
**REGULATORY PERFORMANCE:
Critical Success Factors in Today's Environment**

CMR INTERNATIONAL INSTITUTE WORKSHOP

15-16 September 2003, Washington D.C., USA

SUMMARY REPORT

Margaret Cone and Stuart Walker

SECTION 1. OVERVIEW

Participants at the CMR International Institute Workshop on *Regulatory Performance* found them in the unique position of receiving first hand reports, from FDA and EMEA, of the confidentiality agreement that was finalised between the two parties on Friday 12 September 2003¹. The agreement, which will facilitate the sharing of regulatory information on pre- and post-authorisation issues, underlined one of the main themes that ran throughout the Workshop.

There was consensus that one of the most important success factors for regulatory performance is good communications and the exchange of information between experts in companies and agencies, where such exchanges can streamline the product registration process and make new medicines available to patients more efficiently. The Workshop therefore welcomed the new FDA/EMA agreement and called for cooperation from all sides to expedite its implementation.

A related theme that emerged from the Workshop was the need for a radical re-examination of the limits and constraints of confidentiality placed on regulatory agencies. Whilst commercially valuable information and intellectual property must be fully protected, there are many instances where the authorities have information on general scientific issues that, if shared, could help company researchers to avoid pitfalls, dead ends and, more importantly, potential safety hazards. The Workshop asked that the CMR International Institute's Advisory Board should examine a proposal that industry should take the initiative in agreeing that agencies could pool and share specified information that could be of benefit in improving the efficiency of research and avoid wasting resources.

These issues were discussed against a background of data on the ever-increasing investment in new drug research whilst the output of new medicines has declined dramatically in recent years. Although the research pipeline appears to remain full, products are staying for longer in the early phases of development where the attrition rate is high. Whilst it was acknowledged that it is far more economical to abort a project at an early stage than later, there were concerns that valuable products could be lost as a result of increasing the regulatory and research hurdles in Phases I and II.

An examination of the extent to which the regulatory environment had changed was one of the objectives of the meeting and, in accordance with the working practices of the Institute, a survey had been carried out among regulators and industry, in advance of the Workshop. Among the many conclusions and inferences that could be drawn from the data was the perception that regulators had become more risk averse in recent years.

Another issue of concern, at the other end of the research cycle, was increasing commitments to conduct post-authorisation studies, which are reported to consume up to 20% of clinical research expenditure. One of the recommendations from the Workshop suggested that the CMR International Institute should carry out a study to quantify the impact of conditions and commitments attached to authorisations.

¹ EMEA Press release 12 September 2003 (EMA/D/24478/03/Final) followed by an announcement by EMA of the *First parallel EMA-FDA scientific advice procedure*, Press release, 22 October 2003, (EMA/D/28727/03/Final)

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

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SECTION 2. OUTCOME

Session 3 of the Workshop, during which the syndicate discussions took place, was chaired by **Dr David Jefferys**, Head of Devices Sector, *Medicine and Health products Regulatory Agency (MHRA)*, UK. There were four Syndicates and each was asked to identify key changes that are affecting drug development and regulation and to propose *critical success factors* for optimising regulatory performance, in response to these changes. The four syndicates addressed two topics:

Topic A: Pre-submission: Changes and responses to change in the discovery and clinical development phases of drug development.

Syndicate 1: Chair: **Dr Mike Clayman**, Vice President, Global Regulatory Affairs, *Eli Lilly & Company Limited, USA*;
Rapporteur: **Margaret Cone**, Director of Regulatory Science, *CMR International Institute for Regulatory Science*

Syndicate 2: Chair: **Professor Samuel Vožeh**, Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, *Swissmedic, Switzerland*;
Rapporteur: **Dr Graham Burton**, Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, *Celgene Corporation, USA*

Topic B: Post-submission: Changes and responses to change in the regulatory review and post-authorisation phases.

Syndicate 3: Chair: **Dr Leonie Hunt**, Director, Drug Safety and Evaluation Branch, *Therapeutic Goods Administration, Australia*;
Rapporteur: **Dr Steve Caffé**, Vice President, Head GDDC/US Regulatory Liaison, *Aventis Pharmaceuticals Inc, USA*

Syndicate 4: Chair: **Professor Stuart Walker**, Executive Director, *CMR International Institute for Regulatory Science*;
Rapporteur: **Dr Stewart Geary**, Director, Medical, Regulatory Affairs and Pharmacovigilance, *Eisai Co. Ltd, Japan*

Recommendations from the Syndicates and items from the Rapporteurs' reports are summarised here.

RECOMMENDATIONS ON CRITICAL SUCCESS FACTORS

TOWARDS GLOBAL SCIENTIFIC ADVICE

The signing of a confidentiality agreement between FDA and EMEA was welcomed as a significant step forward and it was hoped that this would pave the way for increased multi-lateral consultation on drug development projects. It was noted that procedural details had to be worked out in order to put the agreement into practice and the importance of having the sponsor 'at the table' was stressed.

It was recommended that industry give its full support and cooperation to this initiative. Noting that there are advantages in having the procedure initiated by a request from a sponsor, companies were encouraged to 'volunteer' in order to help pilot the project. It was hoped that success in information exchange at an international level could be seen as a move towards global scientific advice. The use of videoconferencing, web conferencing and electronic communications were advocated to facilitate the procedures.

SHARING AGENCY EXPERIENCE

There is a wealth of knowledge and experience contained in the closed files held by the regulatory agencies but confidentiality constraints prevent this from being shared.

A scheme was envisaged under which companies could allow the agencies to share information on pre-clinical, clinical and chemistry, manufacturing and control (CMC) issues related to drug development. Participating companies could identify and clear anonymised information for sharing and would, in return, receive other information through the scheme.

Primary objectives would be to avoid waste of resources and the ethical issues involved in allowing companies to pursue research where the agencies have knowledge of specific hazards or where the undertaking is known to be a 'blind ally'. Without compromising intellectual property it should be possible to enhance drug development by allowing unsuitable products to be terminated earlier and promising ones to be accelerated, to the ultimate benefit of the patient. Data sharing would apply, in particular, to new chemical entities (NCEs) for the same target and to clinical experience with the same indication or target population.

It was suggested that unpublished information on abandoned projects and clinical trials with a negative outcome could also be added to this data resource.

Sharing such data would obviously be a sensitive issue that would require a top-down approach from the highest level within companies to address concerns about competition and commercial confidentiality. **It was recommended that the CMR International Institute Regulations Advisory Board should take up the proposal for further discussion.**

POST-MARKETING COMMITMENTS

Commitments to carry out post-marketing studies and investigations, entered into at the time of product authorisation, must be realistic, achievable and likely to yield usable and useful data. It has been claimed that, for smaller companies, up to 20% of the clinical trials budget can be taken up by post marketing studies required as a condition of authorisation.

The procedures for setting conditions for post-marketing studies need to be reviewed to ensure that companies are not being pressured to agree to accept conditions at short notice as the 'price' of obtaining an authorisation. Not only is there a major resource issue but also one of monitoring such commitments and ensuring compliance within specified time limits.

It was recommended that a study be carried out, possibly by the CMR international Institute, to quantify post-marketing commitments in terms of resources and compliance levels. Such a study would pave the way for a review of the procedures for assigning and agreeing post-marketing conditions at the time of authorisation.

GLOBAL RISK MANAGEMENT

Related to the previous point was a **recommendation for companies to plan proactively to develop a global risk management programme.**

Such a plan will drive post-marketing commitments and should involve all parties, including health care professionals and pharmacoepidemiologists.

CONTINUITY IN THE DIALOGUE BETWEEN COMPANIES AND AGENCIES

Acknowledging that there are frequent personnel changes within both companies and agencies, there is nonetheless, a need for a greater continuum in the advice given to companies by regulators and the companies' teams of experts that deal with regulatory issues.

It was recommended that:

- Agencies should ensure greater continuity between the advisory teams and review teams dealing with specific projects;
- Companies should not disband, completely, their teams of experts once a marketing authorisation is obtained and hand the post-marketing care of a product to a new group who do not have the same background knowledge of the product.

Whilst continuity is important, however, it must not be dependent on the views of specific individuals – it must not be ‘personality driven’. Within the EU Centralised Procedure, there may be advantages in identifying the rapporteur and co-rapporteur at an earlier stage, say Phase IIb, and involving them in the scientific advice discussions.

RESOLUTION OF GLOBAL ISSUES

Major scientific issues, which impact on global drug development, require a coordinated approach to consensus building. **It was recommended that workshops should be established** between regulators, industry, academia and practitioners to create consensus on issues as a basis for drawing up global guidance and guidelines.

The example was cited of the ICH Guidance on QT interval prolongation² where a major consultation had been held, involving all interested parties, as part of the development of the guideline.

RISK BASED APPROACH TO REGULATORY REQUIREMENTS

With the advance of science there are increasing demands to gather more and more information and data in Phases I and II of development, a fact that is reflected in the metrics showing that pipeline drugs are remaining longer in these phases³. These include pharmacokinetic, pharmacodynamic and pharmacogenomic issues. There is always more information that could be obtained but research cannot be sustained on this basis.

It was therefore **recommended that requirements should be defined for the safe and effective therapeutic use of new medicines**. This should be a risk-based approach to essential data and must avoid the growing tendency to include ‘nice to have’ information.

RELATIONSHIP BETWEEN INDUSTRY AND AGENCIES

A partnership between industry and agencies is an important success factor but there is a need for education to improve the relationship, which can be marred by a lack of trust and ‘arrogance’ on both sides. There is a need for companies to convey more open and consistent messages with greater transparency. Drug development projects must be discussed, ‘warts and all’, bringing all issues into the open without attempts at concealing difficult issues. Regulatory agencies must be equally open and the outcome of meetings need to be recorded better than at present.

BEGINNING WITH THE END IN MIND

The practice adopted by many companies of defining a target package insert, setting out the desired, ultimate, label claims is a useful way to structure discussions, not only within companies but also with regulators. It creates the basis for a well-delineated and clearly linked clinical development programme and allows critical discussions on the way in which a project is proceeding.

² ICH S7B: Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals, released for consultation under Step 2 of the ICH process, February 2002, ICH website: <http://www.ich.org>

³ Presentation by Dr Neil McAuslane on *What do trends and indicators tell us about the changing regulatory environment?* Session 2 of the Workshop

Companies have found that the approach works well for early discussions with FDA and **it was recommended** that a similar approach should be applicable for discussions during the EU Scientific Advice procedures.

ELECTRONIC SUBMISSIONS

Realisation of the potential of fully electronic, 'paperless' submissions was recognised as a major success factor. The common standards for the ICH electronic Common Technical Document (e-CTD) is obviously a major step towards this, but other tools and developments are required to recognise and accommodate the different ways that submissions are reviewed by the different agencies.

A further commitment and investment was required by the agencies to implement electronic data management that supports the review procedure. It was, however, recognised that electronic data management is not a core competency of either the pharmaceutical industry or the regulators. **It was therefore recommended that a third party (an 'infobroker') should be appointed to manage a database of electronic submissions** to which companies and regulators would have access, under appropriate conditions of confidentiality.

POINTS FROM THE DISCUSSION

CHANGING REGULATORY ENVIRONMENT

CMR International data has shown that, whilst there are an increasing number of NCEs entering Phase I, they are staying longer in Phases I and II with an increasing attrition rate and a consequent decrease in the numbers in Phase III of the pipeline⁴. The following were proposed as factors influencing this observation:

Regulatory environment

- The implementation of the Centralised Procedure in the EU and the accompanying changes in procedures and requirements, including the greater emphasis on comparative efficacy and safety;
- High profile withdrawals in the last six years, and the resulting changes in testing methods and requirements. Examples include QT interval prolongation;
- Increased risk aversion in companies and authorities leading to earlier abandoning of drugs during the clinical development stages;
- Increased complexity of the drug development process resulting from advances in technology and factors such as new privacy rules and their impact on the conduct of clinical studies;
- A changing clinical trial environment including the role of IRBs/ethics committees, controversy over the use of placebos vs. active comparators and the introduction of the EU Clinical Trials Directive.

Company environment

- 'Regulatory creep' resulting from companies carrying out tests that are not necessarily requirements, e.g., in the interests of achieving a 'harder' end point;
- Early abandoning of 'me too' drugs where there are no specific advantages over others on the market;
- The increasing need to take pricing and reimbursement into consideration as well as considerations of return on investment;
- The increased sophistication of targets and therapies, for example the statins, and treatments for diabetes.

⁴ Presentation by Dr Neil McAuslane on *What do trends and indicators tell us about the changing regulatory environment?* Session 2 of the Workshop

OBSERVATIONS ON 'QUALITY'

The meaning of 'quality' in terms of drug submissions and regulatory review needs to be better defined. Regulatory review times can be measured relatively easily but this may simply be a measure of efficiency, which ignores whether the review reached the correct conclusions. From a company point of view, avoiding a 'refuse to file' action is a relatively low standard for quality. An analysis of the lists of questions sent to companies may be a better measure of the quality and completeness of the original application.

There is a danger that there is a greater focus on the speed of review, and on achieving filings and approvals by specific dates than the more important goal of bringing good medicines with appropriate prescribing information to patient, in a timely manner.

OBSERVATIONS ON SCIENTIFIC ADVICE

A formal procedure for obtaining Scientific Advice exists in the EU but there is a perception that it could be more flexible and the scientists more accessible. It is often more useful to companies to go to national agencies for advice than to use the EMEA process. The system is also open to criticism because of the non-binding nature of the advice, in contrast with the system under which FDA provides advice.

Situations might arise where changes in background information have a major impact on the scientific advice previously given to a company. Under such circumstances agencies should be proactive in informing the company. If the change is prompted by a safety issue that has been highlighted by a competitor's application, questions of confidentiality need to be addressed, as discussed in the earlier recommendation.

As a general observation, the quality of scientific advice can be improved by ensuring that the agency understands the company's development plans as early as possible, for example whether the aim is 'first in class' or 'best in class' for a new drug. There should be open dialogue on the full plan as it goes forward, not just in relation to the next protocol. A clinical development plan should be submitted between Phase IIa and IIb.

RESPONDING TO REQUESTS FOR INFORMATION DURING REVIEW

Most companies are establishing 'rapid response teams' to ensure that requests for further information are dealt with promptly. Success can be improved by setting targets for how quickly responses are generated and by anticipating questions rather than a 'wait and see' attitude.

CLOSING REMARKS FROM THE CMR INSTITUTE

Thanking the speakers, organisers and participants, Professor Stuart Walker, Executive Director of the CMR Institute welcomed the recommendations and proposals, especially those that involved the work of the Institute. These would be taken up by the Regulations Advisory Board.

Many of the issues discussed would be integrated into the programme of work for the Institute in 2004. The Institute Agenda 2004 would be published and circulated in November 2003 and Professor Walker drew attention to the following events:

- A Workshop on *Global Drug Development* to be held in Tokyo, Japan, 26-27 May 2004 which would look, in particular, at the integration of Japan into global research programmes;
- A Workshop entitled *Beyond Benchmarking*, 4-5 October 2004 to be held in Washington, that would focus on CMR International studies of key milestones and timelines for regulatory agencies and key performance metrics for companies;
- A Workshop on building quality into the application and review processes to be held in the UK, 2-3 December 2004.

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SECTION 3. MEETING SUMMARY

SESSION 1. CHANGES AND CHALLENGES IN THE CURRENT REGULATORY ENVIRONMENT

Chairman: Dr Robert Peterson

Director General, *Therapeutic Products Directorate, Health Canada*

Referring to the title of the Session, Dr Robert Peterson suggested that part of the challenge will be to decide how 'today's environment' should be defined, since it is certainly a 'changing target' both for those in regulatory agencies and in the industry. The opening Session of the Workshop would set the scene by identifying key issues for companies attempting to gain success in the application process and authorities that are facing the challenge of change. The second session would focus on topics related to the apparent decline in the number of submissions that are being made to the authorities.

Dr Peterson welcomed the opportunity that the Institute Workshops provide for regulators and industry to meet in an environment that allows candid and open discussions and disclosure of information, both in the formal presentations and in the syndicate sessions.

EU REGULATION AT A TURNING POINT

Dr Marisa Papaluca Amati

Deputy Head of Sector, Safety and Efficacy of Medicines Sector, *European Agency for the Evaluation of Medicines (EMA)*

Although EU pharmaceutical regulatory environment is changing, with the imminent expansion of EU membership and the revision of pivotal directives, Dr Papaluca Amati emphasised that the objectives of the European System had not changed since the EMA was set up in 1993. These can be summarised as:

- A single EU market for medicines
- Protection and promotion of public health
- Reinforcement of European industry's R&D
- International cooperation
- Provision of information

Dr Papaluca reviewed the drivers for change in Europe in the political context, in relation to enlargement and the new legislative environment and in the context of the pharmaceutical industry. She referred to the publication of key recommendations from the G10 top level 'think tank'⁵ and quoted extracts to illustrate that, for the first time, the pharmaceutical industry was recognised as having a central position in relation to public health. In particular, she quoted the G10 call for 'enhancing the competitiveness of the pharmaceutical industry in the context of achieving high level EU public health objectives'. In emphasising the need to 'make accessible, efficacious, high quality and safe medicines, including the more recent and innovative ones, to all those who need them regardless of their income or social status', G10 had highlighted the need for regulators to think not only in terms 'traditional' terms of the safety, quality and efficacy of medicines but also about the so-called 'fourth hurdle' of

⁵ COM (2003) 383 final: *A stronger European-based pharmaceutical industry for the benefit of the patient: A call for action*
http://europa.eu.int/eur-lex/pri/en/dpi/cnc/doc/2003/com2003_0383en01.doc

achieving access to new medicines. At present, the European market is very much linked to public health funding with all constraints and difficulties this entails. The G10 report included proposals to make this more dynamic and competitive with full competition for medicines that are neither purchased nor reimbursed by the State.

Completion of the single market was a major objective when the EMEA opened in London in 1993 and the centralised system introduced in 1995 was a pivotal step towards this objective with one dossier, one decision and a pan-European authorisation. New laws had been implemented to make the single market a reality and, although complex, it was believed that the system was sufficiently dynamic, flexible and robust to accommodate the expansion from 15 to 25 members.

Dr Papaluca emphasised that EU enlargement has not 'happened overnight' and that there had been careful planning for the 2004 target for many years. She referred to three main initiatives:

- PECA: Protocol to the European Agreement ... on Conformity Assessment and Acceptance of Industrial Products;
- PIC/S: the Pharmaceutical Inspection Cooperation Scheme and
- PERF: the Pan European Regulatory Forum on pharmaceuticals, established in 1999 to aid accession.

The accession countries themselves had adopted a simplified centralised procedure, undertaken the task of updating old dossiers to meet current requirements and implemented new legislation to bring their regulatory procedures into conformity with the *acquis communautaire*. Since early 2003, the EMEA had been working with the accession countries on a benchmarking project for quality assurance systems and regulatory authorities from candidate countries had been invited as observers to EMEA committees at all levels.

Dr Papaluca noted, however, that the learning experience was not all one way. The acceding countries have many new ideas to share on ways of solving problems and the advantage of having a new input are being realised. Furthermore, since the EMEA relies on a network of expertise throughout its membership there will be opportunities to benefit from a greatly expanded network of experts. At the same time the number of patients that can benefit will be increased with a single pharmaceutical market estimated at 450 million. It is, however, acknowledged that there are obstacles to be overcome in terms of pricing and reimbursement systems.

Referring to key changes and developments in the EU environment, Dr Papaluca cited: the revision of Regulation 2309/93⁶ and the codification of the major pharmaceutical Directives as Directive 2001/83/EC⁷; the implementation of the ICH Common Technical Document (Annex 1 to Directive 2001/83/EC) and the implementation of clinical trials directive (2001/20/EC). Impending revisions to the legislation would change the administrative and scientific structure of the CPMP, with each member state having only one delegate, but the role of the experts would be reinforced with the networks extended to international experts, nominated by the EMEA. The CPMP would be establishing additional working parties and expert groups, including expert working groups by therapeutic area.

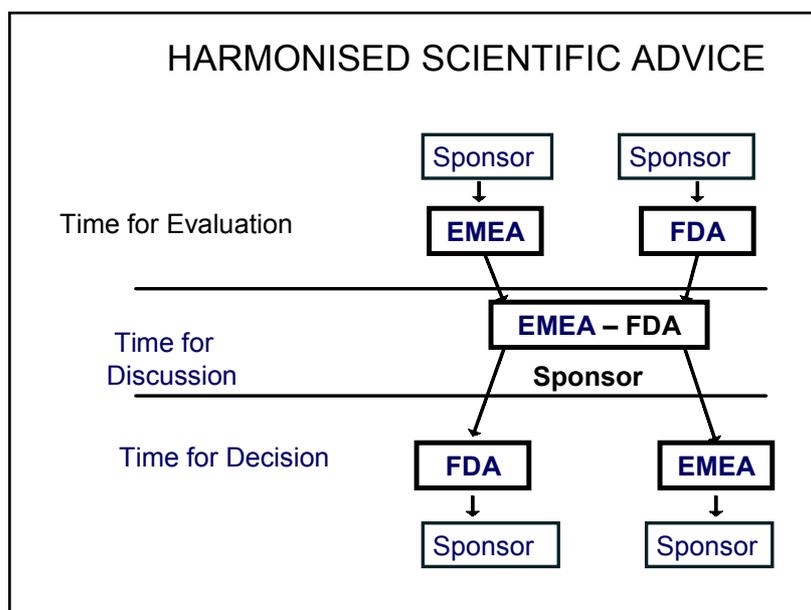
One of the roles of the reinforced scientific expertise and networks would be to support the EMEA's scientific advice activities. A specific working group was being set up with specialised groups on established and new therapeutic areas. Dr Papaluca Amati presented data on the current system which showed that, in 2002, 30% of centralised applications had received Scientific Advice and a preliminary analysis of the outcome of applications had shown a clear correlation between success rates and seeking such advice.

⁶ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

⁷ Council Regulation (EEC) No 2309/93, of 22 July 1993, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

Finally, on the subject of scientific advice, Dr Papaluca Amati made the important announcement that, on the previous Friday, 12 October 2003, the EMEA and FDA had finalised a confidentiality agreement that would facilitate the exchange of information between the agencies and could pave the way to greater consistency and transparency in the advice that is given. Perhaps, she suggested, simultaneous, joint advice could become a reality. In the meanwhile each agency would remain responsible for the advice it provides and the scheme shown in *Figure 1* illustrates the procedures that are envisaged.

Figure 1



CHANGING HORIZONS FOR CLINICAL DEVELOPMENT, AND THE REGULATORY IMPLICATIONS

(Minding our 'Ps and Qs')

Dr Tim Franson

Vice President, Global Regulatory Affairs, *Lilly Research Laboratories, USA*

Referring to the title that he had been given for his presentation, Dr Tim Franson quoted the Webster's Dictionary definition of a horizon as 'a range of perception or experience'. Pointing out that one's horizons depend upon where one sits and the perspective that one has Dr Franson explored how the changing perspectives in drug development were affecting the horizons. He illustrated his presentation by using the old English adage of 'minding one's Ps and Qs (being on one's best behaviour)' and suggested that critical success factors for regulatory performance fell neatly under these initials:

Minding our P's – 'significance' of P-values

- **P**redictivity
 - portfolio (attrition)
 - product-specific guidelines
- **P**rocesses – productivity/other improvements
- **P**re-eminent science (efficacy/safety/quality)
 - pharmacogenomics
 - simulations (confidence?)
 - proactive safety interventions
- **P**artnering, with integrity
- **P**redicaments
- **P**atient impact

Minding our Q's

- **Q**uality
- **Q**uantity
- **Q**uackery (perceptions)

The following reports some of the items from the "'P-list' that were discussed by Dr Franson.

Predictivity and portfolio management: Dr Franson referred to recent CMR Data showing the increased attrition rates between Phase II and Phase III⁸. Predictivity that leads to making rational decisions on the survival of products is becoming increasingly important in the management of multi-product portfolios. It is uneconomic to prolong decisions to terminate a project that is not destined to be a break-through, but precipitate action might mean inadvertently discarding valuable compounds. Dr Franson suggested that there is no longer any such thing as a 'me too' in drug development but there are many cases of 'me too late'. Competitors for the same target can start from the same point but, after a ten-year drug development cycle, the product that wins the race is the innovator and others, even if only six months behind, may be too late to capture the market.

The decision-making process that leads to a 'quick win or a quick kill' must be effective at an early stage and requires the development of reliable predictive markers. Dr Franson, however, cited the recent joint project of FDA, the American Society for the Study of Liver Disease and PhRMA on predictors of hepatotoxicity that concluded that *in vitro* and pre-clinical predictors are only about 50/50 accurate. The study nonetheless provided a useful model to build upon.

Processes – productivity/other improvements: Dr Franson referred to process improvements particularly in relation to electronic capabilities – e-Data management, e-clinical trials and the e-CTD. He cautioned, however, that whilst these may facilitate and speed up the handling of data the volume of information remains the same and must be managed.

Pre-eminent science: Dr Franson discussed two particular areas that are undergoing change. Firstly there is a need to reach agreement between regulators and sponsors about the validation of surrogate markers and biomarkers in association with a disease and the level of certainty that will enable them to be used as surrogate end points. Secondly he referred to the evolving interest in the determination of benefit risk relationships and the information to be gained from early-phase targeting and late-phase trials. He suggested that these can provide a great deal of information but may not help the ultimate decision on the product.

Dr Franson also referred to conditional approvals and label limitations as they relate to the utility of the product to patients and the implications for reimbursement. He cited a recent survey that suggested that 20% of US pharma's clinical trial costs relate to the escalating commitments to post-approval investigations. He questioned whether this was the best use of limited resources.

Pharmacogenomics: Dr Franson suggested that we may be moving to a stage of agreement between sponsors and regulators that the throughput of products based on pharmacogenomics can be significantly improved by allowing approvals to be based on validated surrogate markers. Since outcomes are expected for reimbursement, this could, however, raise problems if the surrogate markers do not have a clear link with the final outcome.

Patients: Meeting patient needs is the ultimate goal and becoming more of a challenge as the patient becomes better informed, has increasing expectations, understanding and involvement.

Turning to the 'Qs' Dr Franson referred to Quality, Quantity and 'Quackery'.

Quality: Whilst there are quality management programmes, these are often more related to efficiency than quality, as defined as 'meeting the expectations of the customer'. Both sponsors and regulators are faced with the problem of defining 'lack of quality' and how to address, and avoid *not* meeting those expectations.

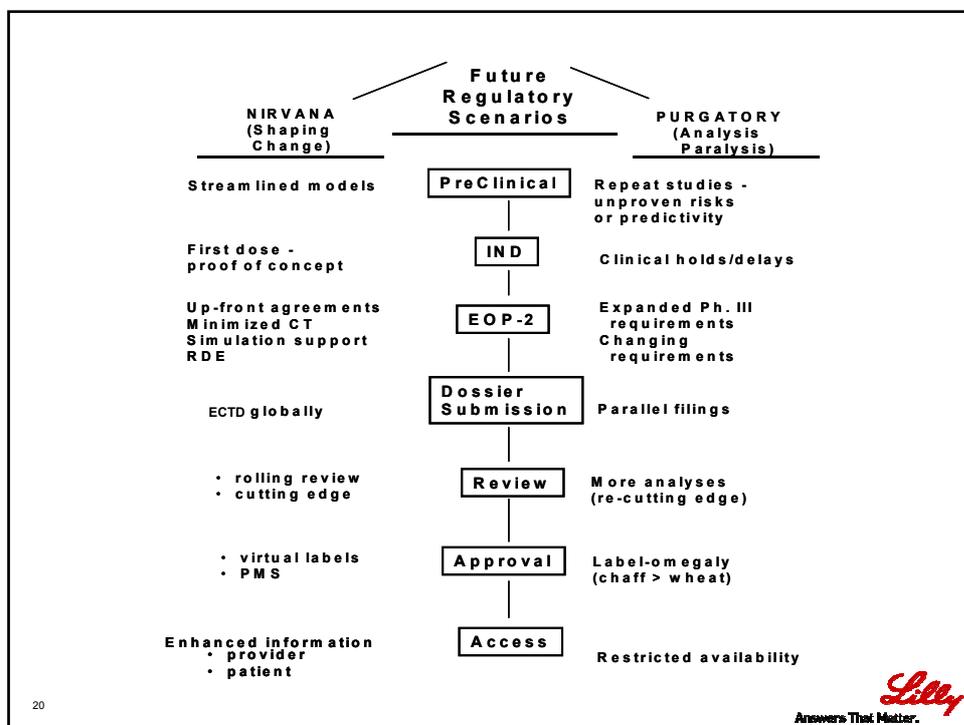
⁸Benjamin, GA and Lumley, CE, *Industry Success Rates in 2003, including trends in success rates*, May 2003, CMR03-202R, CMR International Ltd

Quantity: Even with the development of electronic submissions, as noted earlier, there is a problem to be addressed with the sheer volume of data currently required in a submission. Dr Franson suggested that the next challenge is to agree the essence of an application that is required for its review and remove the 'chaff from the wheat'.

Quackery: By this, Dr Franson was referring to the concern of the public over what they should, or should not, believe of information made available about new medicines and medical 'break throughs'. Often the expectations raised by media reports are not met and patient confidence is also eroded by inaccurate reporting of the safety hazards of medicines. Industry and regulators need to work together on improving information flow on both products and disease management.

In conclusion Dr Franson identified two main elements, for finding solutions: collaboration between industry and agencies, for example on guidelines and standards, and improved communication, including the public and patients. The way forward depends upon developing a level of trust among stakeholders and the ability to challenge each other in a dialogue. He suggested that the regulatory future was at a crossroad which, as illustrated in *Figure 2*, can lead to positive change ('nirvana') or analysis, paralysis and 'purgatory'.

Figure 2



HEALTH CANADA: MEETING THE NEED FOR CHANGE

**Dr Robert Peterson, Director General, Therapeutic Products Directorate,
Health Canada, Canada**

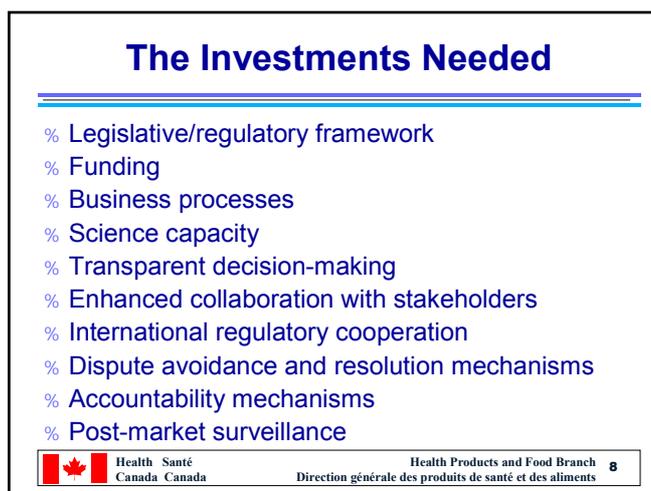
Opening his presentation with the quotation 'Everyone wishes improvement, no one wants change' (Will Rogers) Dr Robert Peterson described the process that had led to the latest proposals for reform of the regulatory system in Canada. Never short of people offering advice on how to make improvements, numerous studies have been conducted and over 500 recommendations have been made in the last 15 years. The common themes that have run through these studies have been the need to improve timeliness, efficiency and effectiveness, the importance of consistency and transparency and the need to harmonise standards, criteria and review processes. An underlying factor, however, is the lack of resources.

Among the issues that have been raised as contributing factors to the timeliness and efficiency of the review process are the management structure and resources and whether organisations within government are best positioned to provide the kind of service required by stakeholders. Communication has also been identified as a major challenge with calls for increased transparency and openness about the basis for decisions needing to be balanced against considerations of confidentiality and the need to protect intellectual property.

Turning to questions of finance, Dr Peterson noted that the funding basis for the review system had changed fundamentally in 1995 when cost recovery was introduced and had replaced the former reliance on public funds. This had followed the introduction of the Prescription Drug User Fee Act (PDUFA) in 1992 in the US but, unlike the PDUFA scheme, fees have remained unchanged in Canada at US\$100K (compared with US\$533K under PDUFA III). Changes are however afoot with a government announcement, in September 2002 of new regulations to 'speed up the regulatory process', followed in the 2003 budget by a tax-based appropriation of \$190 million over five years to improve the timeliness of the regulatory processes.

Health Canada's response to this was that the focus should be on four key outcomes: Safety, which must not be compromised; the timeliness of reviews; increased transparency, especially in meeting the needs of patient advocacy groups; and the impact on the health care system. In relation to safety, Dr Peterson noted that, in North America, there is currently a 3% withdrawal rate of applications that may appear small – with one in 35 products affected - but it is unacceptable in the context of the effort involved. Dr Peterson identified several critical factors for bringing about successful reform (*Figure 3*) but declined to suggest a priority order, as each was deemed essential.

Figure 3



Turning to the response of his own sector, he reported that the Therapeutic Products Directorate (TPD), that deals with medicinal products and medical devices was undergoing a complete 'business transformation'. It had been agreed that no 'new dollars' from the tax appropriation or through renegotiated fees would be spent on the old organisation but would be assigned to the new business processes in order to achieve agreed goals and performance targets that would be internationally benchmarked.

The TPD objectives can be summarised as:

- Quality submission;
- Quality review process;
- Quality decision;
- Measured performance with continuous improvement.

Apart from questions of finance, project management and regulatory risk management have been identified as key components in the business transformation. TPD staff have spent time with the regulatory agencies in the EU, US and Australia, listening and asking questions about key factors in achieving success.

The introduction of regulatory project management has been a pivotal move, with the establishment of milestones for tracking progress and identifying when and why applications are going off track and timelines are being missed. A Regulatory Project Management Division has been established to implement the procedures and project managers have spent time learning from the experience of others, particularly through interaction with the FDA. There are, however, significant backlog problems to be overcome. The efficiency of the review process stands up well to international comparisons, once applications are in the hands of reviewers but there is an unacceptable delay while applications sit for three to four months before being picked up.

Referring to regulatory risk management, Dr Peterson ran through the 'due diligence' factors, including risk mapping and making optimum use of regulatory cooperation and harmonisation. He noted that clinical trials are not powered around safety but around efficacy and 'real world' experience is required in order to provide a true prediction of safety. The growing demand from patients and politicians to hasten the review of new products is not, however, conducive to obtaining this real world experience.

As part of the improved management objectives, considerable effort is currently going into confidence-building among the review staff to ensure that they are comfortable with the decisions that are made. It has to be acknowledged that any data set has limitations. The benefits and risks have to be quantified. If a product has safety issues that may be life threatening then under ideal circumstances the benefits must be life saving, life preserving or provide significant gains for the patient. Different criteria will apply for products that come into the category of 'lifestyle' drugs.

Finally Dr Peterson referred to the need to build the review infrastructure around guidances for good practices. Good Guidance Practices provides early and specific regulatory advice to industry with a view to improving the quality of submissions with a consequence that multiple review cycles should be reduced. Good Review Practices provide review standards for staff aimed at improving the quality of reviews, ensuring consistency in approach and ensuring transparency of the decision making process.

SESSION 1: POINTS FROM THE DISCUSSION

EMEA/FDA Confidentiality agreement: There was considerable interest in the announcement of the agreement between EMEA and FDA to facilitate the sharing of information and speakers and participants from the agencies were asked to comment.

Dr Marisa Papaluca Amati reported that the signing of the agreement had been the culmination of a great deal of work, which had started in 1999. The main focus was on exchange of information on pre-and post approval regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing approval and post authorisation surveillance of products.

Justina Molzon, FDA, noted that the timing of finalisation of the agreement had come as somewhat of a surprise, but a good one. The FDA letter of agreement, signed by Commissioner McClellan, had been taken to the bilateral meeting in London that had just ended and the EMEA side of the agreement had been signed allowing an exchange of letters on Friday 12 September 2003. Ms Molzon pointed out that FDA already has similar agreement with many foreign governments under section 21.89 of the Code of Federal Regulations, but a special solution had been required in the case of the EU since it is not a government. Now that this issue had been resolved it was important to put in place the correct structure and procedures to channel information to the right people. As an example of the constraints that would now be lifted, she noted that it had not, to date, been possible to exchange basic information on, and dates of, applications submitted in CTD format in order to determine how the new system was working.

Dr John Jenkins, FDA, also emphasised the importance of this agreement in allowing reviewers to discuss critical issues in the assessment of applications. He emphasised,

however, the importance of a viable structure to allow this to work, pointing out that he has 17 medical reviewing divisions reporting to him, each with 30-40 people who may wish to consult EMEA. The system would obviously not work with that many potential points of contact.

Transparency of the agreement to sponsors: Asked whether the sponsor will be aware of the exchange of information, Dr Marisa Papaluca Amati confirmed that the normal procedures for confidentiality and interaction with the sponsors will remain. Minutes of discussions will be sent to sponsors. During the 18 months that the agreement has been in preparation, FDA and EMEA had discussed a number of models to find a way to streamline the procedure and not add to the burdens. Both parties were working from the same perspective to find a system conducive to a strong scientific exchange.

Justina Molzon added that some companies had been actively requesting FDA to share views with other agencies. This happens, for example, with Health Canada and therefore the experience and procedures for data protection are in place, it is just a question of formalising the complex organisational structure in dealing with the EU.

Members of the audience welcomed these assurances and expressed the hope that industry could, in the foreseeable future, be included directly as a third party to the discussions.

Failure rate following authorisation: Dr Peterson was asked to comment on the three percent failure rate following authorisation in North America that he had referenced in his presentation and whether, with hindsight, there were measures that could have reduced this failure rate. Replying, Dr Peterson pointed out that the level of post-marketing withdrawals in Canada was running at 1.6% but that this reflected the fact that the agency was often looking at 2 years post-marketing experience, at the time of authorisation. This was because of differences in submission cycles but also a result of the time lag due to application backlog. The challenge was to simulate 'real world' experience during the development phase without making the scale of trials unacceptably large.

Dr Jenkins reported that FDA had looked at the drugs that had come off the market in the last decade and found that the primary reasons were issues of QT prolongation and liver toxicity. In some cases potential problems had been identified before the drug came to market and the sponsor tried to implement risk management strategies that had failed. He cited the case of a nonsteroidal anti-inflammatory where the label requirement restricting use to no more than 10 days because of the risk of liver toxicity had failed to be followed by clinicians. QT issues are often related to drug interactions that were not recognised until the drug was in use. Massive risk management efforts can be undertaken but these can only reduce, and not eliminate, risk.

The dilemma is that detection of problems before marketing, as Dr Peterson had noted, requires massive sample sizes that everyone agrees are not feasible. Management of problems after marketing is like trying to 'put the genie back in the bottle'. Once a product is in widespread use it is very difficult to change doctors' prescribing patterns. There is also the extreme where risk is apparently managed successfully but only because the conditions are so restrictive that the product is not used!

Business transformation: Dr Robert Peterson was asked to comment further on the business transformation that he had described in his presentation and, in particular, on whether it was possible to define 'quality' in terms of submissions and review. In his reply, Dr Peterson said that in seeking a quality review by agency staff, one must look for a level of responsibility among the reviewers that is commensurate with the task being asked of them. The recommendations can only be as good as the data sets that they are asked to review, whether toxicology or clinical trial results and this, again, returns to the question of the quality of the submission. When it comes to product life-cycle evaluation, at the hand-over from pre-market evaluation to post-marketing environment, Health Canada staff are faced with the

limited size of the Canadian population, which may limit the ability to detect 'signals' after the product is launched. This is when the ability to operate internationally and have access to larger markets and databases is of great importance to the reviewer.

In a follow-up comment, the questioner asked if, in the spirit of reviewing quality, the opportunity for 'deconstructing' the review process had been considered to examine it in detail and look for ways to improve efficiency. Company experience had shown that processes that had been allowed to 'roll on' for years without examination were found to include a high proportion of decision-making processes that add no value and are redundant and time consuming. Dr Peterson agreed that this was the basis of the exercise that they were currently undertaking, in particular the problem of the backlog of applications. For some of these there is just a simple delay in being picked up for review but in many cases the application is trapped in an endless 'loop', within the review process. The objective is to bring such cases out from 'behind closed doors' and ask specific questions that reveal the basic problem and why a decision cannot be taken. A sufficient level of management must be directed at asking those questions and finding out why the milestones that were expected have not been met in order to bring the application forward.

SESSION 2: THE DECLINING SUBMISSION RATE FOR NEW MEDICINES

Chairman: Dr Robert Peterson

Director General, Therapeutic Products Directorate, Health Canada

WHAT DO TRENDS AND INDICATORS TELL US ABOUT THE CHANGING REGULATORY ENVIRONMENT?

Dr Neil McAuslane

Chief Scientific Officer, CMR International Institute for Regulatory Science

In his presentation Dr Neil McAuslane provided information from the CMR International Marketed Medicines Database and also from the survey carried out in preparation for the meeting. Starting with 'the current picture' Dr McAuslane cited data confirming the widespread observation that the number of new molecular entities coming onto the market in the last few years had declined significantly. Only twenty-eight had been marketed in 2002 which was the lowest figure seen for well over a decade. These figures must also be viewed in relation to the development time, that is, the time from synthesis until the product reaches its first market. In the last 3-4 years development time has increased raising the question of whether this is related to the regulatory environment or other aspects, for example more complex science or commercial hurdles. In relation to regulatory approval times data for the US FDA, Japanese MHLW and EU centralised procedure the figures indicated an upturn in approval time in the last year, although previous years had seen this fall, especially in Japan. Regarding possible reasons for the declining output and submission rates, Dr McAuslane cited the following:

- Discovery today is more difficult, with yet more potential targets that still need to be validated. In some therapeutic areas excellent products already exist and so barriers to entry are high;
- The changing paradigm in R&D with products remaining longer in Phase II until proof of concept is established, to avoid failures at a later stage;
- The concentration on economically viable products resulting in products being terminated on economic grounds which results in poorer success rates;
- Pharma companies today have to demonstrate the value of medicines and build cost effectiveness studies into the clinical development which may lead to longer development times;
- Mergers and acquisitions can, initially, lead to a reduction in the combined pipelines, in the first years after merger, and hence to reduced output;
- The regulatory environment has recently been characterised by increased caution and other changes that have impacted on productivity.

In preparation for the Workshop, the CMR International Institute had carried out a Survey: *The changing regulatory environment: Reality and perception*. Dr McAuslane reported the results from the 16 companies and 10 regulatory authorities that had responded in time for his presentation. One question had asked about the changes seen in the last three years compared with the mid to late 1990s and the impact on drug development and registration. Fourteen of the sixteen companies (or 88%) agreed that the regulatory environment had changed but only 27% (4 of 15 companies) saw the declining submission rate as a direct consequence of these changes. In the case of the authorities seven of the ten that participated (70%) agreed that the environment had changed but only one (10%) related these changes to the declining submission rate.

From the industry's perspective, and perhaps not unsurprisingly, 15 of the 16 companies agreed that regulatory changes had been responsible for increased costs of R&D. When asked whether regulatory changes had increased the time to bring a product to market, 81% (13/16) responded that it had whereas only 11% (1/9) of the authorities

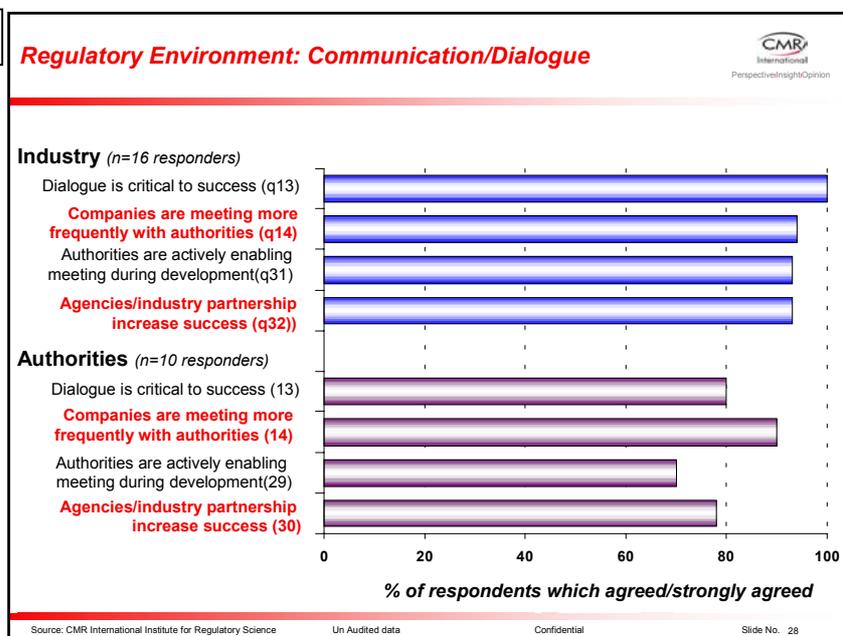
concurrent. Looking at the hurdles to successful drug development, both industry and authorities agreed that the scientific ones were most significant but, whereas industry ranked regulatory hurdles in second place, the authorities saw financial barriers as being of greater significance.

In order to examine the indicators in more depth, Dr McAuslane presented data from the CMR database that tracks the development of some 1,500 NASSs. This included data that illustrated the increased times that compounds are spending in the different phases of development, as noted above, especially Phase I (first human dose to first patient dose) and Phase II (first patient dose to first pivotal dose).

A series of questions had been asked in the survey to identify changes in the regulatory environment that have had the greatest impact on development. There was a strong perception among companies that agencies have become more risk averse and were requesting more safety data. This was a view shared by the authorities. The authorities did not, however, agree with the industry perception that authorities were requesting more comparator controlled trials, although they neither agreed nor disagreed with the industry view that the number of subjects in pivotal trials had increased. When asked about changes in regulatory requirements there was near consensus that the rate of guideline publication had increased and both companies and authorities identified an increase in CMC requirements, although the authorities did not agree with the industry perception of increased non-clinical safety requirements. The existence of ICH was not perceived, by industry, as leading to an increase in regulatory hurdles but there was a strong view among companies that differences in the scientific advice given by regulatory agencies had increased the cost and time of clinical development.

Companies and authorities were asked for their perception of the changes that were having the greatest impact during the regulatory review process. There was unanimity in the view that post-marketing commitments had increased and general agreement that regulatory guidelines were being applied with more stringency. The authorities did not, however, agree with the companies that identified a problem with issues being raised during the review that had not been highlighted in the pre-submission dialogue.

Figure 4



Finally, and in preparation for the Syndicate discussions, the survey had asked companies and agencies what they believed were the main critical success factors for achieving a successful registration. The responses could be summarised under four main areas:

Company strategy: Strong science-based decision making at all stages of the development process and a focus on products that satisfy unmet medical need or demonstrate superiority in terms of efficacy and safety;

Technical data: Well thought out clinical programme that strongly supports the desired label and a good understanding of regulatory precedents;

Regulatory Affairs function: The need for the department to have adequate influence and status within the company and be involved at a suitably early stage in the development process. The need, also, for the function to have an effective understanding of the authorities' interpretation of regulations and guidelines and an understanding of the global 'regulatory landscape';

Communication: Early, open and frequent dialogue between companies and agencies with continuity and consistency in regulatory advice, aligned to clinical and regulatory strategies.

The greatest emphasis was on communication and a further analysis of this had been made as shown in *Figure 4*.

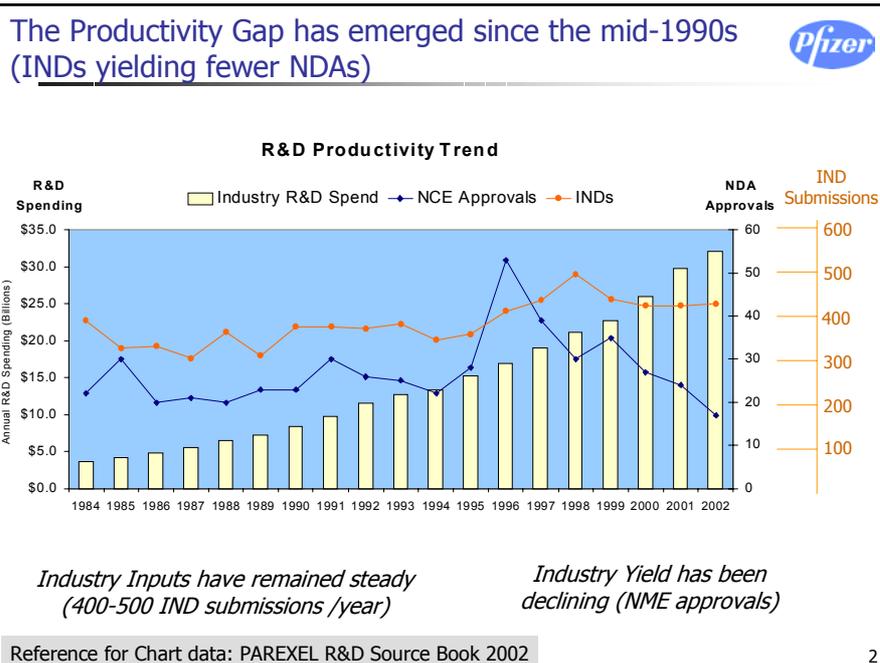
IMPROVING SUCCESS RATES: AN INDUSTRY PERSPECTIVE

Dr Declan Doogan, Pfizer Inc., USA

Introducing his presentation, Dr Declan Doogan suggested that there was too much emphasis on negative aspects of pharmaceutical R&D and not enough concomitant positive commentary. The question of the yields should not be measured only in terms of the number of chemical entities going into development but whether those emerging at the other end are considered to be not only safe but also value added medicines for patients.

Whilst the number of new chemical entities approved over the last 20 years had fluctuated there was no dispute that the last 8-9 years had seen a decline whilst the R&D spend had increased steadily (*Figure 5*). The decline in new approvals is not only of concern to industry but also healthcare providers and, no doubt, regulators as well. The other fact to note, however, is that the increasing spend has been associated with a relatively constant rate of investigational new drugs (INDs) going into development. Ten years ago there was one successful new drug application (NDA) for every 15 INDs compared with a ratio of 1 in 25 today.

Figure 5



This appeared to indicate that research is becoming less effective but Dr Doogan cautioned against a preoccupation with the numbers of new medicines without considering who will pay for them and whether patients and healthcare providers need large numbers of new drugs or are more concerned about the concept of value.

Dr Doogan also cited CMR data showing that, over time, the success rate in Phase I of development has remained almost constant whilst success in Phase II is not only low, but dropping. Success in Phase III and at submission has remained constant, but the overall output is reduced. This must be viewed against the fact that the relative cost implications of abandoning a compound in Phase III versus Phase I is approximately 15 to 1 and it is a very costly mistake to nurse a sub-optimal compound through to Phase III, submission or the market.

He suggested that companies need to look at strategies for identifying and eliminating weaker candidates in order to improve success rates. An analysis of the root causes of product failure indicated that the four major reasons could be categorised under toxicity, pharmacokinetics, safety issues and efficacy differentiation. Pre-clinical plays a large role in culling compounds, mainly in relation to toxicity. Pharmacokinetics (PK) is often a cause of failure in Phase I but there is a view that this is too late and PK problems should be predicted in the pre-clinical stages. In Phase II there is an increasing focus on comparative efficacy and differentiation. This reflects a more critical approach to 'me-too' compounds and a much higher threshold for progression from Phase II to Phase III for, say an antihypertensive that needs to show major differentiation in both safety and efficacy to be a viable product.

The lower success rates and higher costs must also be viewed against the changing scientific and market forces that present greater opportunities and new hurdles:

Science and Technology

- Enhanced safety assays
- Pharmacogenomics
- New tools
- Novel delivery devices
- Proteins and antibodies
- Metabolism science

Market forces

- Public policy funding focus
- HMO and formularies
- The 'voice of the patient'
- Global markets

In view of the length of the pharmaceutical development process the 'decision gates' at which a compound moves from discovery to early development (candidate nomination), to late development (proof of concept) and to submission will be far apart in time. The compounds discovered today may not reach the market much before 2020 and there are many unknowns about what the environment will be like at that stage. Dr Doogan predicted that it will be necessary to take some risks in developing strategies for such compounds in order, not only to increase yields but also to match the expectations of patients, prescribers and regulators in the 2020 world.

This, suggested Dr Doogan, would need a collaborative approach through partnerships that need to take on a different form. Warning that he was entering into controversial ground, he suggested that there was a need for much greater sharing of information between sponsors and regulators. There should be increased scientific collaboration with sponsors sharing non-IP information across company boundaries including toxicity, epidemiology and target validation data (pre-clinical and clinical biomarkers). By working independently companies are not leveraging the scientific knowledge that exists in the world to improve predictions of the usefulness of a compound or disease-related epidemiological data to enhance the denominator for therapeutic effect. Target validation encompasses predictive measures not only of the likelihood that a product will progress but also for abandoning them at an earlier stage. Many biomarkers are not only of benefit to one company but to all. Unless there are strong competitive reasons to keep such information confidential it could be shared to improve the overall success rate of the industry. It should also be borne in mind that, regulators having access to data from all applications, could be a source of vital information

to improve the ability of sponsors to develop future drugs, if concerns about sharing information could be overcome.

Summarising, Dr Doogan stressed once more the importance of partnerships and the need to redefine what the most effective partnerships are likely to be in the coming years. Shared information, through partnership is needed to 'de-risk' portfolios, establish the right sized programmes and foster better joint understanding. More predictive science with better understanding and validation of biomarkers and surrogates can be expected to feature much more strongly. He suggested that the industry needs to become less dependent on blockbusters which are becoming harder to find and more difficult to develop and, for a balanced portfolio companies also need 'smaller' compounds with higher medical need.

THE RELATIONSHIP BETWEEN REGULATION AND INNOVATION: A HELP OR HINDRANCE? A REGULATORY VIEWPOINT

Dr Eric Abadie

Director of Registration and Clinical Strategy *AFFsSAPs, France*

Having been asked to discuss regulation and innovation, Dr Eric Abadie began by looking at these terms in the context of the current EU regulatory environment. Increasingly, there are two types of regulation impacting the introduction of new medicines in Europe. Whilst the marketing authorisation procedures have the primary place, the national regulations and procedures for determining which products are reimbursed by the public sector are having an increasing influence on the business environment. In France, for example, reimbursement is regulated by the transparency committee, in the UK the National Institute for Clinical Excellence (NICE) advises on medicines to be paid for under the National Health Service.

In the ongoing debates about reimbursement, the question arises of the definition of 'innovation', whether this merely means a new mechanism of action, in the context of the disease, which may have no additional benefit to the patient or whether true innovation must also have a recognised added value over established therapies.

Whilst it has always been within the CPMP remit to look at the benefit risk (B/R) assessment of a new medicinal product, there has been a subtle change introduced in recent revisions to the Directives which reflects the trend towards comparative benefit risk. Dr Abadie drew attention to the wording of the revised Annex 1 to Directive 2001/83/EC⁹:

*'In general clinical trials shall be done as controlled clinical trials if possible randomised and as appropriate versus placebo **and** versus an established medicinal product of proven therapeutic value; any other design shall be justified...'* (Emphasis added)

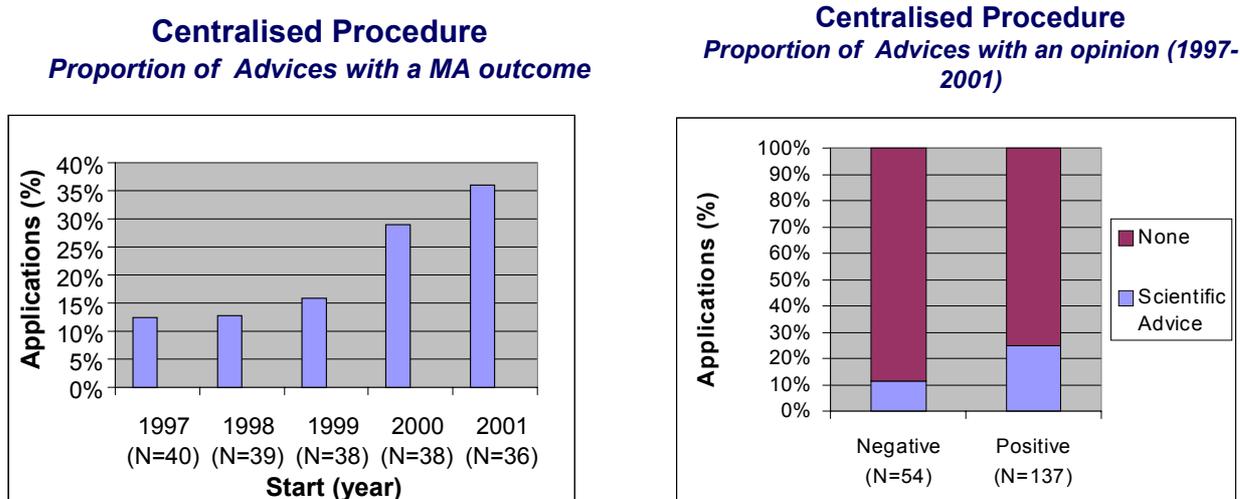
The implication is that:

- Where no established treatment is available the data will need to show a positive B/R in the target population of the indication (through placebo controlled trials where ethically acceptable)
- Where a treatment is available, the B/R must be non inferior to an established active control in the target population of the indication
- Where the B/R is inferior, authorisation might be granted, if exceptional circumstances apply, for a restricted sub-population.

Dr Abadie identified five ways in which regulators could support innovation: through the Scientific Advice procedure, through guidelines, by introducing expedited review, by allowing marketing authorisations to be granted under exceptional circumstances and by encouraging global development.

⁹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use,

Presenting statistics on the increasing use of the Scientific Advice procedure from 1997 to 2001, he illustrated the positive effect of scientific advice in relation to the success rate of applications (Figure 6)



On the development of guidelines Dr Abadie expressed his own view that there should be more input from industry in the early stages of development of guidelines instead of the current system whereby industry is only consulted once the draft guideline has been developed and released for general consultation. There were, however, divided views on this among EU regulators.

On the expedited review, Dr Abadie noted that an S.O.P has been published but, in spite of many requests, the procedure had only been applied to three AIDS compounds, since 1995. There were practical difficulties in operating the system. In the absence of a 'rolling review' in the EU, it was impossible to determine whether a product meets the criteria in relation to unmet medical need without reviewing the data. Revisions to the procedure are being addressed in the current review of pharmaceutical legislation.

The provisions for granting authorisations under exceptional circumstances are more targeted at designated orphan medicinal products and have been applied more frequently. Aimed at medicines for treating life-threatening diseases, where there is a major therapeutic benefit, the procedure allows an authorisation to be granted with limited indications, in a limited patient population, and with a defined post-marketing programme for the company to fulfil. Between 1998 and 2003 the procedure had been applied to 24 of the 144 approvals through the centralised procedure.

Turning to the global development of medicines, Dr Abadie asked whether the target of a global review was 'a myth or reality'. In his own view it was, at present, a myth but should nonetheless be pursued as a goal for the future. He presented data comparing the outcome of applications reviewed by the FDA and EU:

- **FDA positive applications:** A comparison of outcome of 139 applications showed that the EMEA had agreed in 80% of cases but had delivered a negative opinion for 20%
- **EMEA negative applications:** A comparison of 74 applications that had failed to be authorised by the CPMP showed that in 51% of cases the FDA outcome had also been negative but in 49% (n=35) FDA had approved the products. Further data on these showed:
 - 20 products approved by the FDA without a hearing
 - 15 products approved by FDA following a hearing

The submissions were made in the EU and US within two years, which means that the dossiers were, therefore, probably similar. An analysis of the cases approved by the FDA but not in the EU showed that the majority of objections were clinical, rather than pre-clinical or quality issues.

In his concluding observations, Dr Abadie reiterated his view that the increasing regulatory burden on companies that may have an impact on drug development does not result from the marketing authorisation regulations but is related to the increased focus on comparative benefit and cost effectiveness. The rejection rate for marketing authorisations had not changed significantly and he did not believe that changes in regulations had resulted in increased requirements for clinical testing. He quoted an observation made by Dr Terry Eaves at an earlier CMR International Workshop¹⁰:

'The medicines of tomorrow will be judged on their ability to increase value to the patient and the payer, both therapeutically and financially'

SESSION 2: POINTS FROM THE DISCUSSION

Rejection on grounds of efficacy: Referring to the data on rejection of applications, Dr Abadie was asked whether there was a breakdown on cases where the efficacy was felt to be marginal versus a placebo only control and is there a figure on how many rejections occurred where there was a positive control, with a P-value of substance, but even so it was felt that the clinical benefit was too marginal.

Without the specific data to hand Dr Abadie felt that it was not possible to give a precise answer but he recalled several instances where the difference in efficacy compared with the placebo was relatively minor but this was often connected to the population that was recruited in the pivotal trials. With hindsight, and with the benefit of scientific advice it may have been possible, in some cases, to arrive at a different conclusion if a sub-population of patients had been selected for the trials. There were also cases of products that appeared to be inferior with respect to efficacy but superior with respect to safety and, again, it could have been interesting to see if a study in a sub-group of patients would have changed the picture.

Products failing too late: A participant commented on the increased attrition rates that were being seen at the end of Phase II and suggested that industry were killing products at that stage unless they had an obvious relative benefit, judged from a dose-response, positive placebo control (wherever feasible) and getting an acceptable p-value for efficacy. It is worrying, however, to see product failing on grounds of efficacy at the submission and review stage as this suggests, not only that that the industry has different views from the regulators on the products that should be killed, but also that time is being wasted on such applications.

Dr Abadie did not feel that such reviews necessarily constituted a waste of time but it did, once again, highlight the importance of dialogue at the end of Phase II about the design and population selection for the Phase III trials. Dr Papaluca Amati provided information on a recent publication that had analysed the reasons for withdrawal of applications for cancer drugs and the types of questions that had been raised by the CPMP¹¹. EMEA was planning to publish other such analyses and she had noted the suggestion that rejection related to placebo trials should be compared with rejection related to active control trials.

EU requirement for active controlled studies: Dr Eric Abadie was asked to comment on the apparent contradiction between his statement that he did not feel that the regulatory barriers had been raised and the revision to Annex I of the Community Code that meant that the EU would now routinely be requiring active controlled studies.

Responding, Dr Abadie sought to clarify any misunderstanding about the change in Annex 1. In fact, the CPMP has been asking for active controlled trials for several years but there has been no legal basis for the requirement. This came to light some 3-4 years ago in

¹⁰ Proceedings of the CMR International Workshop on *Improving the Regulatory Review Process: Assessing Performance and Setting Targets*, January 1997, edited by Neil McAuslane and Stuart Walker

¹¹ Reference

discussions of the EFPIA position paper on benefit risk assessment. The legal anomaly has been corrected but Dr Abadie re-affirmed that the situation had not changed, in practice, and there had not been an escalation of active control trials.

Attrition rates: Commenting on the trend towards increased attrition rate for NASs at an earlier stage Dr Tim Franson suggested that it would be interesting to compare the rates of, and reasons for, discontinuing Phase II compounds today and some five years ago. He suggested that there is currently a greater tendency to look at projects from the perspective of portfolio selection and anticipated regulatory hurdles. If a new product's profile suggests that it will need, say, a 1000 patient study requiring EKGs, this may be lead to it being dropped in favour of other products in the pipeline where the requirements are expected to be less onerous.

Dr Peterson added that it would be interesting to have better information on the extent to which commercial factors influence decisions to abandon drug development projects. Presumably, if there are sufficient molecules in the pipeline it is easier to decide to stop a project at Phase I and move the next product into early Phase II.

Dr Abadie suggested that the CMR Institute study should be revisited with more specific data, moving from 'perceptions' of regulatory hurdles and barriers and examining the actual reasons why products are abandoned. Dr Papaluca Amati suggested that the rigid model of moving from one phase to the next with specific decision points might need to be changed. She cited the briefing meetings with companies that are being introduced by the CPMP, which can begin as early as needed to discuss, for example, whether a marker is valid for moving from *in vitro* testing to first human dose. These meetings, which are held without any regulatory obligations can give rise to a completely new set of approaches to be explored, particularly in the pharmacogenetic and pharmacogenomic field, which may help shape the decision-making process with regard to products in the pipeline.

Conditional approvals: In closing, the Chairman observed that much of the morning's discussions had been around clear cut decisions on whether or not a product is approved. Conditional approvals had, however, also been mentioned. At Health Canada there is a policy of *Notice of Compliance with Conditions*. He suggested that discussions between all parties on the rules for conditional approvals were needed at an early stage to avoid creating additional confusion to the process.

SESSION 3: KEYS TO SUCCESS AND FAILURE IN THE REVIEW PROCESS

Chairman: Dr Alex Giaquinto

Senior Vice President, Worldwide Regulatory Compliance, *Schering Plough, USA*

Reviewing the discussions that had taken place so far on changes in the current regulatory environment and the decline in the submission rate, Dr Alex Giaquinto suggested some questions that might be addressed in the current session and the syndicates, both of which would be looking at key factors affecting success and failure in development and review:

- Does success mean accepting increasing requirements? If this occurs, who is responsible? Is it a case of regulators increasing requirements or is industry, in fact 'second guessing' changes in requirements?
- Are the available avenues of communication being utilised effectively?
- Where does Good Review Practices come into the process?

He also suggested that in their discussions participants might wish to consider such factors as the impact of the globalisation of development, the perception of a shift hypothesis from efficacy to safety, the importance of the quality of submissions and the perceived differences in regulatory agency approach

CRITICAL FACTORS FOR THE SUCCESSFUL REVIEW AND APPROVAL OF NEW MEDICINES: TACTICS

Dr Bonnie Goldmann

Senior Vice President, Global Strategic Regulatory Development, *Merck Research Laboratories, USA*

In preparation for her participation in the Workshop, Dr Bonnie Goldmann had carried out a brief 'mini-survey' asking colleagues within the company, in other companies and at FDA, to answer, from their own experience, the following question:

Assuming a new medicine has data, which demonstrates it is safe and effective:

- What are the three things that facilitate the review and approval of an application?
- What are the three things that create barriers to the successful review and approval of an application?

Whilst one FDA response had (as reported later) been that a 'complete application' was the answer in all cases, other responses had also contributed to Dr Goldmann's suggestion that the critical factors which can facilitate timely review and approval of an application for a new medicine can be described by the acronym, TACTICS:

Transparency
Anticipation
Communication
Timeliness
Integrity
Compliance

Transparency The first essential is clear, open communication throughout the development and review process. This entails full disclosure of all information 'the good, the bad, and especially the ugly'. The submission must offer a clear discussion of the rationale for the decision making during development and the conclusions that have been drawn.

Similar clarity must extend to all communications between the sponsor and authorities. Without waiting to be asked questions sponsors must put themselves in the position of the

decision-makers and put forward the essential factors that make the case for using the new product safely and effectively to benefit the public health.

Anticipation: An application is a dynamic data set that is never completely static or closed. A decision must be made about the information that must be assembled at the time of application but a proactive approach is needed at all phases of development in order to anticipate the further need for data. Such an approach contributes to smooth agency interactions, and an ability to plan ahead and develop realistic expectations. When assembling applications for different regions it is important to anticipate the context in which the data will be reviewed, including the regulatory environment and cultural influences. In the US context, anticipating the need for an Advisory Committee meeting is an important factor in planning data requirements.

Communication: Honest, open communication both written and verbal with agencies and within ones own company is probably the most critical success factor, Dr Goldmann suggested. Communication should take place early and often with all agencies. The end of Phase II and pre-NDA consultations in the US and the European Scientific Advice facility should be regarded as the minimum. Also, communication does not just imply turning up for such meetings in a passive capacity. Issues should be actively addressed in a dialogue with the regulators and controversy should not be avoided. As the 'warts' come out, said Dr Goldmann, it is important to talk about them openly and make sure that there is a complete understanding of the issues and concerns.

A question that arises is whether a sponsor always needs to do everything the regulator says and this illustrates the point that communication should never be just one way. It should be a partnership in which there is understanding and acknowledging areas of difference.

The Marketing Application itself is pivotal to the communication process and it is absolutely critical that it must be easy to navigate and understand. Dr Goldmann warned that 'full disclosure' in an application did not mean burying a sensitive piece of information in an obscure appendix. A sound piece of advice from one of the regulators consulted is to have the application reviewed within the company by someone who is familiar with regulatory requirements but has not been involved in the programme.

Another critical factor is to communicate realistic expectations within the company based on the advice from agencies and knowledge of the regulatory environment. There can sometimes be pressure from within the organisation to put forward unrealistic labeling proposals that are not supported by the data which leads to frustration all round and inevitable delays in the review procedure.

Timeliness: This refers to the ability to support all aspects of a marketing application in a timely manner. This includes responding to agency requests and enquiries, being available for meetings with regulators and being ready for compliance inspections both in relation to GCP and manufacturing sites.

Integrity: Dr Goldmann suggested that a call for integrity might sound like 'apple pie and motherhood' but is, of course, critical to all aspects of the regulatory process. All aspects of interactions with agencies, as well as the data itself, should reflect the highest degree of integrity. In dealings with agencies it is essential to create mutual respect and trust through open and honest communications, which, as mentioned earlier, must work both ways. Data integrity requires not only a complete application but also well-designed clinical trials with validated endpoints that meet the necessary standards of evidence and clarity of presentation required by the reviewer.

Compliance: Finally, Dr Goldmann underlined the importance of ensuring that all aspects of the development of a new medicine meet the compliance standards for pharmaceutical research and that the application is complete. There are simple checks that can be carried out to ensure that all the components are present using the US refuse-to-file checklist, looking at the data requirements for the EU and Japan and ensuring that all components are present and easily found. The data must verify that the development programme was carried

out under GLP, GCP and GMP and clinical and manufacturing sites must be ready for inspection.

In conclusion, Dr Goldmann suggested that the key to successful development and review of new medicines was a 'partnership' with agencies which is becoming an acceptable term in the changing environment. The criteria for partnership have to be met by both partners and she re-iterated that these could be facilitated by guiding all interactions with *transparency, timeliness, integrity* and adherence to *compliance*.

KEYS TO SUCCESS AND FAILURE IN THE REVIEW PROCESS

COMPLETE OR INCOMPLETE APPLICATIONS: DOES IT MAKE A DIFFERENCE?

Dr John Jenkins

Director, Office of New Drugs, *CDER, FDA, USA*

Dr John Jenkins had no hesitation in asserting that a complete application was the most important success factor in achieving regulatory approval, but he had, nonetheless asked his staff to examine some data on success and failure in relation to the quality of applications.

First, however, he reminded participants of the original PDUFA 'deal' under which it was agreed that sponsors must submit *complete* marketing applications in response to which the FDA would perform an *comprehensive review* within a *specified time* (the PDUFA goal date) and provide a *complete response*, which would be either approval or a full list of deficiencies ('approvable' or 'not approvable' letter). At the time this was a revolutionary change for the FDA who had, until then, been carrying out piecemeal review and it was very difficult for the sponsor to obtain a complete list of problems or be given a specific time frame for the review.

Dr Jenkins posed two questions: Has FDA kept to the 'deal' and have sponsors? He affirmed that FDA had met or exceeded nearly all the PDUFA goals for applications reviewed over the past 11 years. The timelines had, indeed, been so predictable that not only sponsors but also outside observers, particularly investors and the media know exactly what the goal dates are for applications. On the question of complete applications from sponsors, 'anecdotal' response was that sponsors had *not* met their side of the deal. There is a perception that many applications are of poor quality, incomplete and submitted too early resulting in the need for multiple review cycles prior to approval. He acknowledged, however, that there are no well-defined metrics to define a 'high quality' of 'complete' application and the FDA study had set out to address this.

Data on refuse-to-file (RTF) actions by FDA were not found to be a good metric since such applications must have gross deficiencies, for example the entire clinical or CMC section missing and the RTF rate was extremely low. A study of the outcome of 'complete' and 'incomplete' applications was therefore undertaken but it was first necessary to arrive at definitions for these. It was agreed that, for the purpose of the study:

Complete means no major amendments submitted during the first review cycle

Incomplete means major amendment(s) submitted during the first review cycle

The reasons for a major amendment include the late submission of data, for example if a second pivotal trial is not available at the time of filing, and the response to an FDA discipline review letter. The latter could arise from the response to questions raised during the CMC review where the company's response triggers the letter. Dr Jenkins commented that the definition of a complete application was 'generous' as it did not include applications where minor amendments (which can be numerous) were required.

In the data provided by Dr Jenkins it was shown that 31% of new molecular entities (NMEs) received 1997-2001 had at least one first cycle major amendment. The regulatory history of the complete and incomplete applications was examined. It was found that 37% of the complete applications were approved on the first review cycle within the original PDUFA goal date in comparison with 9% of the amended applications. An additional 18% of the

amended applications were approved on the first review cycle following a 3-month extension of the review 'clock'.

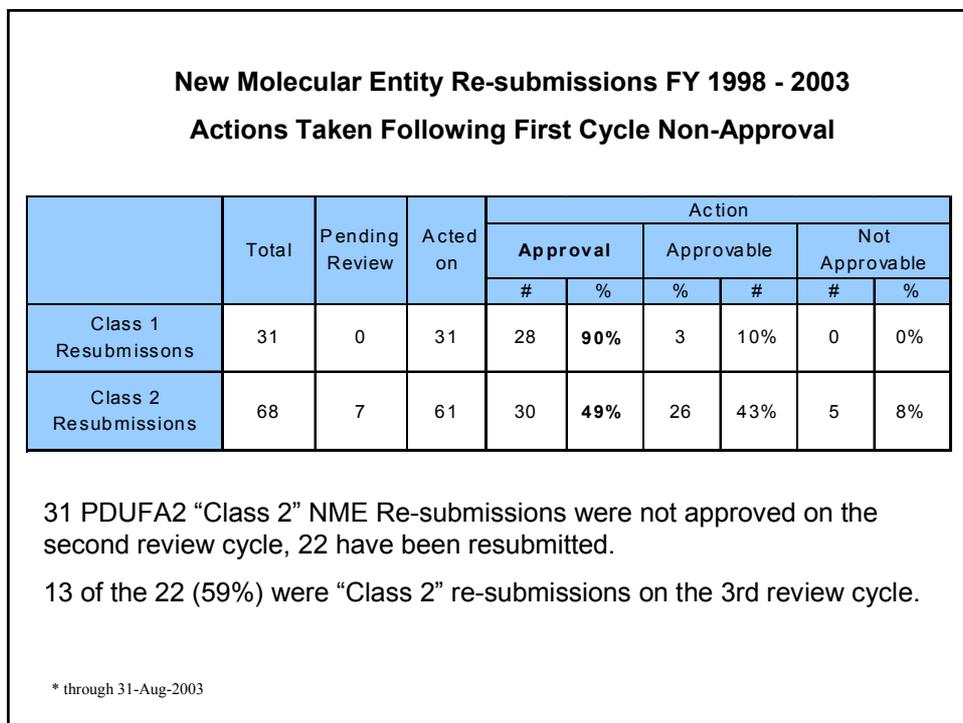
Data on the average approval time for NME applications received 1997-2001 showed the following:

Type of application	Complete applications		Amended applications	
	% Approved to date	Average approval time (months)	% Approved to date	Average approval time (months)
Priority NMEs	86	7.8	75	13.2
Standard NMEs	75	17.9	57	21.8

Dr Jenkins explained that there are two types of resubmission when deficiencies are found in applications. Class 1 resubmissions are those where only minor new information is required and the PDUFA clock can be extended for 2 months. Class 2 require major new information with a 6 month PDUFA clock extension. Examination of the same cohort of complete and amended applications showed that 39% of the complete applications led to Class 1 resubmissions whereas only 19% of amended applications were Class 1 resubmissions. The difference that a complete application makes was further underlined by the fact that 56% led to either first cycle approvals or Class 1 resubmissions compared with 36% of the amended applications.

A further analysis had been carried out on NMEs resubmitted in 1998-2003 following first cycle non-approval (Figure 7) showing that almost all Class 1 resubmissions are ultimately approved. Dr Jenkins expressed the view that this, and the previous data provided powerful data to support the call for submissions to be 'complete' when filed. The pattern was clear. An incomplete application is more likely to lead to a Class 2 resubmission which, in turn is more likely to go on to a third cycle.

Figure 7



A detailed study of the deficiencies in applications had not been carried out although this was planned under PDUFA 3. A study was also underway of applications where approval took more than two years.

Summarising, Dr Jenkins noted that, even using a very conservative definition, FDA continues to receive a high proportion of 'incomplete' applications. These are inefficient for FDA to review and lead to multiple review cycles and significant delays in approval.

Conversely, ensuring that submissions are complete when filed leads to more efficient use of FDA's limited resources and may result in more rapid approval.

PARALLEL REGULATORY SUBMISSIONS

Dr George Butler

Vice President and Head, AZRA Regulatory Affairs, *AstraZeneca Pharmaceuticals Ltd, USA*

Dr George Butler provided an overview of the advantages and disadvantages of undertaking parallel regulatory submissions in the major global markets, not only the US, EU and Japan but also Australia, Latin America (particularly Mexico and Brazil) and China and other Asian countries, including Singapore.

The drivers for parallel registration are two-fold: the benefit to patients and the commercial advantages for the company. The global, rather than sequential launch of a product allows valuable new medicines to become available to a wider community of patients. In terms of the company portfolio, the parallel launch is a means to maximise patent life but also makes best use of the commercial and technical expertise in the company. An enormous amount of planning goes into the launch of a product but, once the product is approved, the project team may be reassigned to other projects. It is inefficient and impractical to repeat a major launch year after year in different regions.

In considering what is required for a simultaneous launch in the US and other parts of the World, Dr Butler emphasised the need for early planning, starting back in 'phase zero' of the drug's development when study designs must take account of different technical requirements, factors such as pricing and reimbursement strategies and the need to address different medical cultures. At the time of filing the application, the demands on the project team are far greater for parallel submission than for sequential applications and it follows that a much larger support team is required.

A major challenge is dealing with the inevitable questions and requests for additional information that will arise during review of the application. The resources and expertise of the team can be stretched to the limit trying to meet the requirements of the EU, US and Japan at the same time. There is a question of tactics and whether, as the major market, there is an advantage in dealing with requests from the US first and, for example, negotiating any label changes before responding to authorities in other regions. A major preoccupation for the company is to achieve labeling that differentiates the product from its competitors, whereas the authorities often seek to introduce class labeling. Other considerations are the implications of parallel inspections by the authorities for compliance with GMP, GLP and GCP.

Dr Butler reviewed some of differences in technical information and requirements that can prove an obstacle to global registration:

Quality/CMC Data: Notwithstanding the ICH harmonised guidelines, there remain differences in the stability testing requirements for tropical countries leading to different conclusions on shelf life. On specifications, there are also different demands relating to impurities and degradation products. Another issue is the different emphasis placed on the inspection of manufacturing plants by the EU, US and other authorities.

Pre-clinical data: There are no major issues and any differences that arise can normally be resolved relatively easily.

Clinical requirements: This is where major problems can be encountered including:

- Requirements for long-term safety data in excess of ICH requirements;
- Late safety issues requiring additional specific studies;
- Differences in approach to minimum dosage requirements;
- Increasing requirements for long-term studies, not only for safety but also for efficacy with requirements for testing against a positive control.

Dr Butler reviewed the factors that could be considered as constituting success (*Figure 8*) and outlined some conclusions that could be drawn from his company's experience of parallel and sequential global application procedures:

- The key to more predictable decisions from health authorities is greater data sharing and review in the pre-and post submission phases;
- A 'wait and see' attitude should be avoided. If additional safety studies or studies in special populations are likely to be required the company should initiate these rather than wait for the health authority to demand them;
- A parallel submission strategy is only expeditious if US approval is relatively fast and easy: a negative review by the FDA has a significant impact on registration in the rest of the world.
- The resources required to undertake a parallel submissions are inevitably greater than those planned and assigned. Provision must be made to meet unexpected situations and make knowledgeable people available quickly;
- More attention should be paid to the impact, both positive and negative, of exposure to public information (particularly financial) during the review process;
- Post-launch risk management requires to be carefully planned with the health authorities, with the emphasis in the US on managing risk, in the EU on pharmacovigilance and in Japan on risk avoidance;

Finally, it is much easier and less resource-consuming to launch the 'first in class' drug than make the case that your product is 'best in class'.

Figure 8

<p>What Constitutes Success?</p> <p>Patients</p> <ul style="list-style-type: none">• Earliest availability worldwide of new medicinal products <p>Purchasers</p> <ul style="list-style-type: none">• Fast availability of multiple therapy choices <p>Health Authorities</p> <ul style="list-style-type: none">• Right first time submissions allowing efficient review and decision-making process; no emerging major safety issues post-launch <p>Commercial</p> <ul style="list-style-type: none">• US approval with competitive labeling with 12 months• Non-US approval (technical plus "reimbursement") at the same time? Or soon after? <p>Regulatory</p> <ul style="list-style-type: none">• Indication approved consistent worldwide• Dosage minimum ~ same in all countries (PK / PD dependant)• Contraindications, warnings, precautions, safety are data-driven• Conditional approval work is realistic• No imposed additional preclinical studies• Sources of manufacture secure• Agreement with authorities to re-review label impositions with 2 years of marketing data• Regulatory dialogue door remaining "wide-open"

SESSION 3: POINTS FROM THE DISCUSSION

Types of major amendments: Dr Jenkins was asked whether the major amendments required for the applications in his study could be split out into different types: CMC, preclinical and clinical and whether there are different patterns in terms of some divisions asking more questions than others. Dr Jenkins replied that the data had not been analysed further to that degree of detail. There were other ways that the data could be split in terms of

whether the amendments related to early submissions or were in response to disciplinary orders, but they had not tried to achieve that level of complexity. He acknowledged, however, that further analyses would be useful.

First cycle approvals: Dr Jenkins was asked to comment on data he had presented which indicated a huge swing from a relatively low percentage of first cycle approvals in 2001 to a significantly higher percentage in 2002, for priority reviews. He replied that there was no simple explanation and that the differences in applications were multifactorial ranging from the quality of the application to the different types of indications and the divisions that handled the applications. He did not believe that it reflected any major policy shift on the part of the agency.

Avoiding major amendments: Dr Jenkins was asked whether he felt that some of the major amendments identified in his study could have been avoided with better communication and transparency and whether the problems could have been identified earlier in the review cycle. What is the way forward to reduce the need for major amendments in future? Dr Jenkins stressed, once more that the most important factor was to submit a complete application. Other factors included taking advantage of the opportunities to consult the agency at the pre-IND stage, during Phase II and at the pre-NDA stage. Not only should the relevant guidances be studied but efforts should also be made, under Freedom of Information, to obtain historical assessment reports on the data submitted by other parties, under similar circumstances. A proactive approach is needed in the first instance as trying to 'fix' a poor application at a later stage is rarely successful. One of the initiatives that the agency is working on to help in this area is the development of indication-related guidances. These, however, take time and resources and this is time taken away from the review process.

FDA is also working on pilot programmes involving more end-of-Phase IIa meetings. This would mean greater involvement in dose-ranging and pharmacokinetic trials to try to formulate better advice when the end of Phase II is reached and the Phase III programme is being discussed. This would allow the FDA to have greater input at a critical stage. Currently the end of Phase II meeting is the most important interaction between FDA and the sponsor but may be too late.

Not hiding the 'warts': Dr Jenkins referred to the advice given by Dr Goldmann in her presentation that it is never worth trying to hide negative information. If problems arise they should be discussed early. FDA has no expectations that drugs are perfect but if the reviewers find out, during review, about a problem that has not been revealed openly they will immediately be suspicious that there are other matters that have not been revealed. This can 'kick the reviewers into overdrive' with a result that they dig deeper and deeper into the submission looking for concealed data. Once trust and credibility has been lost it is hard to retrieve the situation.

Learning from experience: Dr Marisa Papaluca Amati referred to an analysis that will shortly be published that looked at the comparative success rates of different applications from the same company, using as a measure the clinical issues and objections raised. Preliminary results show a correlation between the number of times the company has used the centralised procedure and the length of the process, indicating the importance of learning from experience and improving communications. Whilst she recognised that project teams disperse once an authorisation is granted, she emphasised the importance of building a knowledge base and expertise in the company that can be built up for subsequent applications.

Dr John Jenkins suggested that a further analysis of the data that he had presented might reveal a different aspect of the 'learning experience' in that applications for indications that FDA had approved a number of times might require fewer amendments than those for new indications. He advised strongly that companies should pay attention to the advice given by FDA on the number of studies and viable indications for a product. It should be borne in

mind that the reviewers see all applications and, although they may not be able to reveal why they are giving a piece of advice, they are calling on collective experience of similar applications.

Complete and incomplete applications: A scenario was suggested where, at the end of Phase III, with dates committed for submission of the application, a marginal safety issue arises, for example, a transaminase change observed in a few outliers. The view from the company's clinical experts is that this is not significant and would not alter the labeling. Obtaining the view of an agency reviewer, at short notice may not be possible and it was suggested that the temptation would be to go ahead with filing the application, with the problem openly acknowledged, and let the review process take its course. Would this be considered as an incomplete application?

Dr Jenkins replied that this would not meet his definition of an incomplete application where the company knows that it is going to submit late information that is not ready at the time of filing. This example would be a review issue, as the agency would need to see the full data before being able to advise on the need for further studies. No application is expected to be perfect and there will always be questions. The important thing is to be open about the issues and have as much discussion, in advance, as possible. Dr Giaquinto added that this was another example of the importance of not hiding the 'warts' in an application and ensuring that the issue and the explanation of the action taken by the company is brought out clearly as a discussion item in the submission.

