual reviewers in the agency and the project team that put the application together, or at a more senior level in order to remove any personal and 'emotive' elements from the discussion;
  - The recommendation was for discussions at a more senior level.
- Should feedback be private or public?
  - Both private discussions and public disclosure might be appropriate. Where safety issues are involved there is a case, in the interests of transparency and public confidence, for having open discussions on how the issues were resolved. On the other hand the processes that the parties went through to arrive at the outcome could be a matter for closed discussions.
- Participation of other stakeholders
  - An outcome that is acceptable to both regulatory and company parties might not be the best outcome from a patient and prescriber perspective and these other parties could therefore be involved in providing stakeholder feedback in terms of the applicability of the ultimate label in relation to the way it would be used in medical practice and patient expectations.
- Academic exercise or means of continuing improvement?
  - The proposed scheme could involve a large amount of effort for both parties and is only feasible if it can be incorporated in the current review processes. There would need to be continuing review of the resource and time taken in relation to the value it brings in terms of implementing beneficial change.

Pilot Scheme

It was recommended that the CMR Institute should consider, as part of its future work plan, undertaking a pilot study on building a post-review quality assessments into regulatory procedures. This would need to take account of previous schemes that have been undertaken, or are currently being used, by agencies. One of the objectives would be to determine the business case for introducing a routine feedback procedure and looking at the resource implications versus the anticipated value and benefits.

The pilot would need to be carried out on projects that are currently at a late stage of development in order to involve the parties concerned, in a timely manner. The quality review cannot be 'bolted on' retrospectively once the process is finished and therefore this has the potential for a CMR International project no earlier than 2006.

1.2 Other quality-related metrics for future studies

The following topics were also discussed by the Syndicate groups as aspects of the review process that could be incorporated into future studies of the regulatory submission and review process.

End-of-Phase II meetings and first cycle success

It was suggested that a set of metrics should be developed to monitor the reasons that applications fail to be approved in the first cycle. This could then be monitored, over time, against changes in review procedures, particularly the trend towards end-of-Phase II meetings between companies and regulatory agencies.

In discussion of end-of-Phase II meetings it was noted that, currently, the company is the primary driver for setting the agenda for these meetings. With better information on first-cycle success and failure, a more structured 'template' and guidance for end-of-Phase II meetings could be developed. In particular, the future management of safety issues could be addressed at this stage with the early development of risk management programmes and a pharmacovigilance plan that that could be piloted during Phase III.

It was recommended that guidelines were needed for end-of Phase II meetings and that first cycle success rates should be monitored in relation to the advice sought and received before the initiation of Phase III.

Validation and refusal to file

It was suggested that the number and percentage of applications that are refused at the validation stage should be recorded and a more detailed study made of the type of deficiencies that result in refusal to file.

Unanticipated questions

The number of 'unanticipated' questions was discussed as a potential performance metric but the definition might be difficult. Sponsors might be confronted by an issue that they had not anticipated at all, or it might be 'unanticipated' because the agency's view of the magnitude of the problem was greater than the company's. From the agency point of view, it might be an issue that had not been appropriately highlighted by the company, in the submission.

The 'unexpected' should, theoretically, be decreased by better end-of-Phase II meetings and their adoption as routine. The relationship between unanticipated questions and the use of such meetings could therefore be studied.

Metrics related to questions

It was suggested that the number of questions asked by the agency during review could be a metric for measuring the quality of the dossier, but questions would need to be categorised as major and minor. A further categorisation could be whether the data was missing from the dossier or present, but not readily found by the regulator.

Meetings

A metric related to the number of meetings held during development and review was considered but it was not pursued. It was felt that counting the number of meetings with agencies was not a useful measure of whether the company's regulatory department was providing a good service to its management. Any such metric should take account of the quality of the meetings and whether the advice given by the regulators was followed and improved the outcome.

Advisory Committees

It was noted that there appear to be two patterns of use of the US Advisory Committee process: reference to the committee early in the review or at the end, as an appeal body. It was suggested that the impact of advisory committees on review times could be studied, in particular whether there were benefits in having a committee meeting in the first cycle of review.

1.3 Points from the Discussion

Definition of 'quality': This must be the starting point for taking forward the recommendations for future studies relating to the quality of dossiers and of the review process. The concept of 'meeting customer expectations' should be re-visited, but other factors, in today's environment, include the transparency of the process and the willingness of both parties to enter into constructive dialogue to solve labelling issues on a sound scientific basis, taking account of the public health obligations of the agency with the commercial viability of the product.

Priorities and the level of detail: It was agreed that the 'scorecard' proposal would only be feasible if the number of items was confined to the essentials. The Syndicates had proposed comprehensive lists of topics but these would need to be refined, even before a pilot study was undertaken. On the other hand, the concept of looking at a 'global' assessment of the procedures was rejected since the real value of the project is in the detail and being able to identify the pieces of the process that worked well, rather than an overall scoring system.

Study objectives: It was suggested that any study based on a scorecard approach should be designed to allow comparisons of the assessment of similar applications across different agencies. It could also explore the frequently-implied assumption that poor quality applications are more likely to emanate from smaller rather than larger companies.

Current feedback on applications: It was noted that the EMEA Centralised procedure already includes feedback on the quality of the application. The review template includes a check lists on the quality of the dossier which is completed at the 70-day point (preliminary assessment report) by the Rapporteurs and at 150 days (preliminary conclusions) there is a report on the quality of the company's response to questions. Feedback is provided to companies at these two points and, at the annual meeting with the European industry association, EFPIA, there is an opportunity to discuss overall performance rates and levels of satisfaction with the review system.

2 BUILDING ON CURRENT METRICS AND INFORMATION

2.1 The CMR International Institute Benchmarking Study

General Observations

The benchmarking study has focused primarily on timelines for the review process and is unique not only because the data has been predominantly provided by the regulators themselves, but also because it analyses and compares the times for different stages in the review process and allows more perceptive comparisons to be made between the different processes. The survey started at a time when there were concerns about delays in regulatory approvals and the lack of transparency in the processes and spans a seven-year period that has seen approval times reduced and transparency increased.

It was agreed that the study was extremely valuable and should continue. It was recognised that the Institute and participating agencies might wish to modify the study design, especially in view of the increasing availability of data on the Internet, but it was emphasised that the focus should remain on overall review times and identifying the success factors and impediments to achieving an optimal label within realistic timelines.

It was hoped that the continuing study would include data that had been missing from the current study:

- Data from Japan
- Data on biotech/biological products from the USA (CBER applications)
- Data on all applications submitted to the EU centralised procedure (the current study does not cover withdrawn and refused applications)
- Data on applications for new chemical entities processed through the EU Mutual Recognition Process (MRP)

The ongoing study, regularly updated and published will be a considerable asset to companies in predicting the timing of reviews by different agencies. It should also provide valuable support for agencies when discussing resources and procedural changes needed to improve the efficiency and effectiveness of the review process.

Further harmonisation of metrics between agencies

The review 'milestones' used for the Benchmarking study were examined and consideration was given to whether further harmonisation would be useful, for example of the way authority time is measured (review versus administrative time) or by adopting a more uniform way of measuring company response time to questions. It was agreed that it would be unrealistic to expect actual procedural changes, especially where there might be legislative implications.

The comparative metrics are useful for identifying bottlenecks in the procedures and providing a basis for discussing best practices to overcome unnecessary delays. A convergence of business practices, leading to the goal of efficient and timely reviews is a more feasible goal.

Post Authorisation delays

The current study measures the time from filing the application to receipt of an authorisation to market. From the company perspective, however, the most valuable endpoint is the date on which the product can actually be marketed. Post-authorisation delays in effective marketing can be caused by:

- Reimbursement negotiations;
- Listing in relevant drug formularies;
- The need for the legal status (i.e., prescription only) to be established;
- Clearance of promotional activities, e.g., DDMAC approval in the USA

It was recommended that these potential delays should also be monitored in future studies

New drugs approved by all five agencies

It was recommended that the cohort of 29 new active substances that had been reviewed and approved by all five agencies, within the time limits of the study, should be examined in more detail to evaluate the impact on timelines of such factors as:

- Scientific advice, the timing (e.g., end of Phase II) and the extent of follow-up advice
- Orphan status
- Degree of innovation (see below)

Labeling: A study could also be carried out to compare the indications, dosage, target patient population and contraindications agreed in the final labeling by the different authorities.

Comparison by level of innovation

It was suggestion that the products in the study should be categorised by the degree of innovation to see if this could be correlated with differences in review times. Examples include:

- First in class, second in class or additions to an established therapeutic category;
- Products of new biotechnological or other scientific developments;
- Products eligible for orphan status.

Simultaneous submissions

It was recommended that submissions should be regarded as 'simultaneous' if they were submitted to more than one agency within six months. Further analyses could be carried out on simultaneous applications made to three or more agencies in order to compare:

- Review times, number of review cycles and outcome

  in relation to:

- Whether scientific advice was sought and followed or ignored

Exchange of reviews

It was suggested that data could be collected on the exchange of information and reviews, between regulators, particularly for non-simultaneous applications. This could provide a metric for measuring the impact of confidentiality agreements on the communication between agencies and, ultimately, on review times and outcomes.

Line Extensions and Supplemental applications

With the diminishing number of applications for new molecular entities, companies are looking to maximise product use and revenues through line extensions into new therapeutic uses and dosage forms. As a consequence, regulators are increasingly involved with the review of major variations and supplemental applications. It was therefore suggested that the benchmarking study could be extended to include metrics for such applications, especially as information is not readily available, in the public domain.

Participants were, however, informed that this had been the intention when the study was first proposed but that it had been agreed that this provided too great an additional workload on the participating authorities.

CLOSE OF MEETING

Closing the Workshop, Professor Stuart Walker, President and Founder of CMR International thanked participants for their contribution to the discussions. The report of the CMR International Institute Benchmarking Study had not yet been released for circulation beyond the Institute's Advisory Board but a paper on the study would be submitted to a peer-reviewed journal early in 2005. The future of the study was still under consideration and the views from the Workshop would be taken into consideration by the Board.

The Workshop recommendations for looking at quality issues in relation to submissions and regulatory processes were particularly timely in view of the forthcoming Institute Workshop on Quality, in December 2004.

[1] A report on the CMR International Institute project 'Benchmarking the regulatory review process: A study of major regulatory authorities' was presented to the Workshop by Dr Neil McAuslane (see Section 3 page 2)

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Workshop Report

SECTION 3: SUMMARY REPORT OF THE WORKSHOP PRESENTATIONS

PROGRAMME

SESSION 1: CURRENT BENCHMARKING EXPERIENCE

SESSION 2: SYNDICATE DISCUSSIONS ON BENCHMARKING FOR TOMORROW

SESSION 3: BENCHMARKING AND BEYOND

[1.] Paper prepared jointly by the authors and presented by Dr McAuslane

BENCHMARKING REGULATORY REVIEW PROCESSES

Dr Neil McAuslane
Chief Scientific Officer, CMR International Institute

Dr Neil McAuslane opened his presentation by acknowledging the contribution of the five regulatory agencies (*Box 1*) that had participated in the study for the past seven years and the work of Dr Mayu Hako, CMR International Institute, in preparing the report of the study. Although Dr McAuslane presented data from the report to illustrate his presentation, these data could not yet be released to participants, as the report had not been finally cleared for wider release, by the contributing agencies.

Background to the Benchmarking Study

Describing the history of the project as 'a journey' Dr McAuslane explained how the design of the study had evolved in discussion with, initially, ten regulatory authorities, starting in 1996. The 'classic' study for comparing regulatory processes, he said, looks at overall median review times from the time of receipt of the application to the date of approval. This can produce information on trends and show the impact of significant changes to the regulatory process. Dr McAuslane illustrated this with data on mean approval times from 1992-2001 that showed, for example reductions in the review times in Canada and the USA, following the introduction of user fees, and a considerable improvement in times for Australia following adoption of the Baum report.

It had been agreed, however, that the CMR International Institute study should extend beyond overall review times and look in more depth at the individual stages in the different processes followed by the agencies.

Box 1

Benchmarking Study

Participants:

USA: Center for Drug Evaluation and Research - CDER

EU: European Medicines Agency - EMEA (Centralised Procedure)

Australia: Therapeutic Goods Administration

Canada: Therapeutic Products Directorate, Health Cananda

Switzerland: Swissmedic

Study Objectives:

- To encourage systematic measuring of the processes which occur during the review of new drug marketing authorisations;
- To accurately compare the processes used in the review of new drug marketing authorisations;
- To provide benchmarking data which can be used to define performance targets and focus on ongoing performance improvement initiatives

History

Dr McAuslane outlined the history of the project:

1996 – 1998: CMR International and 10 major international regulatory authorities worked together to achieve an understanding of the different processes employed by individual authorities, highlighting the areas of the review which the authorities considered particularly important;

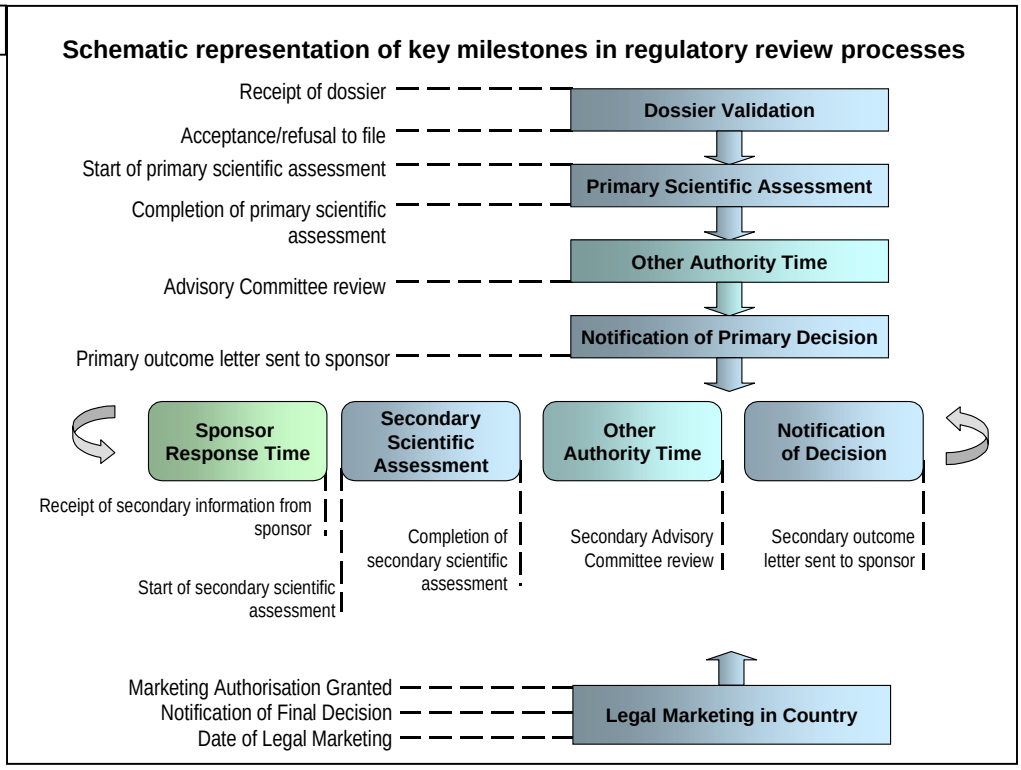
1999 – 2002: The initial data collection from the five agencies (*Box 1*) for applications submitted 1 January 1997 to 31 December 1998, was carried out on a prospective basis to test the methodology and to provide a baseline of data for comparisons to be made in future years. The study was completed in February 2002 and results reported back to participants;

2003-2004: It was agreed, in 2003, that the study should be updated to include compounds submitted to the authorities from 1 January 1999 to 31 December 2002 with outcomes through to July 2003.

Methodology

The study of the different procedures followed by the agencies enabled key milestones to be identified that could form the basis of a comparative benchmarking project. These are identified in *Figure 1* and allow each application to be tracked from submission of the dossier, through its scientific review to the notification of the decision.

Figure 1



Referring to this schematic representation, Dr McAuslane noted that the preliminary decision, after scientific assessment, can be an approval, rejection or a notification that there are questions to be answered ('approvable' letter in the USA). In the case of additional data being required the application is recorded as entering a second review cycle. The EU Centralised Procedure, however, is designed on the premise that there will always be a 'list of questions' (at day 120 in the process) for all applications and therefore, as he showed in data presented later, almost all EU applications are counted as being subject to more than one review cycle.

Data collection

Data was collected according to the year of submission of the application rather than by the year in which the review of the application was completed. Dr McAuslane explained that this decision was made on the basis that collection by year of submission allows cohorts of compounds to be tracked prospectively to approval, rejection or withdrawal and also means that the compounds will have been submitted and reviewed in the same regulatory environment, which is important when studying time-related trends and the impact of major regulatory changes.

The inclusion criteria for products in the study is given in *Box 2*. CDER, Health Canada, Swissmedic and TGA provided the dates on which each application in the study reached the different milestones. For EU applications, however, EMEA was unable to provide data on applications that were withdrawn by the sponsor or rejected, and information on approved applications had to be extracted, by CMR, from the European Public Assessment Reports (EPARs) published by EMEA. Furthermore, the EU data relates only to the Centralised Procedure and does not capture products registered through the Mutual Recognition Process (MRP).

The total number of applications included in the study was just over one thousand.

Analyses of data

Dr McAuslane outlined the different aspects of the data that had been analysed and presented in the 185-page report that was, at the time of the Workshop, still being reviewed by the regulatory agencies. These included the following:

Characterisation of applications

The active ingredients of the products in the study were characterised as chemical entities, biotechnological substances and biologicals, the majority being chemical entities. As noted, however, products reviewed by CBER were not covered and the data from Switzerland did not include vaccines.

Other characteristics that were recorded included whether applications were classified as benefiting from expedited review and whether there had been pre-submission dialogue with the agencies. On the latter point, Dr McAuslane noted that the EU Centralised Procedure includes a pre-submission consultation for all applications, on administrative matters, but, for the purpose of the study, the information was restricted to Scientific Advice, and only where this was recorded in the EPAR.

Box 2

Inclusion Criteria

Any **new active substance** (NAS) that has not previously been approved by the authority in question, where a NAS includes

- chemical, biological and radiopharmaceutical substances that have not been previously available for therapeutic use in humans to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.
- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available;
- A biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process;
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available

Outcomes and approval times

In addition to overall timelines and outcomes, the study had tracked the time taken for each application to pass through each stage of the review process, between the milestones identified in Figure 1. In discussing the findings, Dr McAuslane made the following points:

- Very few applications are rejected at the validation stage ('refusal to file').
- When the percentage of applications approved, rejected or withdrawn are calculated for products that reached a *final outcome* by 31 July 2003 the approval rate for TGA, Swissmedic and Canada is similar whilst CDER appeared higher. This could be explained by the FDA practice of allowing products to remain in the system following a 'non-approvable' letter and being recorded as 'ongoing' rather than having reached an outcome. CDER rarely, if ever, reaches a rejection for an application. (The calculation of percentage outcomes was not relevant for EMEA applications as the study was restricted to approved applications for the EU).
- When the median and the range of overall approval times are compared, by year, for the different agencies, the impact of the statutory time limits for reaching a decision, in the TGA and EMEA procedures is notable. There are fewer outliers and the difference between the fastest and slowest approval is far less than for the other agencies. The wide range of approval times found with, for example, CDER, also reflects the two communities of application: those undergoing standard review and those that are expedited.
- The methodology for the study allows the length of the different stages between the milestones set out in *Figure* 1 to be studied and compared, and the following were noted:
  - The mean delay from receipt of the dossier to start of the scientific assessment was almost 200 days for Canada, at the time of the study[1], but only a single day for CDER. In Canada,

[1] See presentation by Dr Robert Peterson, Section 3 page 22, for information on changes to this situation

applications are picked up when resources become available but in the US the procedure lets the validation be carried out in parallel with the assessment, and allows 60 days for a refusal to file.

- In Switzerland there is a noticeable time lag between announcing the outcome of the review and issuing the licence to market, whereas in the US and Canada the outcome letter and marketing authorisation are synonymous. The lag in Switzerland reflects the procedure whereby label negotiations only take place after the decision, in principle, has been made to approve the application[2].

Box 3

'Clock stop' (Sponsor time)

TGA: Tracks clock stop both within the review process (when an application is on hold, waiting for a company to respond to questions raised informally) and between review cycles. Both these times have been included in this study

Health Canada: Only formally tracks clock stop time between review cycle. Health Canada seek information from companies during the review using *Clarifaxes*, but no clock stop time is measured during the review. This study only includes between review cycles clock stop.

Swissmedic: Tracks both company time during the review and between cycles, both sets of time are included in this study.

CDER: Seeks information during the review but only the time between review cycles is counted as clock stop

EMEA: All time taken for sponsors to answer the consolidated list of questions between review cycles is counted as clock stop in this study.

Sponsor time (Company response time)

One of the key differentials, when looking at mean review times, is the division between 'authority time' and 'sponsor time'.

Dr McAuslane explained that the methodology for the study allowed differential analyses to be carried out and these had highlighted major differences in the way that sponsor time is recorded by the authorities, as shown in *Box 3*.

In the EMEA Centralised Procedure there is a routine 'Consolidated list of questions' and clock stop bult into the process. For TGA and Swissmedic it is less formalised but both can stop the 'clock' during scientific assessment whilst they wait for answers to questions. Health Canada and CDER have the ability to ask questions during the scientific assessment, without interrupting the review, and in Canada, if answers to requests for information ('Clarifaxes') are received within 15 days, the sponsor time is not recorded. As a result, the sponsor time for applications to Health Canada was noticeably and consistently lower than for other agencies.

Impact of pre-submission dialogue

Dr McAuslane provided data on applications submitted to each of the five agencies between 1997 and 2002 which compared the median approval time with and without pre-submission advice from the agency. The comparison could not be made for applications to CDER since all products were subject to pre-submission advice. For Australia, Canada and the EMEA the median approval time appeared slightly shorter where pre-submission advice had been given but the proportion of applications receiving such advice was small for both TGA and the EMEA. For Switzerland there was a marked reduction in median approval time where advice had been given but other factors, such as expedited review, might be the driver in many of these cases.

Same products approved by different agencies

Although the data in the report is blinded with respect to the identity of products, information on the companies and active ingredients was provided by the agencies for authorised products, which allowed products that have been submitted to, and approved by, more than one agency to be tracked. Out of the total number of applications in the study, there were 144 such products had approved by two or more agencies. Of these, 29 had been approved by all five agencies and Dr McAuslane described ways of looking at comparative data between these compounds.

[2] See presentation by Professor Samuel Vožeh, Section 3 page 17, for further details

The different agencies' review times (split into authority time and sponsor time) had been compared for the same products and the results also enabled the sequence for submitting the applications and the time lag between submissions to be studied. In some cases the impact of expedited or accelerated reviews were apparent from reduced review times, but this also raised the question of why the same application was treated as priority by some agencies but not by others. This could reflect different rules between the agencies, or could mean that the company had not applied for an expedited review in some countries.

Dr McAuslane commented that further in-depth analyses could usefully be carried out on this group of 29 compounds,

In conclusion

Summarising, Dr McAuslane observed that the study, using methodology based on common, agreed milestones, has provided a basis for a detailed analysis of the timelines for review and approval of submissions made to five authorities between 1997 and 2002. The unique methodology has enabled comparisons to be made both within agencies and between different authorities and has identified differences in the length of time that applications spend in different stages of the review as well as highlighting differences in activities and the order in which they occur.

The study has, however, only evaluated time and does not include any information related to the quality of the review. Dr McAuslane also noted that the study had not covered resources or the variation in the content of applications sent to different authorities within the same time-frame. All of these would help to place the results in full context.

Concluding, he expressed the view that the value of the study was that it:

- Identifies major differences in the processes involved in reviewing new drug applications at five major international regulatory authorities;
- Allows authorities to assess their own cycle time performance compared with other authorities;
- Provides a baseline against which the impact of changes can be measured;
- Allows participants to focus improvement initiatives and set realistic targets
- Facilitates detailed internal discussion within the agencies on reviewing their regulatory processes.

MEASURING PERFORMANCE IN EUROPE
Experience of collecting and analysing key performance metrics

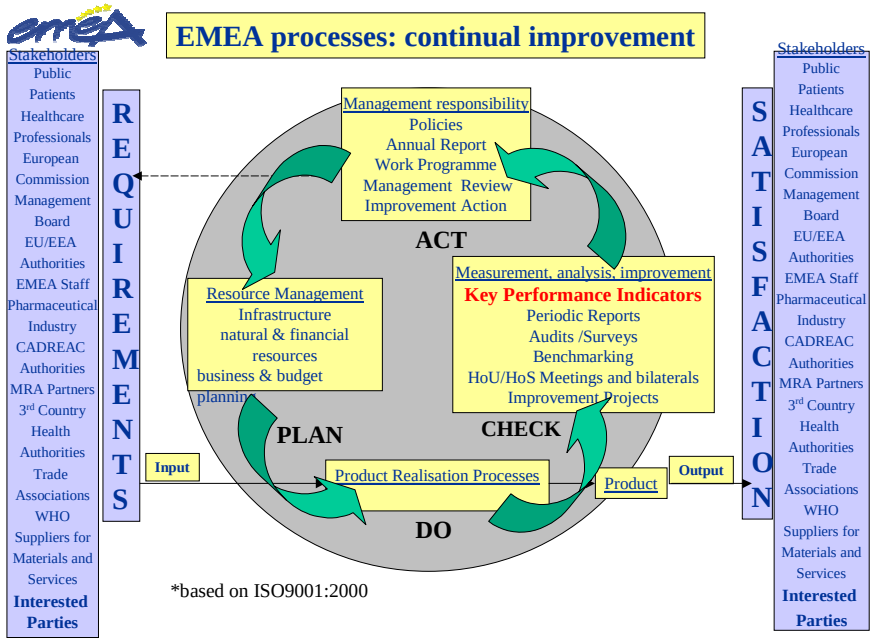
Dr Bo Aronsson
Principal Scientific Officer, EMEA, EU

Introducing his presentation, Dr Bo Aronsson said that he would be addressing the question of measuring performance in Europe from two angles. First there was the recent experience gained in Europe from the enlargement and the benchmarking activities that took place in that context. Secondly there are some particular performance metrics that can be studied in the context of the scientific assessment and the 'gap' between the expectations of industry and regulators.

Quality Management

Performance indicators, suggested Dr Aronsson, need to be viewed in the wider context of quality management, The illustration of the implementation of quality management systems (QMS) by the EMEA are illustrated in the cycle for continual improvement (*Figure 1*) adapted from the ISO 9000 document. Key features of this are that the stakeholders' requirements and expectations (left hand side) drive the process and the objective is to capture the satisfaction of those same stakeholders, as illustrated on the right of the diagram. Performance is measured and analysed not only through the identification of key performance indicators but also through periodic reports, audits and surveys and benchmarking activities.

Figure 1



Special features of the EMEA

Dr Aronsson stressed that the particular and unusual features of the EMEA need to be understood when discussing QMS. It is not a single administration on the FDA model but it operates through decentralised networking. The network is currently made up of 42 agencies covering both the human and veterinary medicines. The Agency acts as the service provider for the network when it comes to IT and databases and it also has a pivotal coordinating role, for example for the Centralised Procedure, inspections and pharmacovigilance.

In addition, the EMEA has a 'contractual' relationship with national agencies in the network when it appoints *Rapporteurs* and delegates the assessment of applications.

Current challenges

The main challenges facing the EMEA are:

- Implementation of the new European pharmaceutical legislation;
- Enlargement of the European Union.

The primary objective of the EMEA, Dr Aronsson said, is to be successful in managing these challenges.

Referring to the EU expansion, he reminded participants that in 1995, when the EMEA was established, the membership of the EU increased from 12 to 15 states, with Sweden, Finland and Austria joining. In the major expansion of May 2004, ten states had joined, made up of countries from central and eastern Europe, Malta and Cyprus, and the total became 25. In 2007 it is anticipated that Romania and Bulgaria will join, bringing the membership to 27 with a total population of over 400 million.

For the EMEA to be successful, in the face of this expansion, it must maintain an operational network that can carry out the necessary assessment work and this needs to be developed in accordance with the principles of good governance and integrated quality management (IQM).

One of the immediate results, Dr Aronsson reported, is that work has started on auditing the scientific committees. The first audit of the Committee for Human Medicinal Product (CHMP, formerly CPMP) took place in 2003 and an audit of the veterinary committee had recently

commenced. Another resulting action is a plan for benchmarking all EU regulatory national agencies and training for this has begun. In this context key performance indicators will be developed and Dr Aronsson referred to an early draft which identified 13 key performance metrics and posed over 70 questions. He described the project as a 'holistic, long-term approach which is based upon self-improvement and sharing of best practices following IQM methodologies'.

Pan-European Regulatory Forum

Taking a step back to the beginning of the millennium, Dr Aronsson discussed the work of the Pan-European Regulatory Forum (PERF) which was set up to prepare the accession countries for entry into the EU. EMEA was responsible for coordinating activities and, in mid-2000, discussions started on a self-assessment questionnaire to be used for a benchmarking exercise. The objectives were:

- To enhance the implementation of an integrated quality management system;
- To ensure good regulatory practices in the EU;
- To facilitate harmonisation, consistency and best use of resources;
- To provide a target for training participating quality professionals in the EU and accession countries.

Based upon ISO 9004:2000 (*Quality Management Systems – Guidelines or Performance Improvements*), the questionnaire focused on managerial aspects of the agencies' activities but there were also some priority action areas related to dossier assessment and pharmacovigilance for which more specific questionnaires were developed. A number of benchmarking visits started in 2002 and a database was established.

Methodology - rating

Maturity level	Performance level
1	No formal approach
2	Reactive approach
3	Stable formal system approach
4	Continual improvement emphasised
5	Best-in-class performance

Dr Aronsson described the benchmarking project undertaken in 2003, under PERF III, which involved visits to 17 agencies by a small team of quality professionals sourced from EMEA, EU member states, the European Council and candidate countries. The areas that were assessed were scored using the ISO scale for measuring maturity level shown in the box and he provided an overview of the subjects that had resulted in the highest average scores:

Management responsibility	3.2
Work environment	3
People	2.9
Information	2.8
Needs and expectations of interested parties	2.7

Future for benchmarking

Dr Aronsson reported that the benchmarking exercise for EU accession countries had been greeted with enthusiasm, not only by the countries in question but also by other EU member states and the European Council. It was concluded that benchmarking is an essential tool for achieving and maintaining continual improvements in quality management processes within the future EU and that all member states should be involved. This has now been agreed by the heads of agencies with the UK and Germany taking the lead.

He referred to the EMEA 'roadmap'[3] which sets out the vision for pharmaceutical regulation to the year 2010 and specifies the need for a 'regular cycle of benchmarking to achieve a strengthening of the QA system …of all European Regulatory agencies'. Other relevant quotes from this

[3] 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

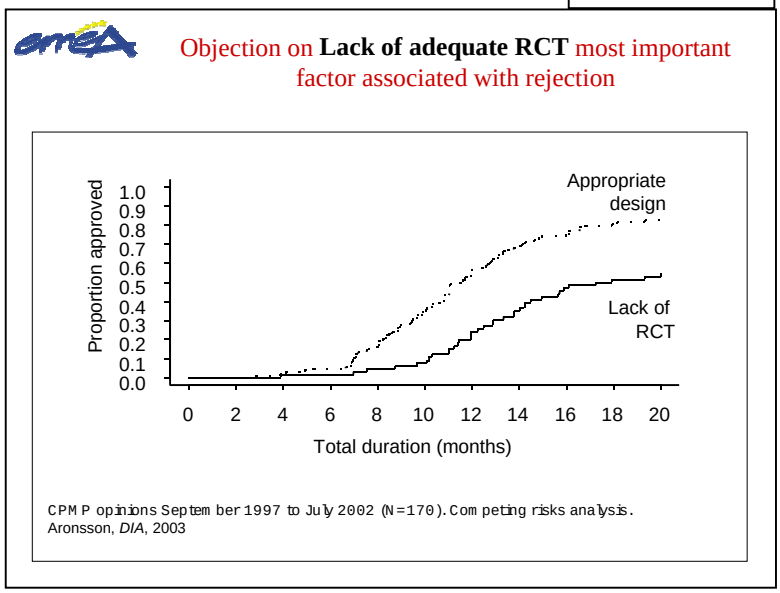
publication were that 'The EMEA will have to demonstrate that after the enlargement, the networking agency is still able to perform competently…' and 'Contractual arrangements should include…detailed indicators to measure the quality of the work undertaken by the selected providers…'

Key performance metrics for the review process

Turning to the question of specific performance metrics for the submission and review process, Dr Aronsson discussed two examples.

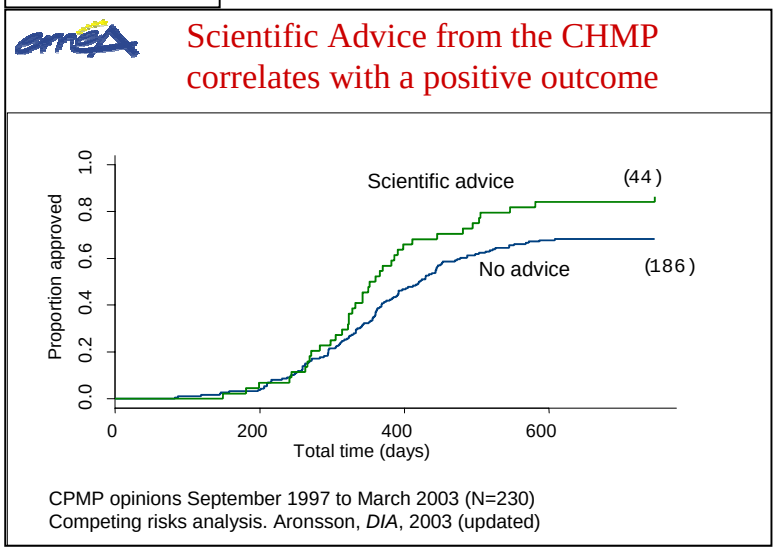
Firstly, the failure rate for applications (negative opinions or withdrawals prior to such an opinion) were examined in relation to the major objections by the scientific committee. It was found that the most important factor in terms of the probability of a successful application is whether or not the clinical data follows an appropriate design, in particular that the lack of randomised, controlled clinical trials (RCT) reduces the probability of approval significantly, as shown in *Figure 2.*

Figure 2



Dr Aronsson also provided data showing the impact on review times of the number of major objections raised during the review. The study covered 165 applications with positive outcomes that had been received after July 1997 and tracked through to July 2004. For products with no major objections (n=44) the average time to determine the application was about 250 days but this increased to over a year for applications with between one and four major objections (n=92) and applications with over five major objections (n=29) took more than 400 days to resolve.

Figure 3



A further correlation related to scientific advice and the probability of approval of the application. 44 applications that were preceded by scientific advice were studied and the results (*Figure 3*) indicated 85 –90% approvability for applications with scientific advice versus 60 percent without. It is therefore somewhat surprising, Dr Aronsson remarked, that scientific advice is only sought on some 30% of applications. He also commented that there was a lack of feedback from companies on the impact that scientific advice has on their development programmes.

Summary

In conclusion, Dr Aronsson summarised the European approach which is to use benchmarking of performance indicators to set standards and define opportunities for improvement. The indicators

that are being developed are key performance indicators and are substantiated by sub performance indicators with some quantitative measures. These form part of the QMS benchmarking activity that will start, in the near future, in order to improve the organisation throughout the EU. He also noted that the EMEA would be measuring more defined performance indicators in order to monitor the 'science gap' that exists between the applicants' anticipations and the regulators' expectations.

IMPROVING THE REGULATORY REVIEW PROCESS*:*
What are the key factors for companies?

Dr Joseph Lamendola
Vice President, Global Regulatory Sciences, Bristol Myers Squibb, USA

In his presentation Dr Lamendola examined the different parts of the development continuum in order to identify areas where benchmarking might help to streamline development and enhance the agency review and approval process. This review was not intended to be exhaustive but should be viewed as a starting point to stimulate creative thinking on how to move forward, whilst viewing the subject, in a collaborative manner, from 'both sides of the fence'.

The challenge of identifying the key benchmarking factors for companies is a daunting one, he commented, in view of the way that previous attempts to predict the future have turned out. He looked back to the time of the implementation of the FDA Modernization Act (FDAMA) some seven years ago. Many had been excited by the Act which was a product of industry, academia and FDA and was designed to enhance public health and bring the promise to patients of early access to safe and effective medicines.

The belief, at that time, was that robotic chemistry and streamlined discovery were going to create a massive rise in the number of new drug applications and many wondered how the health agencies would be able handle the dramatic increase in the number of new chemical entities that was expected. ICH had also been making major progress in regulatory harmonisation and companies were poised to 'ratchet up' investment in Research and Development.

Dr Lamendola suggested that we need to question why the promises of that time had not all been realised and what could be learnt from the past. 'What should we measure', he asked, ' to enable us to be more successful in the future?'

Investment in R&D

The predictions about increased investment in R&D were, indeed, correct, Dr Lamendola noted, referring to the doubling of NIH and pharmaceutical research budgets since 1995. The frequently-quoted Tufts analysis showed an increase from US$ 400 million to develop a new drug ten years ago to the current figure of US$ 800 million, with 50% of the development costs in Phase II and III.

Predictions of globalisation had also been correct, with most large PhRMA companies, over the past 5 to 10 years, setting a goal of simultaneous submissions all over the world. Spend was considered acceptable to meet global requirements. For example, it was common practice to conduct clinical studies for the FDA that were placebo controlled and also conduct comparator studies for Europe. Sponsors did not appear to question the value of duplicating these studies but tailored their research to meet regional regulatory requirements in order to submit applications almost simultaneously in both Europe and U.S. with a subsequent submission to Japan.**Falling output**

Attrition -- FDA's Metric

- Approvals of new drugs and biologics are at the lowest level in 10 years
- NCE approvals are down 50% from 1996
- Numbers of new biologics are also significantly lower
- 50% of Phase III studies fail

The conundrum that must now be faced is that the agencies

have not, during this time frame, been 'bombarded' with a flood of applications for NCEs, in fact, as shown opposite the number of new applications decreased significantly during this period of predicted growth.

This begs the question, suggested Dr Lamendola, of whether the current process, with the substantial increase in development costs, is sustainable and whether sponsors will need to move to more sequential development.

He believed, however, that industry was on the cusp of enabling technologies that will allow a new approach to development and it needs to be poised to take advantage of the opportunities these new technologies will provide. He noted that FDA has begun the process under the banner of the Critical Path Initiative[1] and suggested that there are metrics that could be considered to help meet the challenges.

Clinical Development

When initiating the development of a clinical programme sponsors are faced with several issues. Primary emphasis is on strategic design based upon:

- Agency interactions;
- Therapeutic guidances;
- Scientific Advice and
- Efficacy and safety considerations learned as the program moves forward.

As sponsors attempted to develop a global programme, they are often faced with inconsistencies in different geographical areas. This, Dr Lamendola suggested, could be one of the reasons why simultaneous submissions have seemingly fallen by the wayside. In addition, the increased expense cannot be overlooked. Perhaps a metric to establish the impact of such differences could lead to more harmonisation within therapeutic areas that could, in turn, lead to more streamlined development programmes. In any event, Sponsors need to benchmark their successes and failures as a result of their process of selecting compounds to move forwards and, in particular, their criteria for dose determination.

Dr Lamendola was of the view that the Critical Path Initiative in the US represents an exciting opportunity for collaboration between FDA and sponsors to bring medicines to patients faster. Action would, however, be needed to benchmark the differences between the US and the rest of the world as result of implementing the Critical Path Initiative. We should continue to do all that we can to maintain harmonisation.

Chemistry Manufacturing and Control (CMC)

Dr Lamendola noted that much has been achieved, and was in progress, to increase harmonisation in the CMC arena. There remain, however, apparent differences in interpretation when it comes to levels of drug product impurities and/or degradation products and the toxicity studies that may or may not be needed to support these findings. In addition, the setting of specifications can vary from region to region.

The extent to which these have an impact on drug development and on the product that eventually reaches the patient could provide areas for evaluation in future benchmarking studies, he suggested.

International Conference on Harmonisation (ICH)

Another potential area for study would be the impact of ICH. Much has been done over the last several years to harmonise requirements for quality, safety and efficacy, through ICH, but there remain significant differences in approach between regulators when it comes to the ultimate review and approval of new medicines. Dr Lamendola suggested that it might be useful to assess the implementation of the ICH guidelines in order to identify the gaps that may still exist, regionally, and to look at opportunities for further improvement and streamlining.

Summary

Dr Lamendola concluded that there are several areas that should be benchmarked with a view to producing more global consistency in development programmes. These include:

- Evaluation of CMC regulations;
- Clinical development guidelines;
- Interactions between Sponsors and Agencies;
- New Procedures resulting from the Critical path Initiative;
- Preclinical issues such as the interpretation of carcinogenicity results.

> "We are living in a truly remarkable era in science and in medicine… Enabling these safe and effective new medical technologies is a fundamental part of FDA's principle mission—to protect and advance the public health."
>
> *Dr. Mark McClellan, former FDA Commissioner*

He believed that these areas represented a good start and should lead industry and agencies jointly to improve the efficiency and timeliness of bringing new medicines and treatments to patients.

SESSION 1, PART 1: POINTS FROM THE DISCUSSION

CMR SURVEY

Post-authorisation withdrawals: The study had only tracked products from submission to authorisation and not beyond. There was no correlation, for example, of review times and subsequent withdrawal of products from the market, and the rate of such withdrawals would, in any case, be too low to support any meaningful conclusions.

Number of review cycles: It was noted that the number of review cycles is not necessarily related to the overall review times. Although the smaller agencies try to complete their reviews within a single review cycle, they can still have longer median approval times than FDA and EMEA which may have multiple review cycles but deal with the scientific review and questions in a shorter period.

EU QUALITY MANAGEMENT

Performance indicators for the quality of review: The EMEA is putting together operating procedures and criteria to be fulfilled during the peer review phase between the *Rapporteurs* and other CHMP members, in order that comments are not 'random' but are more targeted, in order to trigger improvements.

Lessons from benchmarking: Dr Aronsson suggested that one of the most important outcomes from the quality benchmarking initiative was the impact on the people involved, within the network of EU agencies. Ownership is particularly important such exercises and the contribution of individuals is the ultimate key to success.

GENERAL POINTS

Scientific Advice: There was a suggestion that a study could be carried out on failed applications where scientific advice was *not* sought to see whether the reasons for failure correlate with the types of questions covered in scientific advice on similar, successful applications. One concern is that the advice being sought in the early days of the procedure is too narrow.

National *vs* EMEA Scientific Advice: A low percentage of companies (30%) take advantage of the EMEA Scientific Advice procedure, whilst national advice is sought to a greater extent. It was suggested that that one advantage of national advice was speed, but another reason may be that companies, from experience, are often comfortable with the soundness and consistency of advice from particular national agencies and will only seek EMEA advice if they encounter a conflict.

ICH guideline implementation: Views were expressed that differences between Europe and the US with respect to the acceptability of clinical programmes and endpoints were a major concern and also that interpretation and implementation of guidelines could be dependent on differences in the opinions and backgrounds of individual reviewers. There were concerns about topics that had not yet been addressed, for example, differences in therapeutic guidelines and the determination of primary endpoints in clinical study design.

Differences in medical practice: With the range of existing treatments and diagnostics available in different parts of the world, problems can be encountered when clinical studies are carried out against comparator products that are not available on the market of the country in which registration is being sought. The problem may be exacerbated in future as economics become and increasingly important issue and agencies will be looking for comparisons with products that fall within current government healthcare systems.

DRIVING REGULATORY PERFORMANCE: BENCHMARKING PLUS

Dr Sandra Kweder
Deputy Director, Office of New Drugs, CDER, FDA

In her presentation, Dr Sandra Kweder discussed the drivers for improving regulatory performance from the perspective of the Director's office ('driving from 50 feet above the ground') and from the perspective of those 'closer to the road' who run the Divisions within the Office of New Drugs (OND) as well as the reviewers themselves. The key drivers that she identified included:

- The Prescription Drug User Fee Act (PDUFA)
- Good Review Management Principles (GRMP)
- Quality systems
- The FDA 'Critical Paths' White Paper[4]
- Keeping abreast of scientific developments
- The tools required to do the job

[4] 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

Prescription Drug User Fee Act

The implementation of PDUFA, Dr Kweder said, marked the beginning of both FDA and sponsors having to be more accountable and to work within specified timelines and goals. Before the implementation of PDUFA 1, in 1992, she recollected that there was no obligation on the part of reviewers to process applications within time limits, but applicants were equally lacking in discipline and might produce a major additional study, without prior notice, when the reviewer's assessment was at an advanced stage.

Since 1992, graduated performance goals have been introduced that have 'revolutionised' FDA's approach to the review process and building quality into the procedures. This has also been facilitated by the additional resources brought in by the Act. The initial goals, Dr Kweder noted, focused almost exclusively on speed and the idea of bringing new drugs to the market more rapidly and making them available to the population.

The second round, whilst retaining these public health goals, introduced additional objectives for helping industry to reduce development times by formalising the interactions between companies and the Agency. These included putting in place goals on the management of meetings, the time taken to schedule a meeting and the procedures for clearing the minutes. Other items included working with companies on clinical hold issues, and the time taken to review special protocols.

PDFUA 3 did not change the goals themselves but focused on refining the numbers and adding qualifiers to enhance the process. In particular, Dr Kwerder noted that it allowed user fee resources to be used for post-marketing concerns, thus giving the opportunity for FDA to consider the whole spectrum of development up to and beyond the actual approval day. It also enabled FDA to introduce the process of 'continuous marketing applications', in which they work with the company through frequent meetings at milestones in the development process, as part of the concept of a 'rolling review'.

PDUFA 3 also provided the stimulus for building quality into the review process through the formalising of Good Review Management Principles, as described later.

Management Tracking Tools

The development of tools for tracking progress and performance has been essential for the implementation of PDUFA, Dr Kweder said. In the beginning, only the upper management of CDER was involved in collecting information on how well the goals were being met. Tracking tools have, however, been developed that involve workers at all levels and provide regular updates, on a monthly basis, from all of the 17 clinical divisions within OND. This provides information on the applications and supplements that are pending and their goal dates. It provides managers with a break-down, for the year-to-date, on the percentage of applications reviewed within the PDUFA goal dates, the number that were first cycle approvals and those involving multiple cycles. Directors are able to see whether their divisions are meeting management goals and makes them accountable at the Office level for reporting on any problems and how they will be rectified.

Good Review Management Principles

Guidance on GRMP was published in draft in 2003 and a final version is reaching completion. Whilst the focus has been on meeting timelines and goals it is important not to overlook quality and consistency in the decision-making process. 'Faster is not necessarily better' Dr Kweder warned. GRMP was designed to address variable practices within FDA and in the agency's interactions with industry.

She suggested that one of the most important roles of GRMP, as an extension of benchmarking, is to try to establish expectations for both FDA and the industry with regard to interactions at critical points during development as well as during NDA reviews. Whilst some of the items included in the guidance may appear 'quite mundane', everything is included for a reason, in order to address critical areas and ensure the quality of development and review processes. Dr Kweder gave examples of topics covered in the GRMP guidance:

- **Constitution of a review team**: The expectations for the division to establish a review team and a plan for the review of a dossier;
- **Designation of review priority:** General guidelines for making policy decisions on fast track reviews;
- **Determining signatory authority**: When the application should be signed off by the Division Director and when is an Office Director's signature required;
- **Filing meetings and reviews:** Guidance on the level of preparedness for meetings with applicants, including being aware of potential obstacles and having a view on the need for additional internal or external consultations, including the use of Advisory Committees;
- **Communication between FDA and the Applicant:** The expectations for keeping applicants informed of progress with the review, alerting them to deficiencies and issuing approvable and non-approvable letters;
- **Management of the review process:** Monitoring timelines and troubleshooting;
- **Levels of review:** Dealing with questions about primary and secondary reviews, how to deal with differences in scientific judgement and determining which reviews need to be written at Divisional Director level;
- **Advisory Committees**: Guidance on how these should be planned and conducted including the roles of the FDA and sponsor.

From FDA's standpoint, Dr Kweder said, GRMP guidance establishes process and role expectations that have to form the foundation for meeting benchmarking goals under PDUFA. Without these basic processes we can expect continued variability and 'ultimately chaos' she suggested, because variability will affect the ability to meet benchmarks. 'We see this', she said, 'as the qualitative aspect of some of benchmarks that we have been using'.

Drivers 'closer to the road'

Those at the divisional level, where the day-to-day review work is carried out, are directly impacted by PDUFA, user fee issues and GRMP. But, as Dr Kweder pointed out, they are also concerned with adequate resources to address the workload in order to meet the PDUFA goal-dates. On the latter, she emphasised that these dates are now an integral part of the planning process and that meeting goal dates has become a source of pride among reviewers. They are also very aware of the importance of maintaining an up-to-date scientific knowledge and having the right 'tools' for their tasks.

Balancing work and resources

Dr Kweder believed that, from the Division Director's perspective, determining the balance between the workload and resources had been greatly facilitated by the focus on goals and benchmarks. There has, however, been a dramatic shift in product development trends in the last decade. Ten years ago, for example, the anti-infective field was 'booming' but antimicrobial development has diminished in recent years and such changes have not been reflected in the organisational structure of the OND, which has not been changed since 1994. As a result, she suggested, there has been an overall loss of balance between work and resources which is being addressed through a realignment of product groupings and a planned reorganisation of the OND, in 2005.

In preparation for this re-organisation, a workload and process analysis has been carried out using outside consultants. Multiple data sources, including the benchmarking studies were used to develop a weighted model that would address such questions as the amount of work in a new drug NDA and a thirty-day safety review of an IND and the difference in work load when an application has a single and multiple clinical indications.

The model was tested by Division-level and Office-level staff over six months and it provides a basis for a regular assessments of short- and long-term trends, by organisational unit or by therapeutic area.

One outcome is the reorganisation shown in the *Box* and Dr Kweder explained the way in which this was designed to provide a more logical grouping of products by clinical therapeutic area and integrate biological therapeutic products (previously reviewed by CBER) into the OND structure. The goal was to create better balance in the workload and staff resources across the organisation.

The reorganisation is expected to improve the consistency of the regulatory advice provided to companies as well as improving the efficiency of OND staff in maintaining and improving their scientific expertise. Most importantly, Dr Kweder said, the changes should minimise redundancy and conflicting approaches both within the organisation and in its dealings with industry.

Reorganisation of the Office of New Drugs

- **Office of Oncology Products**
  - Division of Drugs Oncology
  - Division of Biologics Oncology
  - Division of Medical Imaging and Hematology
- **Office of Drug Evaluation I**
  - Division of Cardiovascular and Renal
  - Division of Neurology
  - Division of Psychiatry
- **Office of Drug Evaluation II**
  - Division of Pulmonary & Allergy
  - Division of Endocrinology & Metabolism
  - Division of Analgesia, Anesthesia & Rheumatology
- **Office of Drug Evaluation III**
  - Division of Gastroenterology
  - Division of Reproduction & Urology
  - Division of Dermatology and Dental
- **Office of Drug Evaluation IV**
  - Division of Anti-Infectives and Ophthalmology
  - Division of Special Pathogens & Transplant
  - Division of Antivirals
- **Office of Non-Prescription Products**

Clinical Review Template

Dr Kweder described the development of a template for clinical reviews as an 'important tool' for those working to meet benchmarks on quality and consistency. She commented on the historical picture where every review had looked different, with no consistency in approach or standard format. The result had been confusing both internally and externally. Work has therefore been in progress, with the scientists in the Divisions, to develop a clinical review template that establishes a standard format and also provides guidance on content and on how to approach the review from a scientific perspective. The template was piloted for a year and revised before being launched a few months ago.

Clinical Therapeutic Guidances

Other tools that are essential for consistency are the Clinical Therapeutic Guidelines that FDA has issued and Dr Kweder referred to on-going work to develop these further. The guidances provide transparency with respect to the standards that are expected and help to overcome the potential problem that different advice may be obtained when different reviewers are consulted.

An important factor, she said, is that these guidances have to be publicly vetted for scientific rationale but, at the same time, they cannot be 'cast in stone' and have to be written in a way that allows some flexibility. One of the reasons that there are not more of these guides is that they are very time consuming and the individuals charged with writing them are also heavily committed to assessment work. The OND has therefore put together a special team to try to facilitate development of the guidances, train staff and provide additional resources for editing, formatting and processing.

Conclusion

Dr Kweder summarised by re-affirming that performance benchmarks are an accepted and important part of CDER's work. They are widely utilised within the organisation but FDA has found that it is also essential to address the underlying qualitative aspects, in order to improve performance. These include analysing the workload in order to provide appropriate resources and adopting measures to improve consistency and build scientific excellence and improve quality.

BENCHMARKING IN ACTION: VIEWPOINT FROM SWITZERLAND

Professor Samuel Vožeh
Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic

Professor Samuel Vožeh opened his presentation with a description of the organisation of Swissmedic and an outline of the review process before discussing the ways in which the Benchmarking study had helped make critical comparisons between different regulatory processes and had highlighted critical differences.

The organisation of Swissmedic

Describing the organisation of Swissmedic, Professor Vožeh pointed out that the organisation, which has a total for some 280 employees, is responsible not only for prescription medicines but also the non-prescription medicines, narcotics, veterinary medicines and medical devices. The benchmarking study covered only prescription medicines which are a relatively small part of Swissmedic's activities. The divisions dealing with these products have a staff of 69 full-time employees and 43 reviewers.

The Marketing Authorisation Process

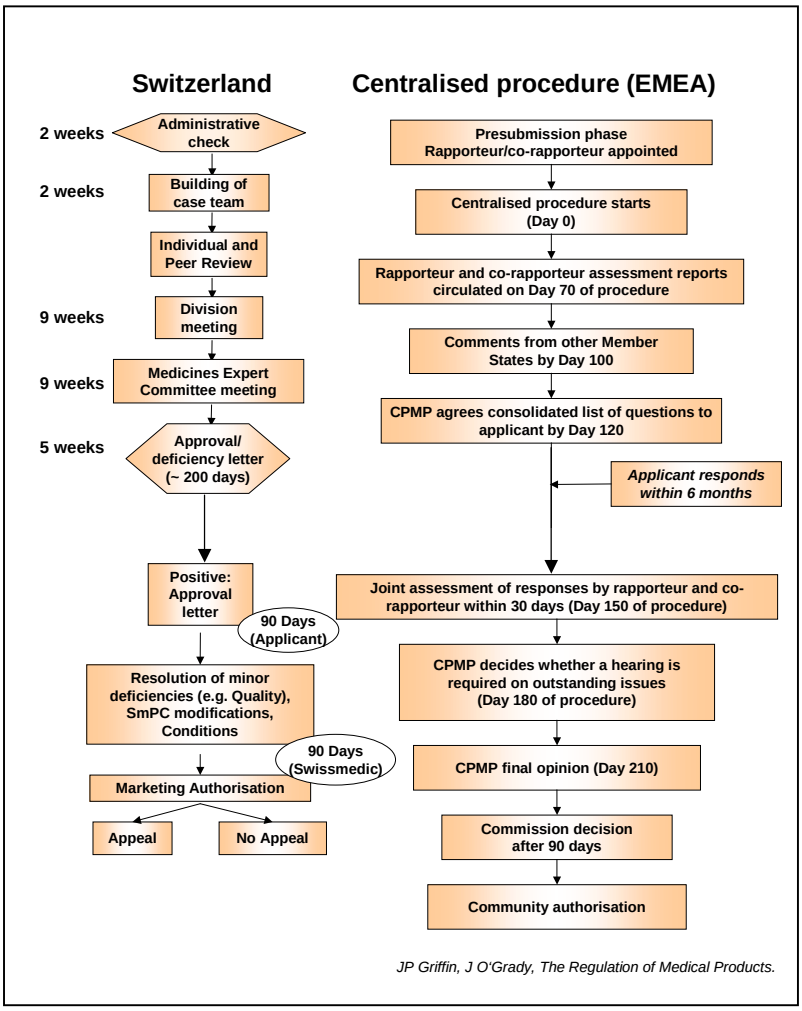
Professor Vožeh noted the similarities between the marketing authorisation process in Switzerland and those of the other agencies in the study. Looking specifically at the scientific assessment stage he described the following steps:

- **Building a case team:** A project plan is formulated for each review and a case team is designated. The team consists of a regulatory, quality, pre-clinical and clinical reviewer;
- **Individual review:** The review starts with the three sections of the dossier being assessed, in parallel;
- **Peer review:** The individual assessment reports are read by other colleagues who discuss the content with the reviewer. At the same time, if there are areas of expertise that are not adequately covered by members of the advisory committee, the Medicines Expert Committee, the opinion of an external expert will be sought;
- **Division meeting:** The application is discussed at one of the weekly meetings, in which the head of Division and head of the Business normally participate. The whole report is not reviewed at this stage but the meeting focuses on any problems and issues related to the application;
- **Medicines Expert Committee:** The full report is referred to the committee, which meets each month, The Committee has ten members, mainly from the universities, with expertise in pharmacology, toxicology, clinical pharmacology and internal medicine.
- **Division meeting:** If there are unresolved issues or problem areas, the application is referred back to a further internal division meeting
- **Final opinion and decision letter:** This is agreed by Swissmedic and communicated to the applicant.

In presenting this brief overview of the review process, Professor Vožeh stressed that, although there is no formal quality management system in place, some three to four quality assurance steps have been built into the process, for example, peer review, division meeting and Medicines Expert Committee meeting.

Comparison with the EMEA process

Figure 1

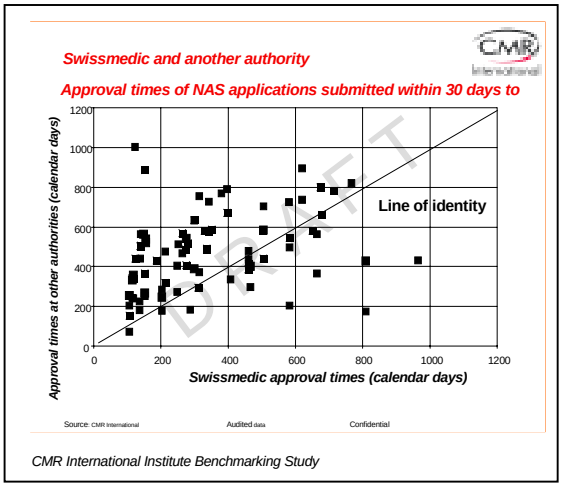


JP Griffin, J O'Grady, The Regulation of Medical Products.

One of the major achievements of the benchmarking study, said Professor Vožeh, has been that it allows valid comparisons to be made between the regulatory processes in the different agencies. In this, he believed, the study was unique.

From the Swissmedic perspective it had, for example, allowed a systematic comparison with the EU Centralised Procedure (CP) administered through the EMEA (*Figure 1*). The first important difference is identified in the first cycle. The primary opinion from the EMEA is reached in 120 days whereas it takes about 200 days for Swissmedic to reach this stage. The difference, however, is that, in the Swiss system the result can be an approval, whereas in the CP it is always a consolidated list of questions and not a definitive opinion.

A significant difference in the two processes is that Swissmedic leaves the detailed discussion of labelling and the resolution of any minor deficiencies until after the decision, in principle, has been made on the application. In the case of positive opinions, therefore, a further 180 days are needed before the marketing authorisation can be issued. The CP system also has an additional 180 days 'regulatory time' but this is after the 6-month 'clock-stop' that may be required for the company to answer the questions. On balance, therefore, the approval time is generally shorter for the Swiss process, Professor Vožeh concluded.



CMR International Institute Benchmarking Study

Comparison of approval times

Professor Vožeh used a chart from the CMR International Institute benchmarking study to illustrate what, in his opinion, was one of the most valid ways to look at comparative review times, in this case comparing the time taken by Swissmedic with the other agencies (*Figure* 2). This takes applications that were submitted to another authority within 30 days of the submission to Swissmedic and records the time from receipt of the dossier to approval. Those points above the 'line of identity' indicate applications where the approval time was slower than in Switzerland and those below were processed more rapidly.

The Swiss review compared with the EU/US

Having first highlighted the most obvious difference between Switzerland and the US – the comparative sizes of the two countries – Professor Vožeh identified three main differences between the Swissmedic approach to regulatory review and those of FDA and EMEA:

Depth of evaluation: Swissmedic would not undertake a reanalysis of raw data in the way that, for example, the FDA often does. Design, method and end-points might be questioned but the results are taken as valid, provided they appear plausible. If a reanalysis is needed the company will be asked to carry this out.

Decision is based on the submitted dossier: The review system is designed to deal with complete dossiers. Applications that are premature or seriously deficient receive a negative opinion at the 200 day stage (Figure 1). There is no 'consolidated list of questions' resulting in a clock-stop period and only minor deficiencies can be dealt with during the review process.

Scientific advice: Swissmedic has limited resources for providing advice prior to submission of an application. Major pharmaceutical companies are expected to be informed of international developments, for example within ICH, and the applicant should ensure that the reviewer is given a clear picture of the rationale behind the development of the product.

Overall, the system favours applications of high quality that are submitted as part of a global development and Swissmedic is able to operate within short review times for such applications. Incomplete and premature dossiers, on the other hand, are at a major disadvantage.

The advice that Professor Vožeh offered was to concentrate on the harmonisation of principle issues, in particular the proof of a positive benefit-risk relationship, and to be prepared to negotiate on the details of the wording of indications and warnings in the *Summary of Particulars*, for the Swiss market, as these may be influenced by medical practice and the cultural background of the country.

Conclusion

Referring back to Swissmedic's participation in the CMR International Institute Benchmarking study, Professor Vožeh concluded that it had been valuable in positioning the agency in the regulatory world and learning more about the details of the way other, larger agencies operate. The 'benchmark' that Switzerland can offer to other agencies is a relatively fast review carried out with minimum resources for 'clean', good quality dossiers.

HOW BENCHMARKING IS BEING USED TO STREAMLINE AND CHANGE REGULATORY PROCESSES: Australian perspective

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

Dr Leonie Hunt opened her presentation by quoting the fundamental 'truism' from the CMR International Benchmarking Study that '*all regulatory agencies have overall the same responsibility which is to evaluate new drug applications for safety efficacy and quality, however the processes in place to undertake review of medicines differ between agencies'*. By identifying the similarities and quantifying the differences in the regulatory review processes the study had allowed the agencies to:

- Compare their performance against other agencies, at a simplistic level;
- Monitor performance over time;
- Look at individual product areas within agencies and between agencies;
- Look at the impact on timelines over several years as the study has been ongoing since 1997;
- Identify alternate processes for adoption, through interaction with other agencies.

All agencies, suggested Dr Hunt, must have some form of performance monitoring and she cited the Australian Therapeutic Goods Administration (TGA) procedures under which quarterly reports are sent to industry associations and annually to parliamentarians. She noted, however, that the level of data required in the Benchmarking Study has been quite different and just collecting that data has allowed the participants to reflect on the outcomes. Of particular importance has been the workload review and trend analysis embodied in the study. Comparisons within and across the agencies have highlighted the falling work load of new chemical entities over the last few years that has been mirrored across several agencies.

Identifying targets for improvement

Dr Hunt emphasised the importance of being able to look at the comparison of processes used by different agencies and how these can impact at different stages of the review procedure. These comparisons have, primarily, been made by monitoring the timing of submissions and, within TGA, the outcome has been to suggest targets for further improvements that could be made to the review process. She outlined several examples:

Company time

The Benchmarking Study differentiates between the time the application spends with the agency and the period designated as 'company time'. In 2000, TGA and the industry looked at a number of initiatives to reduce company time in Australia. For example, the agency agreed to be more careful about the questions that were asked and the companies agreed to answer in a more timely manner. The benchmarking data for 2001 and 2002 gives a strong indication that his approach was successful with a noticeable reduction in company time and a consequent reduction in the overall approval times.

Second cycle reviews

The level of analysis that the Benchmarking Study makes possible allows a detailed analysis of the number of review cycles that applications go through before approval in the different countries and the impact on approval time. In Australia there are relatively few second cycle reviews but it was clear that, once an application enters a second cycle the time for approval and market entry is significantly extended. The obvious target is to reduce the need for multiple review cycles, which might be brought about by working with the evaluators, but also through improving the guidance that is given to industry.

Pre-submission meetings

Although Australia has always had provision for pre-submission meetings with industry it has only been in the last few years that records have been kept on whether or not such meetings were held. Since this record-keeping started, it has been possible to correlate the holding of such meetings with the median time to approval and show a reduction. The impact of pre-submission meetings has, however, been more marked with other agencies than with TGA and therefore one of the targets would be to improve the outcome of the pre-submission process in order to have a bigger impact on reducing approval times in future.

Type of application

The benchmarking project divided products into chemical entities biotech and biologicals which enabled a comparative assessment of the way that different types of application were handled. Dr Hunt pointed out that, unlike some of the other agencies, the shortest median evaluation times for TGA occurred for applications relating to biological products.

The TGA target is therefore to examine the differences in procedures for different types of product to identify what is working best for biologicals in order to apply it to other areas and ensure the most efficient process is being used for all types of product.

Timing of submissions

Comparative data from the benchmarking study had shown clearly that applications for new medicines are likely to be lodged with TGA at a later date than with the other authorities. This, Dr

Hunt suggested, is understandable in terms of the size and therefore the commercial importance of the market. When the Australian and New Zealand markets are combined they only represent approximately 2% of the global pharmaceutical market. TGA, however, wishes to encourage companies to submit applications to Australia earlier in order to allow earlier patient access to new medicines. A possible target is therefore to discuss process changes that would encourage companies to include TGA registration at an earlier stage in global drug development.

Quality of submissions

Dr Hunt referred to two areas where the benchmarking data had highlighted the unexpected. Firstly, TGA had always had the impression that they rarely refuse an application, but the comparative data from the study showed that Australia's rejection rate of 6% was high compared with other agencies. Furthermore TGA was also the agency more likely to refuse to file an application, in the first place.

The second revelation was that the designation of products for priority or expedited review has very little impact on the overall approval time. In fact, Dr Hunt noted, it was sometimes hard to see why companies asked for priority review it 'appeared to make the process really slow!'

For both these examples the answer appeared to lie in the quality of the submission and Dr Hunt suggested that a target was to work with industry on improving the quality of submissions, including those where priority review is requested. Again, this would include improving the guidance from TGA to communicate their expectations.

Products approved by all five agencies

The CMR Institute Benchmarking Study identifies a cohort of 29 products that were submitted to, and approved by, all five agencies. These, suggested Dr Hunt, allow interesting cross-agency comparisons but the one thing that is noticeable is the great variation in the times at which the submissions were made, the approval times and the company time during review. No clear pattern or explanation for the differences was apparent from the analyses and this gives rise to many questions that might, perhaps, be answered by other studies and comparisons between the data.

Impact of the Benchmarking Study

Participating in the CMR International Institute Benchmarking Study, Dr Hunt said, has provided TGA with insights into many aspects of the review process and this has inspired the agency to look at ways of moving forward and changing its procedures in order to make improvements. Over the last two years, TGA has been working with representatives of the innovative industry in Australia, through the Association 'Medicines Australia' and with the generic industry association GmiA, as well as consumer groups to look at business practices associated with the review process.

The different phases of the review process had been discussed and it was agreed that the priority areas for change were validation, scientific assessment and post assessment. The fourth area considered was the Advisory Committee process. Although this stage in the review is relatively long, taking a minimum of two months and often four, Dr Hunt noted that there was general satisfaction with the process which is very formalised. Companies receive a copy of all evaluation reports and have the opportunity to comment, in writing, to the Committee. The only issue to arise related to transparency but it soon became clear, Dr Hunt commented, that each party viewed this from their own perspective, seeking greater transparency for their own association but not necessarily for everyone in the room!

Options for improvement

Validation stage: Options were discussed for minimising the validation stage and reducing the number of refusals-to-file. These included the introduction of a formal pre-submission process with options for a meeting. In order to work, Dr Hunt emphasised that this would need the agreement of all parties to share information 'up front', before the application was filed and there would also need to be a commitment to fulfil any undertakings agreed at that stage, as far as is scientifically possible.

Scientific Assessment: Consideration has been given to introducing more predictable time-lines for the first phase evaluation, including a single target completion date at which stage a final set of questions would be issued and a the 'clock' would be stopped. At present the different sections of the application are reviewed in parallel and there are informal arrangements for seeking further information from companies and stopping and starting the clock, by mutual agreement. The target for the revised procedure would be to have only one review before going to the Advisory Committee and the benefits would be to increase predictability for industry and improve resource allocation for TGA.

Informal communication with the company would be maintained, in order to answer questions and provide clarifications that do not warrant a 'clock stop' and Dr Hunt emphasised the importance of good and rapid communications with the appropriate company staff, during the evaluation, whether or not they are located in Australia.

Post assessment phase: Dr Hunt suggested that, with cooperation, commitment and better forward planning it would be possible to virtually halve the time taken for the post assessment stage of the approval process. This is the stage at which outstanding issues are finalised, for example final versions of the labelling and clearance of GMP certification, most of which could be dealt earlier in the process.

Transparency: The consumer groups, in particular, see greater transparency as the main area for improvement. Their priorities are to have a better understanding of the process and for industry and the agency to be more open about the content of applications and the reasons for decisions. They have also called for early access to labelling and post-marketing information.

The next step

Dr Hunt reported that TGA had appointed a consultant to prepare an options paper for further consultation, based on the proposals discussed during the two year process of working with industry. She believed that this would lead to changes to the business process and lead to a better regulatory system in Australia for both the regulators and companies, with improved access to patients.

BENCHMARKING AS A KEY DRIVER FOR CHANGE IN ACHIEVING EXCELLENCE IN REGULATORY PERFORMANCE:

The Canadian experience

Dr Robert Peterson

Director General, Therapeutics Products Directorate, Health Canada

Dr Robert Peterson opened his presentation by reaffirming that Health Canada had been pleased to participate in the CMR International Institute's Benchmarking Study and noting that the outcomes had been used as part of the Therapeutic Product Directorate's (TPD) strategy to improve regulatory performance. The main motivation for Health Canada's participation in study had been the desire to be open and transparent about processes and performance.

Health Canada has been subject to numerous international comparisons in the past but these have been fairly superficial, focusing on overall approval times and the relative speed of the review processes of the different agencies. Whilst overall approval times are the priority of the industry, it has clearly been of benefit to agencies to invest time and effort in providing more detailed data on the different steps in the process and information on unsuccessful applications – withdrawals and refusals..

TPD's Strategy

Dr Peterson referred to recent changes being undertaken by Health Canada in order to meet expectations and take better control of the regulatory process. TPD's response has been a *Business Transformation Strategy,* a portion of which is shown in *Box 1*.

Participating in the CMR Institute benchmarking activities has been one element of the strategy that has allowed TPD to respond to the Canadian governments direction to improve performance and modernise regulatory activities. An important outcome has been the ability to give factual information that allows for identification of improvements that are resource-dependent in order to make a stronger case for the additional resources.

Box 1

TPD's strategy combines:

- Participating in benchmarking process and implementing best practices
- Delivering on Canadian Government commitments
- Responding to Stakeholder expectations
- Anticipating Industry Trends
- Undertaking consultations with other regulatory agencies

Dr Peterson discussed the last three items in *Box 1* in greater detail:

Responding to stakeholder expectations

The benchmarking exercise, through comparison of different procedures had highlighted stakeholder expectations for regulatory performance. Dr Peterson identified these as a review process which:

- Renders timely decisions.
- Is predictable in how we arrive at decisions.
- Has *consistent* practices/protocols.
- Is *sustainable* over the long run.
- Is characterised by *transparency* and *openness*.

The overall focus is on quality but this is a very difficult concept not only to define but also to identify suitable metrics for monitoring. Dr Peterson suggested that this is something that CMR International and others would be spending time on, in the future.

Anticipating industry trends

TPD has invited the Canadian industry associations to discuss the types and numbers of products that are likely to be coming forward in the immediate future. TPD has been taking advantage of the slump in the number of new active substances that have been submitted for review over the last few years, as an opportunity to clear the backlog of applications.

Dr Peterson was, however, in no doubt that this was a temporary phenomenon it was important to look at the sustainability of competencies in future, in terms of internal scientific expertise and links with external scientific advisory panels. He said that projections from industry were for a substantial increase in the number of filings, starting in 2005. If, as predicted, there are 'revolutionary' new products on the horizon, the agency will need to contend not only with larger numbers of submissions but also with greater complexity of the dossiers and the potential for the size of the datasets to increase.

Consultation with other regulators

Dr Peterson discussed consultations with other regulators in order to identify best practices that are applicable in the Canadian context. The benchmarking exercise has clearly been valuable in raising questions about different activity levels in one organisation compared to another. Taking the two larger agencies, EMEA and CDER he highlighted some of the lessons for Health Canada in relation to the following:

Upstream activity: Both agencies undertake considerably more work than Health Canada, on applications before they are submitted, particularly with respect to the design of clinical trials and the identification of the endpoints to be measured. For the smaller agencies that do not look at the

raw data or carry out their own analysis, it is also important to discuss with the applicant the manner in which those data should best be presented in order to facilitate the regulatory evaluation process. This is something that TPD has now initiated.

***Resources*:** The Benchmarking Study has helped TPD identify and justify the resources needed for a successful review process in Canada. It has been made clear throughout the organisation, however, that 'new dollars and new resources will not be put into old processes and old ways of doing business'. The information provided on the regulatory profiles for EMEA and CDER provided some useful comparators that TPD used in their resource planning.

***Proactive management of the review process*:** Another lesson learned from the other agencies is the need to take control of the review process and be proactive both in the upstream approach as well as in looking at the way in which applications flow through the process.

***Quality in-quality out*:** Considerable work is now going into trying to improve the quality of applications that are submitted to Health Canada. There is a clear dependency between the quality of the dossier - the way in which the information is organised and the datasets are presented - and the quality of the subsequent review.

***Contemporary external charging regime*:** User fees were introduced in Canada in 1995 but have not been indexed to the cost of living. The question of the level of these fees is therefore being reviewed, in relation to the experience of other agencies.

Health Canada has also sought further insight into the way in which other medium-sized regulatory agencies operate, and Dr Peterson cited the Irish Medicines Board and the Australian TGA as examples. Of particular interest are the way external advisory committees are used in the process, and the ability to work with other regulatory agencies in building trust in mutual recognition.

Business Transformation Strategy

Dr Peterson outlined some of the strategic investment that had driven the TPD's Business Transformation Strategy:

Workload and Project Management:

A complete reorganisation of the Therapeutic Products Directorate took place a number of years ago, in order to address the distribution of workload and look at ways in which the review groups could work together in a facilitated fashion. Project management was also improved based on useful discussions with EMEA and CDER, and adoption of control processes similar to those implemented by FDA CDER. (Further details in See *Box 2*).

International regulatory cooperation:

The ability to look, in a contemporary fashion, at what other regulators are doing has led to discussion of whether portions of the review would be amenable to an international cooperative venture to share the work of reviews and provide access to external scientific capacity. This appears feasible for the review of quality (CMC) and pre-clinical data but the clinical portions pose major problems in terms of allowing for the review to be carried out by external agencies.

Box 2

Project Management

- Modeled from other regulatory agencies: TPD in 2003 began to institute a project management approach to Drug Review
- Approach to submission review
  - Proactive approach
  - Team-based
- Submissions managed as projects
  - Each submission is assigned to a Project Manager
- Emphasis on planning, coordination and management of activities to ensure
  - Early upstream interactions with sponsors to facilitate timely review
  - Reviews are completed within performance targets
  - Internal and external communication is optimized
  - Early identification of issues
  - The need for contingency planning
- This initiative is yielding more timely reviews and facilitates successful workload management
- Entire organisation trained in essential aspects of PM

E-Review

The adoption of an electronic ICH Common Technical Document (CTD) is recognised as an important step to move harmonised reviews forward. The CTD, however, it only addresses the format of the application and further work is needed on harmonising the content of applications in order to make further progress towards the concept of an 'E-review'.

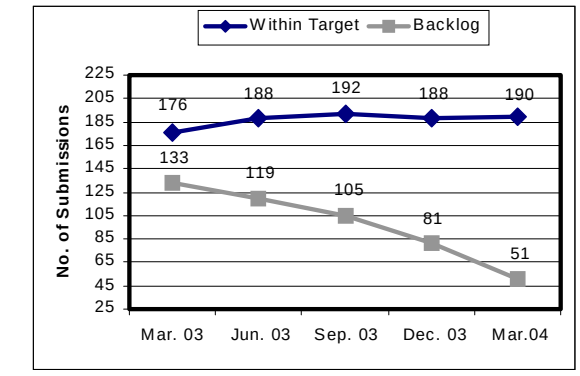
Workload management

Dr Peterson elaborated further on the steps taken by TPD to improve workload management and particularly the reduction of the backlog of submissions. The problem of the review backlog has haunted Health Canada for a long time, and this was highlighted in the CMR study which indicated that applications wait an average of 197 days before resources become available to commence the review. As discussed, many improvements in project management were being implemented in order to manage, proactively, submissions as they are received, but, said Dr Peterson, 'You cannot really be measured in terms of performance if you are always working on an application about six months to a year beyond the due date'.

Reduced backlog

Through improved workload management, and by taking advantage of the respite in the intake of NME applications, a major drive had been undertaken to tackle the backlog. *Figure 1* shows the improvements achieved between March 2003 and March 2004 and Dr Peterson was able to report that, as of 30 September 2004 more than 80% of the backlog had been cleared. Furthermore, he predicted that they were well on target to eliminate 90% of the backlog by March 2005.

Figure 1 **TPD Workload/Backlog**



Dr Peterson also provided data on the time to complete reviews for the period January to June 2004 (i.e., beyond the time limits of the CMR Institute Study):

- 8 Standard NAS reviews had been completed:
  - Average review time 248 days (Target 300 days)
- 2 priority NAS reviews had been completed
  - Average review time 177 days

These applications were received after TPD's Business Transformation Strategy commenced in April 2003.

Timing of submissions and length of review

Dr Peterson referred to the analyses that had been carried out in the CMR International Institute Benchmarking Study on products that had been approved by all five regulatory authorities. One analysis had been a comparison of the review times for the different agencies in relation to the point in time at which the application was submitted. These data indicated that the longer the delay before an application was received by an authority, the longer the review time. Dr Peterson suggested that one of the factors was that the smaller agencies such as Health Canada, often receive applications after the product has been launched onto the market elsewhere. Whereas the earlier reviews were based solely on the results of the original clinical trials, Health Canada must take into account the first six months – or in some cases a year to 18 months – of post-marketing information and consider any safety issues that this raises. In addition, labeling negotiations may be protracted as the sponsor will be reluctant to alter labeling that has been agreed with other authorities.

Conclusion

In summarising, Dr Peterson re-affirmed the importance of benchmarking to agencies in the face of continual questions and criticism about whether their processes are too slow or too hasty. Benchmarking is extremely valuable in identifying best practices in the international community and the CMR International Institute study has provided a model for looking 'beneath the surface' to identify the ways other regulators are meeting their performance targets.

He cautioned, however, that benchmarking is by no means a casual endeavour and the resource implications must be taken into account. It is also important to recognise the limitations of benchmarking. In particular, the comparisons that are made relate to different review systems and metrics have not yet been developed around the quality of the processes.

Nonetheless, the TPD has made good progress recently and has been able to make good use of the data from the study and the lessons to be learned from benchmarking, in bringing about its business transformation. 'We will continue to be engaged', he concluded.

PANEL ON 'BENCHMARKING IN ACTION': POINTS FROM THE DISCUSSION

USA

Institute benchmarking study: The study had identified the basic similarities between the different international systems, in terms of procedures, and yet the agencies often come to different decisions on the same application. A next step might be to find out more about the underlying factors and the extent to which differences can be attributed to medical practice or requirements for placebo-controlled *versus* comparator-controlled studies.

Cost and productivity: The way that FDA operates does not lend itself to costing the services that it delivers, although some projects have been undertaken in which staff record how they have spent their time over a fixed time period.

Quality of review: A good quality review is one that does 'enough' but not more than enough - striving for a '100% review' is often a waste of valuable time. One does not need, for example, a review document for an NDA supplement, that exceeds the length of the application itself. The FDA clinical review template addresses quality in relation to whether the sponsor has met the required standards but the quality of the review itself needs to be addressed through upgrading processes and procedures.

Workload predictors: The size clinical report forma (CRFs) and the number of patients in a study are not automatically tracked by FDA when looking at workload and resource requirements, but this might be studied in future.

Switzerland

Impact of the Benchmarking Study: The agency is discussing whether to introduce a 'consolidated list of questions', or similar procedure into the scientific review stage. Switzerland is the only agency, of the five, where labelling issues are only discussed after a letter of approval has been issued but this is unlikely to change in the immediate future since it has been found more efficient, with respect to resources, since negotiations on labelling are time-consuming and need only be undertaken once a positive decision has been taken on the product.

Scientific Advice: Swissmedic rarely, if ever, disagreed with scientific advice on development given to sponsors by agencies in the ICH regions, although there are often points of detail on which they did not agree, and sometimes additional studies would be proposed.

Medicines Expert Committee: The agency, and not the Committee, made the final decision on an application and it was very rare that the Expert Committee advice would not be followed. If necessary Swissmedic could call on a panel of some 70 external experts for a second opinion in the case of unresolved issues.

Australia

Assessment reports: The TGA generally finds that assessment reports from other authorities are very helpful, provided the timing was such that it was clear that both agencies had received the same data package. In view of the statutory timeframe for the TGA review (which is linked to fee recovery) TGA may feel compelled to proceed without waiting if the report from another agency is late. Australia also provides copies of its reports, with the agreement of the company, to other regulators in the region, for example in Indonesia, Malaysia and Singapore.

Trans Tasman Agency: A single, joint regulatory agency for Australia and New Zealand, under the 'Trans Tasman Treaty' signed between Australia and New Zealand in December 2003[5]. The agency is scheduled to be inaugurated in July 2005. The new Agency will be formed from the two existing agencies and identical legislation and guidelines will be implemented in both countries.

Institute benchmarking study: Priority should be given to studying the compounds approved by all five agencies in order to identify the real differences and the reasons for those differences. This analysis should also be extended to compounds approved by only three or four of the agencies and particularly those submitted in a time frame that would mean that the different agencies were considering virtually identical dossiers.

Canada

Reasons for delay: Health Canada is concentrating efforts on improving internal processes to ensure that applications can be reviewed within the expected time frame before focusing on advice to industry on improving the quality of applications. Reasons for delay may include deficiencies in the applications but might also result from a lack of internal scientific expertise to deal with specialised applications and a failure to use external advisers effectively.

Skill sets for assessing data: Health Canada has addressed concerns, particularly in relation to quality (CMC) data, where personnel have gained experience in the offices of other agencies, particularly EMEA. Of particular concern was the need for adequate SOPs to prevent inconsistency in implementing international agreements such as the ICH guidelines.

Exchange of review information: Receiving information on the reviews of other agencies under international co-operation agreements is very valuable, particularly in seeing the questions that had been raised. Based on public expectations, the stage has not, however, been reached where the Canadian regulators can make decisions based on the previous reviews of others. Even joint reviews are some way off but there would be great advantages in synchronous reviews during which the agencies could exchange information and, in particular, co-ordinate the questions put to the sponsor and any requests for additional information.

Questions during the review: The 'clarifax' is for clarification of data in the application with a 15-day response time and responses are normally received within the time limits. Problems can arise when multiple clarifaxes are sent and review time is then extended whilst responses are awaited. This might be improved by having questions synchronised so that a single batch of questions was sent for each section of the application.

[5] Agreement between the government of Australia and the Government of New Zealand for the establishment of a Joint Scheme for the Regulation of Therapeutic Products, 9 September 2003, signed by both governments, 10 December 2003 and submitted to both parliaments, March 2004, http://www..jtaproject.com

OVERVIEW OF THE CMR INTERNATIONAL REGULATORY PERFORMANCE PROGRAMME

Dr Cyndy Lumley
Executive Vice President, Business Development, CMR International

Dr Cyndy Lumley was both Chairperson and speaker for the final Session of the Workshop, which was held jointly with participants of the CMR International Global Regulatory Performance Metrics Programme who were also meeting in Washington.

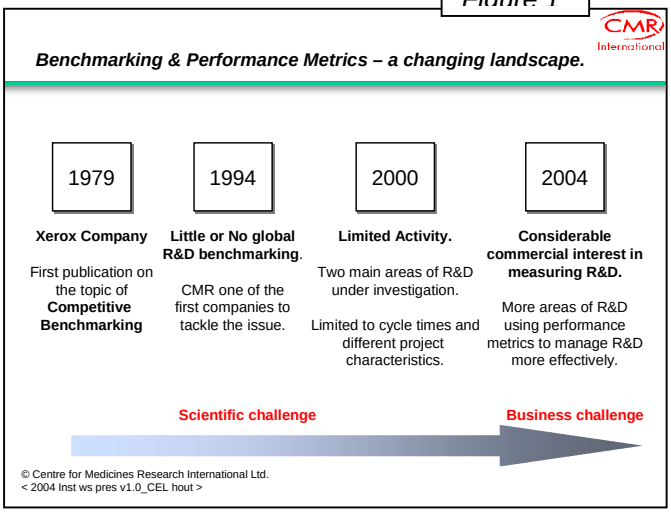
Dr Lumley introduced her presentation with a brief reminder of the structure of the CMR International Group within which there is both the Institute for Regulatory Science and the business sector, which is focused on working with the industry and providing information that will help companies to measure and improve their effectiveness and productivity in pharmaceutical R&D. She highlighted the parallels between the Institute work with the regulatory authorities on Benchmarking the Regulatory Process and the CMR International programme on regulatory performance that is focused on the regulatory affairs function within the pharmaceutical industry.

History of Benchmarking

The pharmaceutical industry was relatively late in adopting benchmarking and performance metrics as a management tool, compared with other industries (*Figure 1*).

Dr Lumley noted that methodology was first published in 1979 but there was little or no R&D benchmarking by pharma companies when CMR first addressed the subject in 1994. Over the latter half of the 1990s CMR International developed two programmes, with pharmaceutical companies, one to look at the overall R&D process, including clinical development, and the other to identify suitable metrics for the number of products in development with markers for their progress.

Figure 1



It is only in the last few years, however, that CMR International has focused on the business challenge of generating data and information on performance that can be fed back to companies in order to improve programmes and procedures.

Drivers for measuring and managing performance

Dr Lumley provided a 'snapshot' of trends relating to the pharmaceutical industry over the decade from 1994 to 2003 in order to highlight some of the factors that were driving the increased interest in measuring performance. There has been a steady rise in global R&D expenditure which has doubled over the 10 years, although this has been matched by an increase in global sales. The most disturbing trend, however, is that, in spite of the increased investment in R&D there has been a decline in the number of new molecular entities reaching the market, which reached the lowest point for many years, in 2003. The fact that global sales has continued to rise, Dr Lumley suggested, possibly reflects the way in which companies are improving life cycle management of their products as well as expanding markets and the increased value of their products.

With respect to development times, the figures indicated that, despite investment in re-engineering and trying to reduce cycle times, the interval from discovery to the launch of a product has remained fairly constant at 10-12 years.

Dr Lumley also provided data for the number of new active substances entering each phase of the development pipeline over the last five years. She noted that there had been talk of a surge of new products emerging from the discovery phase, as a result of the application of new technologies and genomics. This was not, however, borne out by the data which had been collected by CMR

International which showed little to suggest a large upturn in the number of new product launches in the near future.

The spectrum of studies being carried out by CMR International now includes: Global R&D, Project Investment (dollars and personnel), clinical development, Japan metrics, Discovery, Regulatory and CMC (chemistry, manufacturing and controls). Dr Lumley explained that all these programmes are based on data that is collected directly from companies and has enabled CMR to look at the whole history of individual projects and programmes from the time of discovery to the outcome be it project termination or the successful launch of the product.

Regulatory Performance Metrics

Against this background, Dr Lumley described the development of metrics for measuring the regulatory performance in industry. The initial focus of all benchmarking activities had been very much on timelines for the different stages of development from discovery to launch. Within the regulatory stage, there had been a similar emphasis on the overall approval time but the Regulatory Performance programme was looking at more detailed metrics and indicators that might help improve timelines for registration and the accuracy of predictions of approval dates.
Dr Lumley presented data from CMR International's Global R&D performance metrics programme to discuss some of the key intervals that may be relevant to the regulatory function:

Last patient, last visit, to first submission: Although this is one of the measures applied to regulatory affairs, Dr Lumley noted that RA professionals had been quick to point out that this interval was not entirely under their control and that the important date is the receipt of the last document that is essential for the submission. (The median duration, for a cohort of 36 submissions, was just under 200 days).

First submission to first approval: This is the interval between filing the first application anywhere in the world and receiving approval, anywhere in the world. One of the challenges for the regulatory team is to predict how long it will take to receive approval so that the commercial groups can be ready for roll-out. (A cohort of 45 projects had shown a median interval of 361 days but, as noted, filing and approval may not occur in the same country or region).

First approval to first launch: The figures showed a median interval of 49 days for 29 first launches and raises the question of why the company was not ready for launch on the day of approval. The answer, in some markets, may be the need for further negotiations on price and reimbursement, but in many cases it may be that the regulatory department had not anticipated such a quick review. Improving predictions could lead to a reduction in this interval.

Launch in first core market to launch in the last core market: Activities had been tracked in the five largest markets in the EU along with the US, Japan and Canada and nine products were identified that had achieved a launch in all markets in the period of the study (2000-2002). The median duration from first to last launch was just over three years but this relatively long time lag could, Dr Lumley suggested, be skewed slightly by the delay in submitting products for registration in Japan. If, however, the aim is for simultaneous submission and launch this raises the question of whether there is anything that the regulatory group can do to compress the timelines.

Success rates

Dr Lumley also provided data on success rates for products entering the different stages of development from pre-clinical, the phases of clinical testing to submission and marketing. The statistic of most direct relevance to regulatory affairs was the success rate of 90% from submission to the market for a cohort of 70 products. Success rates were considerably lower at earlier stages of development and of particular concern was the finding that the probability of success for a compound moving from Phase II to Phase III (first patient dose to first pivotal dose) was less than 30% based on a study of 236 projects that entered a development phase in 1998-2000 and were followed to the end of 2003.

Dr Lumley suggested that there might be a role for regulatory affairs not only in looking at success in the final, registration phase but also in contributing to the decision-making and to the

information process within organisations to help to improve success rates at the earlier stages of development.

Lifecycle management

Expanding on this theme, Dr Lumley suggested that there is scope for regulatory affairs to expand its traditional role and become involved throughout the lifecycle of a project (see *Figure 2*). She cited, as examples, establishing a realistic and achievable therapeutic profile at a very early stage and ensuring that appropriate information is collected that will clearly established the safety and efficacy profile of the compound.

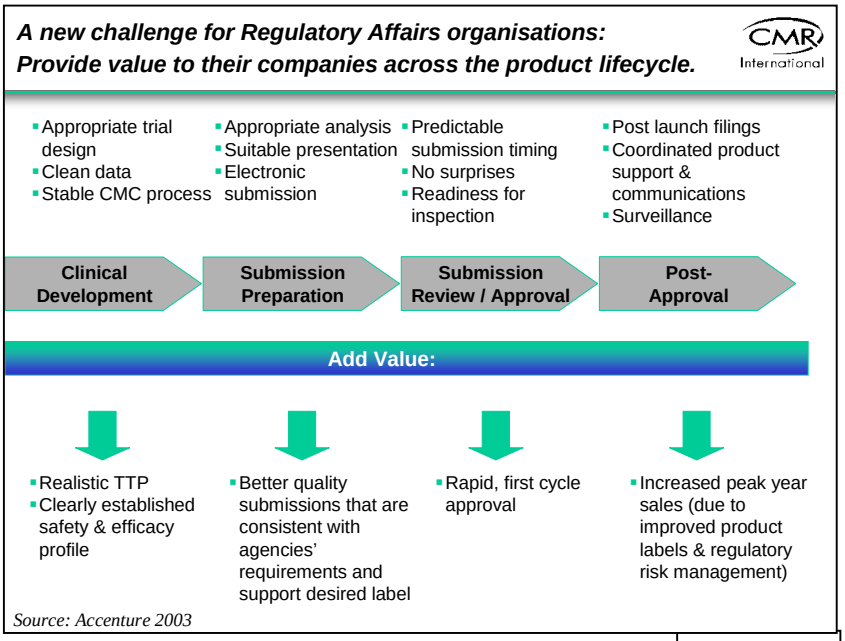


Figure 2

CMR International Regulatory Performance Metrics Programme

The vision for the CMR International Regulatory Performance Metrics Programme has been developed by working with a number of companies, Dr Lumley explained. The programme has been set up with the aim of providing a source of reliable, contemporary and comparable data that allows participating companies to:

- Compare their performance with that of the industry;
- Set targets against which their management teams can appoint realistic internal goals and objectives;
- Provide management with information on areas of regulatory performance that require development and improvement;
- Gain insights into the ways in which Regulatory Affairs can add value to the R&D process.

The discussions with companies have also identified a number of key business questions to be addressed in relation to an expanded role for regulatory affairs and Dr Lumley gave examples:

- Is regulatory affairs resourced appropriately, compared with other companies?
- What is the quality of the submitted dossier and how can quality be measured?
- Where should changes be made to optimise processes in RA?
- How frequently does RA meet its targets?
- How productive is regulatory affairs and how should productivity be measured?

The last of these questions, Dr Lumley suggested, is one of the most fundamental and one of the most difficult to address. There are many components to be taken into account when looking at productivity, not just the time and effort to move a project through the process but also elements of 'success rates' and 'quality' that are difficult parameters to measure. The performance metrics programme has been designed to address these aspects.

Design of the Regulatory Performance programme

Outlining the scope and structure of the Regulatory Performance programme, Dr Lumley explained that key metrics are collected at two levels:

- Overall company effort (Section 1 of the Programme)
  - Resources in $ and full time employees (FTEs)

- Individual project data (Section 2 of the Programme)
  - Interaction with core Regulatory Authorities
  - Regulatory cycle times and outcomes

Company Effort

One of the greatest challenges has been trying to find comparable elements at the higher level of how regulatory affairs is organised, because of the wide differences across the industry and across companies. Some of the markers for the way the value of regulatory affairs is perceived within the company include:

- The involvement of regulatory affairs in decision-making at different stages of the development process;
- Whether the head of regulatory is represented on the highest decision-making body in the company.

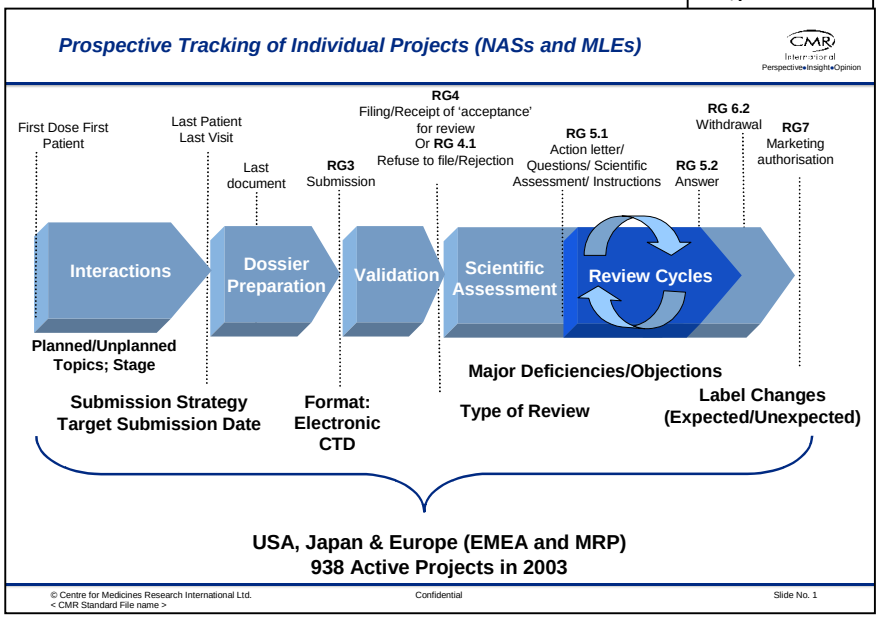
Data is also collected on resources, staffing and expertise, and workload (for new active substances and major line extensions).

At present, because of the complexity and diversity of organisational structures the programme is restricted to the regulatory affairs functions of companies in the ICH regions (including Switzerland) and excludes local operating companies.

Individual projects

In discussing the data that is being collected on individual projects, Dr Lumley drew attention to the similarities with the CMR Institute Benchmarking study for regulatory procedures (*see Section 3, page 2*). Each individual project is tracked from the stage when it reaches the first dose and the first patient anywhere in the world through to the final outcome (termination of the project, withdrawal of the application or issue of a marketing authorisation) as shown in *Figure 3*.

Figure 3



Dr Lumley emphasised that, at this early stage in the programme, the focus is on the US, Japan and Europe and the tracking is confined to major scientific interactions in the R&D process that involve the regulatory affairs department. The ultimate goal, having collected the history of these interactions is to see if there are correlations between the involvement of RA in the early stages and events that occur later on in the review procedures. The ability of regulatory affairs departments to predict the timelines for review and approval are important and this is tested in the tracking system. When the project reaches the 'last patient last visit' milestone companies are asked about their strategy and target submission dates for simultaneous submission in two or more regions Later checks will show whether the targets have been met.

The format of the application (paper, electronic or both) is recorded in order to determine if there are correlations with subsequent activities. Other items in the study include the type of review – e.g., priority, standard or rolling – and any major deficiencies in the data or label changes. Of particular importance is the incidence of totally unexpected and unanticipated problems that caused major delays, since one of the objectives is to avoid such difficulties. One of the indicators of regulatory success or failure that the study includes is whether any label changes that are made

in order to achieve authorisation have a significant impact on the intended therapeutic use of the product.

Vision for the future

The programme is only in its second year but has 20 participating companies which include ten of the top 15 multinationals, categorised by R&D investment. At this early stage, Dr Lumley noted, the focus is still on establishing and confirming goals and definitions and identifying common processes and activities in order to collect comparable data across companies. As the programme develops, however, and confidence is established in the robustness of the data, they will be analysed in more depth and in different ways.

In conclusion, Dr Lumley looked at future possibilities for the project. Whereas the current programme is concentrating on performance within individual companies and across companies, the next stage is to consolidate these individual metrics in order to look at productivity and particularly to assess how much value has been created relative to the investment made. In this case it is a question of how much value regulatory affairs is adding to the R&D process and to the predictability of future performance. In particular, the aim is to identify where changes should be made and new initiatives implemented in order to ensure that that performance does not deteriorate and, if anything, improves as we go forward.

HOW REGULATORS PERCEIVE COMPANY PERFORMANCE

Dr John Jenkins
Director, Office of New Drugs, CDER, FDA

'Applicant benchmarking' has been the forgotten metric in performance studies, Dr John Jenkins suggested in his opening remarks. There has been much focus, over the past decade or more, on benchmarking the application, review and approval process, he said, but the spotlight has been almost entirely on the regulators and how they are conducting their business. The key driver for a successful outcome, however, is the quality of development programmes and the resulting application, and this is the primary responsibility of the applicant. An agency can provide advice and let the company know what the regulatory expectations are, but the responsibility for managing the development programme in an efficient and effective manner rests entirely with the company. 'We could have a perfect regulatory process', he said, 'but this will not result in an approval if the application you submit is not up to standard and fails to meet regulatory and statutory standards'.

It is much more difficult, however, to find metrics for benchmarking the applicants' performance than it is to measure timelines and outcomes. The measurement of a company's 'competence' requires metrics for quality which are difficult to define and much more subjective. Such metrics would need to include the reasons why certain applications encounter problems and fail. Dr Jenkins pointed out, however, that such details are often protected by commercial confidentiality. FDA does not, for example, publish its reviews and conclusions for products that are not approved.

Refusal-to-file

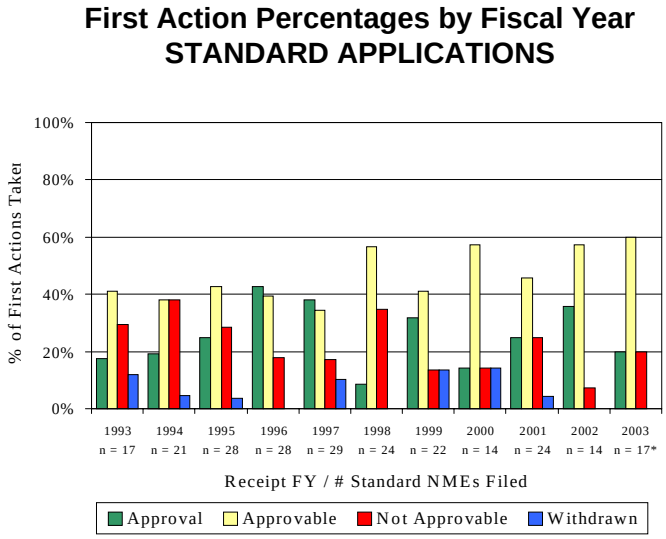
There are, nonetheless, some metrics that can be used for benchmarking the applicant. The first that might appear an obvious and useful metric is the refusal-to-file rate. In the US, however, the refuse-to-file threshold has deliberately been set high and the refuse-to-file rate is only about 3-5%. An application would need to be grossly deficient before it is turned away at the start of the process, and Dr Jenkins gave the example of applications where both the Phase III pivotal clinical studies failed to meet the primary end points and yet they are filed because FDA is obliged to consider the sponsor's argument for assessing the trials on the basis of the secondary endpoint. He explained that the thinking behind this strategy is to avoid refusal-to-file being used as a means of regulating intake when the work-load is high.

First cycle approvals

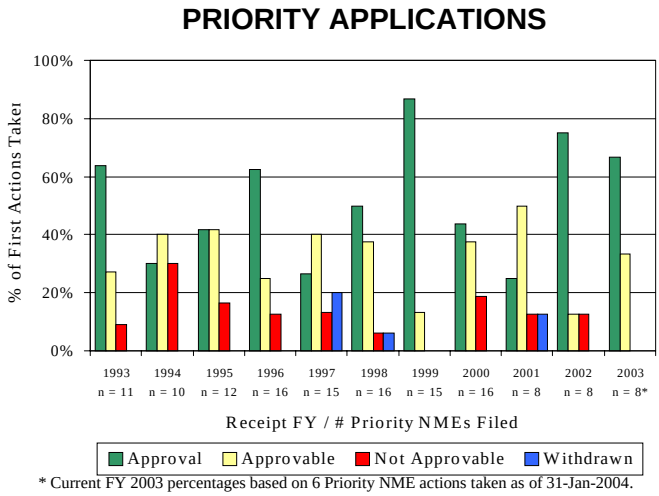
Historically, some 75% of new drug applications (NDAs) for NMEs are eventually approved if their progress is followed for long enough, but relatively few will be approved on the first cycle. Taking the rates for fiscal years 1993 to 2002 (see Figure 1):

- Standard applications result in 26% first cycle approvals (range 9-43%)
- Priority applications result in 51% first cycle approvals (range 25-87%)

Figure 1



* Current FY 2003 percentages based on 10 Standard NME actions taken as of 31-Jan-2004. Seven FY 2003 Priority NMEs are pending a first action decision.



* Current FY 2003 percentages based on 6 Priority NME actions taken as of 31-Jan-2004. Two FY 2003 Priority NMEs are pending a first action decision.

Dr Jenkins commented that, despite FDA's success in improving performance under PDUFA, the large gap between 26% approved on the first cycle and 75% that are eventually cleared indicates that the system is still very inefficient. Whilst this might be seen by some as a problem for the regulators he felt it was as much – if not more – the applicants' problem. There is little more that FDA can do, in terms of process improvements, to increase first cycle success. When the applications are examined the problems do not lie with the process but with issues of safety, efficacy and manufacturing.

There is an assumption, Dr Jenkins suggested, that review procedures are built on the premise that approvals will be multi-cycle but this is not true of the FDA system. This has been designed to operate most effectively and efficiently as a first-cycle approval system.

Also referring to the charts in *Figure 1,* Dr Jenkins suggested that they help refute the arguments that it is changes in FDA's attitude and standards that are responsible for changes in approval rates. There is no pattern, he said, to justify the suggestion that reviewers systematically become more conservative or more liberal in their view of the risk-benefit equation.

Looking at the figures for priority applications, he argued that FDA could not move from being very liberal, in 1999, to conservative in 2000 and back again to a liberal policy in 2002. The mindset and thinking of reviewers cannot be changed within that timescale and it is much more likely that the variations reflect the quality of the applications and how well they meet standards for approval.

Comparison between companies

Dr Jenkins noted that one of the most frequent questions he is asked to address is how companies compare and whether large companies are more successful, at the regulatory review stage, than smaller companies. Now that biologics applications are reviewed along with chemical entities, there is also the question of whether conventional drug companies are more successful than biologics companies. By anecdote, Dr Jenkins suggested that the answer was 'yes', applications from the larger, more experienced companies were of better quality, but he also noted that there

was great variability between the quality of applications submitted by the same company, such that it was sometimes hard to believe that they came from the same source.

NMEs submitted FY1998-2003

- 80 sponsors submitted one NME
- 14 sponsors submitted two NMEs
- 7 sponsors submitted three NMEs
- 3 sponsors submitted four NMEs
- 4 sponsors submitted five NMEs
- 3 sponsors submitted >five NMEs

Novartis (12), GSK (7), BMS (6)

One of the problems in providing comparative data, however, is the low number of NME submissions per company (see box). Over 100 sponsors had submitted NME applications in the fiscal years 1998 to 2003 but 80 of these had only submitted one such application during this period and only three had submitted 5 or more. It is hard to assess comparative quality when individual companies have submitted so few dossiers, and the fact that the review can be spread over 17 clinical divisions within FDA, makes any comparison even more difficult.

Nonetheless, Dr Jenkins was able to show charts (figure 2) that indicated a correlation between first cycle approval rates, median approval times and the number of applications filed in fiscal years 1998-2003. The first cycle approvals, in particular, indicated a higher success rate for the companies that had submitter a larger number of applications and these, in turn, were predominantly the larger companies.

Criteria for success

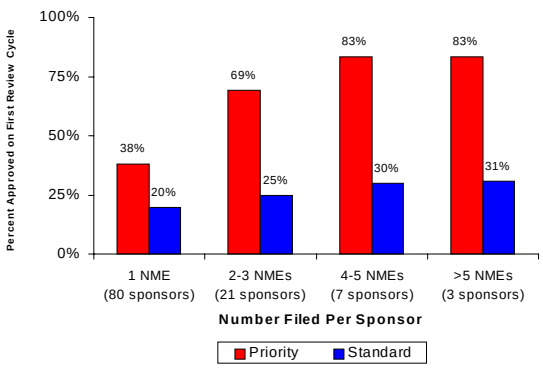
Taking and understanding FDA Advice

Dr Jenkins turned to the subject of the criteria for success over the regulatory hurdles, but emphasised that he was giving his own perspective on the issues and from an FDA viewpoint that might not apply in Europe or Canada.

Firstly, he pointed out that pre-submission consultation in the FDA is free and companies should take advantage of this. There are indication-specific guidances, and the FDA reviews that are made available under the Freedom of Information Act (FOI) provide insight into what has been done in the past, study designs and the benefit-risk equation that has been accepted in similar areas.

Figure 2

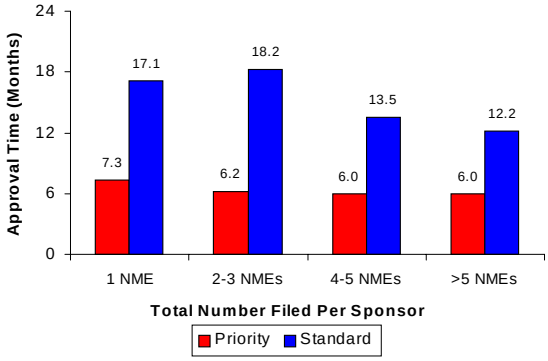
First Cycle Approval Rates for New Molecular Entities
based on # of NMEs Filed by Sponsor
during Fiscal Year 1998-2003



Number of Applications Filed

Priority	34	13	12	12
Standard	46	36	20	13

Median New Molecular Entity Approval Time
based on # of NMEs Filed by Sponsor
during Fiscal Year 1998-2003



Number of Approvals

Priority	25	13	12	12
Standard	28	25	13	7

CDER also holds some 1400 formal meetings a year between regulators and companies, and most of these are pre-submission meetings. Dr Jenkins encouraged companies to make good use of the pre-IND, end of Phase IIa, end of Phase II and pre-NDA meetings that are offered, and to heed the advice given. He also referred the Special Protocol Assessments available to carcinogenicity

studies and Phase III protocols but noted that, whilst the latter were important for novel products or new therapeutic areas, they were unlikely to be needed in areas with a well-documented history.

Dr Jenkins stressed the importance of ensuring that the answers and advice provided by FDA were clearly understood. It is incumbent on the sponsor to make sure that they are clear about any guidance before leaving the meeting and he warned against following advice that was not fully understood or carrying out studies that do not make scientific sense. Regulators are human and fallible and it is not pleasant to be challenged, but advice can be questioned in a non-threatening, polite and professional manner that will lead to a positive outcome for both parties.

Incomplete applications

Dr Jenkins returned to a theme that he had expounded at an earlier CMR International Institute Workshop[1], about the impact on the review and approval process of incomplete applications. Although the validation procedure allows applications to be accepted in the knowledge that additional data will be provided later, he stressed that the submission of complete applications is a fundamental principle of PDUFA that is reiterated in the new Good Review Management Practice (GRMP) guidance.

The Division can more effectively plan the review within the agreed timeframe for a first cycle approval if the application contains all the data from the outset. Human nature is such that, if reviewers know that a second study is expected in six months time they may not review the first until the second arrives, with the result that the work is compressed into a short time-window at the end of the process and deadlines may be missed.

Post-action meetings and re-submission

Dr Jenkins advised companies to request a post-decision meeting if the outcome of the review is unfavourable or results in less than the company had anticipated, in order to understand the issues and deficiencies.

Similarly it is very important to hold discussions with FDA before re-submitting an application that has been found deficient. As with incomplete applications, FDA is obliged to accept incomplete responses, if arguments have been made to justify a review, but this is not an efficient way to proceed and can be avoided by ensuring that there is adequate consultation.

In conclusion

Summarising, Dr Jenkins re-iterated his view that, benchmarking of applicants' performance has been overlooked, whilst attention has been focused almost entirely on the regulators. Metrics might be difficult to capture and assess but the 'bottom line' is that the sponsors have the primary responsibility for the quality of their development programmes and submissions. The new GRMP guidance, he said, goes so far as to say that a well formatted, complete application that is the result of the well carried-out development programme, and that meets regulatory and statutory standards, will be approved on the first cycle.

SESSION 3: POINTS FROM THE DISCUSSION

Advisory Committees: There has been no specific study on the impact of the FDA Advisory Committee process on first cycle success and the timing of the review. Although FDA was reputed to follow committee advice in almost all cases, this is not necessarily the rule as they are often more stringent with sponsors than FDA would be because they do not have the regulatory perspective of what the statutes require and they sometimes have unrealistic expectations that need to be put back into context.

Priority reviews: These have a higher first-cycle success rate than standard applications but this does not necessarily reflect better submissions. In fact they may be less well put together because they are often prepared in a hurry. By definition priority applications are expected to have a therapeutic advantage over existing therapies and are often for serious and life-threatening disease. In the interest of public health, reviewers will work with the company in order to achieve approval in the first cycle.

Draft labels and Phase IV commitments: These are covered in the forthcoming GRMP guidance which includes a model setting out the steps that need to occur in a first cycle review including: when the five years review should be finished; when the secondary reviews should be finished; and when the package should go to the signatory authorities. The objective was to move these events further away from the end stages of the process, in order to leave time for the labelling negotiations and discussions of Phase IV commitments.