PREDICTABLE OUTCOMES:

WHY DO POTENTIAL WINNERS FAIL?

WORKSHOP
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WORKSHOP REPORT

CMR International
INSTITUTE FOR REGULATORY SCIENCE

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The CMR International Institute for Regulatory Science is a not-for-profit division of the Healthcare and Science business of Thomson Reuters. It works in the regulatory and policy arena and in close association with the research-based pharmaceutical industry and regulatory authorities around the world. The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme.

The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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Section 1: Overview

Background to the Workshop

A little more than 10% of new compounds that are at the first-human-dose evaluation milestone will reach the market. The costs of pharmaceutical R&D keep spiralling upwards, whilst the rate of new molecular entity (NME) approval applications decreases.

The regulatory approval system should be relatively predictable and risk free for medicines developed in accordance with current guidelines. However, it could take 12 to 14 years for a pharmaceutical company to bring a product to the market, and during that time the regulatory guidelines and scientific advice may have changed to keep pace with scientific progress.

Participants in this Workshop focused on identifying critical success factors (CSFs) that are needed for the success of new medicines and examined the best use of scientific advice to provide a predictable outcome for the drug development process. In addition, the results and future directions of the CMR Institute for Regulatory Science's Scorecard Project, a metric designed to measure the quality of submission dossiers from the perspectives of agencies and companies, were discussed.

Syndicate Discussions

The Syndicate groups (breakout sessions) focused on two topics: making the development of new medicines more predictable and making the review of medicines more predictable. The aim of these syndicates focused on a framework of CSFs and strategies to foresee and/or avoid hurdles and pitfalls during development that could be developed into guidance for companies and agencies.

Outcome

Making the Development of New Medicines More Predictable

Two syndicate groups discussed two different aspects of this topic. One group focused on *developing a new medicine in a disease area where other therapies already exist, and the other discussed developing a new medicine in a new therapeutic field with no, or inadequate, competing products*.

For the first topic, early differentiation of the new medicine amongst its competitors is a key priority. It is important to collect input from all the various stakeholders early in the process and establish benefit-risk (BR) models early in development. Since long-term outcome studies may be needed, companies should be prepared to perform them or perhaps consider not developing the drug if deemed not cost-beneficial.

For the second topic, development of a new medicine will depend upon the perception of the disease state. Diseases considered "lifestyle" in nature will have a more rigorous development process than diseases considered life threatening. Communication with agencies is necessary for success as there may be a lack of understanding of the role of the compound, its mechanism of action, and/or the use of biomarkers to assess its profile.

Making the Review of Medicines More Predictable

Interacting with agencies and seeking and following scientific advice are important for success. Companies need to focus on key issues and avoid noncritical issues when soliciting scientific advice. Ideally, a standardised benefit-risk assessment that addresses the CSFs would allow a more predictable outcome.

Specific Recommendations

The following are some of the specific recommendations proposed by the participants:

- A clear target product profile (TPP) needs to be established describing the criteria for the improvements needed in the management of the target disease.
- It is very important to agree on surrogates and biomarkers early in the process.
- Good safety screening is necessary at all stages.
- Identifying the correct dosage and comparator are key to building the BR profile.
- Labelling should realistically reflect the product profile.
- The phase 3 timeframe could be used to educate the reviewing agency about novel or complex compounds, and identify data gaps.
- Companies do not always follow the agency's advice, which can smooth the review process.

- As research moves forward, a company's position regarding the product profile can change.
- The use of "Scorecards" and the move toward greater transparency in regulatory activities can lead to a process of open discussions between companies and agencies.
- The Scorecard Project should change from a retrospective to a prospective model. The future study should include a larger dataset consisting of multiple companies (CMR membership companies) and multiple dossiers across therapeutic areas. It also should extend beyond the current jurisdictions to include emerging health agencies (eg, Singapore and Taiwan). Unsuccessful dossiers should also be included in the study.

Workshop Highlights

The first session addressed *Improving Predictability* and was chaired by **Dr Peter Honig**, *Senior Vice President and Head of WRAPS-GSDO, Merck & Co Inc., USA*. Dr Honig opened the meeting with a discussion about the unsustainable nature of the current research and development model being followed by most of the pharmaceutical industry.

Dr Robert Ruffolo, *Former Executive Vice President for Research, Wyeth Pharmaceuticals, USA*, then spoke about why potential winners fail. There is no single reason why potential winners fail. Pharmaceutical companies are focussing on diseases in which the failure rates are typically high. Clinical trials have become longer and more complex. Portfolio consideration is an avoidable cause of failure. The lack of harmonisation amongst the global regulators has prevented an agreement about requirements for drug approval.

Dr Neil McAuslane, *Director, CMR International Institute for Regulatory Science*, discussed the productivity challenge, trends in success rates, characteristics of success rates to be considered, time to termination and reasons for termination. Based on only industry-level success rates, companies will require seven to eight projects coming into phase 1 to produce one new approved medicine. There has been no change in median time to termination of a project from first human dose during the 2000-2007 timeframe. A lack of efficacy and poor safety profile are the main reasons for phase 3 terminations.

Dr Eiry Roberts, *Vice President, Transitional Phase Development, Eli Lilly and Company, USA*, described the current state of phase 3 success rates, the types of risk reduction, tools to understand risk profiles, and management of portfolio risk. Several key actions can be taken by companies to alter their risk profile. Becoming knowledgeable in the disease, patients, therapies, regulation, and understanding the variability of biology and physiology are critical.

Dr William Mattes, *Director of Toxicology, The Critical Path Institute, USA*, discussed past and present preclinical safety assessment methods, the current tools and their limitations, biomarkers, and the Predictive Safety Testing Consortium (PSTC). The PSTC is focused on using combined resources and expertise to identify and approve biomarkers.

Dr Charles Shear, *Vice President & Development Team Lead, Pfizer, USA*, presented a case study of the failure of a late-stage drug, torcetrapib. After years of investigation, no corresponding relationship was found between the in vitro/in vivo findings and clinical risk. As late-stage failures will continue to happen, project planning teams should include a contingency for early termination.

Predicting Winners

Session 2 looked at whether certainty could be built into development and review, and was chaired by **Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK*.

Dr Janet Woodcock, *Director, Center for Drug Evaluation and Research, FDA, USA*, addressed the question of whether the US regulators have become more conservative and less predictable. Dr Woodcock discussed several issues concerning the perception of fewer first-cycle approvals, the issuing of more approvable letters, and discordance with other regulators in other jurisdictions.

Dr Paul Huckle, *Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA*, gave an industry perspective on publicly available data about applications submitted to the EU and US. Dr Huckle presented several potential reasons for the discordance in outcomes between the FDA and EMEA.

Prof Tomas Salmonson, *CHMP/EMEA Member (Vice Chairman), Medical Products Agency, Sweden*, discussed how to improve regulatory outcomes. Two methods of obtaining scientific advice exist

in Europe, either through the CHMP/EMEA or national agencies. Following scientific advice likely increases outcome predictability. The industry must continue to develop methods for better estimating the clinical value, for dealing with "complicated data sets", and for identifying patients likely to respond to the drug

Ms Andrea Mallia-Milanes, *Research Fellow, CMR International Institute for Regulatory Science*, presented an overview and the results of a pilot study to evaluate a scorecard approach in which companies and agencies rate the submission and review of approved dossiers. Three agencies and seven companies participated in the study of eight products submitted between 2004 and 2007.

Dr Leonie Hunt, *Assistant Secretary Office of Prescription Medicines, TGA, Australia*, spoke about the purpose of regulation and review practices and the TGA perspective on the Scorecard Project. Agencies want and need good review practices as part of their decision-making processes. The Scorecard Project has the potential to facilitate qualitative feedback amongst agencies and companies so that systems can be improved.

Michael Doherty, *Global Head of Pharma Regulatory Affairs, F-Hoffmann-La Roche Ltd, Switzerland*, outlined the current and future states of predictability in the R&D process and review process. The lack of predictability is a function of the different position of different authorities, the timing of interactions with sponsor, the interpretation of validity of endpoints and communications. Key Performance Indicators (KPIs) and scorecards are only of value if there is a good open dialogue on the findings and if there is a willingness to act on them

Section 2: Outcome

Syndicate Discussions

Session 3 of the Workshop, during which the Syndicate discussions took place, was chaired by Prof Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK.

The Workshop participants formed three Syndicate groups to address the following:

- Developing a new medicine in a disease area where other therapies already exist
- Developing a new medicine in a new therapeutic area where there are no other, or poorly effective/tolerated products available
- Making the review of new medicine more predictable.

The Chairpersons and Rapporteurs for the three groups follow:

Syndicate 1	Chair:	**Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada*
	Rapporteur:	**Dr Barry Sickles**, *Vice President US & Global Therapeutic Areas, Wyeth Research, USA*
Syndicate 2	Chair:	**Dr Joyce Korvick**, *Deputy Director, Division of Gastroenterology Products, FDA, USA*
	Rapporteur:	**Dr Simon Larkin**, *Head of Development, Europe, Celgene International, Switzerland*
Syndicate 3	Chair:	**Dr Thomas Salmonson**, *Vice Chairman CHMP (EMEA), Medical Products Agency, Sweden*
	Rapporteur:	**Tracy Baskerville**, *Head of Global Regulatory Affairs, Liaison, Cardio-Metabolic, Solvay Pharmaceuticals, France*

Background And Recommendations

Previous Discussions

This Workshop followed up discussions at previous Institute Workshops on critical success factors, benchmarking and regulatory dossiers and the review process. At the Critical Success Factors Workshop in December 2003, several factors were identified to improve the predictability of outcome success in drug development, including dialogue between companies and agencies and the appropriate use of scientific advice. It was felt that there was a need for companies to convey more open and consistent messages with greater transparency. Drug development projects should be discussed in an open manner without attempts at concealing difficult issues.

At a Workshop on Benchmarking, in October 2004, the Institute proposed a metric to measure company and agency performance on submission dossiers: the Scorecard Project. The Scorecard Project was further discussed and refined at the Regulatory Dossiers and the Review Process Workshop in December 2004.

A pilot study was proposed with two scorecard forms (one scorecard to be completed by the companies about their interactions with the agencies, and the other scorecard to be completed by the regulatory agencies about their impressions of the company dossiers) and tested by selected participating regulatory agencies and companies.

Recommendations

Making the development of new medicines more predictable

Critical success factors and strategies were identified around the following key decision stages in the R&D process:

Discovery to development:

- Early differentiation of new medicines is essential. Input from key shareholders must be received early in the development process.
- Having agreed-upon surrogates and biomarkers is very important. Good safety screening is necessary.

Proof of concept:

- Clinically relevant dosages/forms should be obtained as soon as possible. Companies must address liabilities of established therapies early in clinical development. A discussion with the health authorities about validation of tools is critical.
- Interaction with the agencies is important. Gathering key opinion leader (KOL) advice is necessary. Focussing on products with an acceptable safety profile is always important.

Phase 3:

- The choice of comparator is crucial.
- Companies should be prepared to make a significant investment as long-term outcome studies always require many resources.
- Developing realistic labelling that accurately reflects the product's evolving BR profile is a key concern.
- If there is any lack of recruitment in a company's trials, it could signal underlying problems (eg, competition, lack of interest in the product).

Submission:

- Companies need to provide a "good story" to make the review of the new medicine a success, and have validated tools that can demonstrate differentiation.
- KOL advocacy is needed.

Company culture:

- Abandoned projects should not necessarily be viewed as failures by management, especially if no-go criteria are not met. A culture of advocacy within companies could make it difficult to "let go."
- The company circumstances will regulate how a company will predict its future. The company that has many compounds will have more options than a small company with a sole drug.

Making the review of new medicines more predictable

Identifying avoidable errors in applications and the interaction between companies and regulatory agencies were discussed:

- Prospective measures for a successful review
- The procedures offered by the major agencies for advice at the pre-submission stage could be improved. When advice from different agencies is in conflict, the rationale needs to be transparent. Companies do not always follow the advice; it is important to note that as research moves forward, a company's view of the development process can change. Companies want agencies to communicate information about the evaluation of a therapeutic class (or drug) that could potentially impact the company's development plan. However, the challenge is the multiple filters on that advice could create different interpretations.
- Companies and agencies need to be better prepared to identify cases in which there are no regulatory precedents for the introduction of new technologies and concepts. The phase 3 timeframe could be used to educate agencies about novel or complex compounds, and identify data gaps required for the agency to make an informed decision.
- A new category for truly novel (but not first in class) compounds or applications that employ novel design paradigms could be created. This could allow for a new pathway to allow additional facilitated discussion, and an opportunity for continuous, flexible and broader dialogue (first-in-man [FIM] to phase 2).
- After 10 years experience with the ICH Common Technical Document (CTD), companies are still being criticised for the quality of their submissions. At the Institute's Measuring Benefit and Managing Risk Workshop (June 2008), a proposal for the data framework for a benefit-risk assessment was discussed. Development of the current EMEA BR template should be continuous: focus on critical issues, determine value, make it a model for other jurisdictions, acknowledge output may be qualitative or at best semi-quantitative, and have a goal of standardisation.

Retrospective measures

- The use of scorecards and the move toward greater transparency in regulatory activities should lead to a process of open, frank discussions between companies and agencies following a dossier review. Scorecards are important, but could perhaps be designed to be more straightforward and easier to use. The use of a scorecard must be integrated into the review process. An emphasis on the educational component should be made. A real-time, on-line evaluation with easy-to-use,

drop-down menus is one potential option to consider for scorecard assessment; data would immediately be uploaded to a central repository. Then the data could be useful in performance management.

- Companies and agencies should utilise feedback mechanisms (from internal reporting, scorecards, etc) to detect procedural flaws, communicate internally between different units and bring about change. Peer reviews, quality management audits and benchmarking are key feedback mechanisms.
- The Institute's Scorecard Project should change its current status from retrospective to prospective. The next phase of study should include an appropriately large dataset consisting of multiple companies (Institute membership companies) and multiple dossiers across therapeutic areas. It also must extend beyond the current participants to included emerging regulatory agencies (eg, Singapore, Chinese Taipei). Unsuccessful dossiers should also be included in the study.

Details From The Syndicate Discussions

Developing a new medicine in a disease area where other therapies already exist

Incremental improvements to current therapies are important to patients, and development of these medicines should be encouraged through responsible development plans and responsible regulation.

Objective: This syndicate group focused on the scenario of developing a new medicine in a therapeutic area where the aetiology and clinical endpoints of the disease, and the mechanism of action of the drug, are relatively well established.

In this scenario, it became clear that early differentiation of the new medicine is a top priority. Gathering input from the various stakeholders early in the process is required for success. Benefit-risk models should be applied as early as possible to differentiate the product's profile. In addition, comparator studies may be needed earlier in the development process. Long-term outcome studies may need to be performed to fully characterise the uniqueness of the new product.

Points from the discussion

Critical success factors: discovery to development

- A clear target product profile (TPP) needs to be established with clear criteria about the improvements the products offers over existing practice. If necessary, liabilities (ie poor safety profile, pharmacokinetic limitations) should be engineered out of the product.
- Early differentiation of a potential new drug is critical. In early preclinical models (comparative studies), there needs to be criteria for this drug to separate itself from competitors in its field.
- Obtain input from key stakeholders (ie, payors, health economists/ Health Technology Assessors [HECON/HTAs]) earlier in the process. The discussions could indicate the basis for a clear no-go decision.
- Companies should develop more discriminating clinical endpoints to demonstrate value to payors and to gain regulatory acceptance.
- If the identification of target populations is deemed a potential improvement in a certain therapeutic area, then patient selection by early biomarker approach is needed.
- Niche markets should be considered.
- The creation of alternate formulations or delivery mechanisms designed to improve compliance is another consideration.
- To better define success, companies should organise joint meetings with payors and regulators to discuss success factors and tools that could be applied to demonstrate differentiated elements.
- Benefit-risk models should be applied as early in the process as possible. Establishing risk-sharing strategies between agencies, sponsors and target users early is also key.

Critical success factors: Proof of competitiveness

- Companies must address the limitations of established therapies early in clinical development.
- Engage other stakeholders (eg, HECON/HTA) early to gain input.
- A validation of assessment tools in a discussion with health authorities is critical.

- It may become necessary to have comparator studies done in phase 2. Also, an adaptive design approach could potentially be used.
- The expected clinical dosage should be defined early in the development process.
- There is a high probability that these drugs will work since there is typically a sufficient knowledge base developed. However, it is not known whether they will work well enough to be a differentiating aspect.
- It is still difficult to measure risk before major phase 3 investments; therefore, developing a product profile early on is critical.
- Companies need to develop more discriminating clinical endpoints to demonstrate value to payors, and also gain regulatory acceptance.

Critical success factors: Phase 3

- The choice of comparator is a critical decision.
- Futility analyses for key criteria should be performed.
- Companies should implement differentiation tools in phase 3 (patient reported outcomes [PRO]/HECON tools, etc) that were validated in phase 2.
- Statistical significance and clinical significance of safety variables should be clearly defined.
- There is a possibility that improvements will be seen in one set of variables, but a worsening in a different set of variables.
- A top concern for primary care drugs is that outcome studies are often required. Companies should be prepared to make a significant investment as outcome studies are resource intensive.

Critical success factors: Submission

- Companies need to provide:
- A good story to make the product review a success.
- Validated tools demonstrating differentiation.
- Companies should already be involved with pre-submission meetings to ensure that reviewers are familiar with the approach (especially important if new reviewers are assigned).

Company culture

- If clear no-go criteria are met, companies should view abandoned projects as successes instead of failures. One company has "black cake" parties to mark occasions when management has decided that a compound has met no-go criteria. However, there could be a culture of advocacy within individual sections of a company that have problems "letting go" of marginal products.

Developing a new medicine in a new therapeutic area where there are no other, or poorly effective/tolerated, products available

The development of medicines depends upon the disease state. Therapies for diseases considered life-threatening may have a less stringent development process than those for a disease considered less serious or those to improve lifestyle.

Objective: This syndicate group focused on the scenario of developing a new medicine in a novel treatment area which, if successful, will be a first-in-class or a major advance in an area with poor therapeutic options. The aetiology of the disease and the mechanism of action (MoA). of the drug, may be poorly defined. The need for the medicine may be high (serious life-threatening conditions), but the scenario may also cover products with a new commercial potential (lifestyle medicines).

The direction of the development of the new medicine in this scenario will depend upon the disease state. There may be more "wiggle room" for new medicines for treatment of life-threatening diseases (eg, a good disease model may be lacking, unclear MoA). Interaction with the agencies is important, as proposed biomarkers may be new, and understanding on both sides is needed for success. In the current environment, a good safety profile is always a necessity.

Discovery stage

- This depends on how the disease is classified (ie, mild vs lethal). For a mild disease, there should be a realistic TPP. The commercial team needs to be realistic about market penetration opportunities. For a fatal disease, there may be more "wiggle room" because a thorough exploration of that disease may not be required to determine if a cure or significant improvement is possible. Also at this stage, alternate TPPs are important to consider, because subset populations within this serious disease may give a return on the company's investment.

- A clear MoA is very important in generating confidence for treating mild disease.
- Good disease models are necessary for generating confidence between the Sponsor and external stakeholders. However, creating "validated cures for mice" is of no value, as the ultimate goal is to make the compound available for safe human use.
- Agreed-upon surrogates and biomarkers will be important in getting this medicine to the patients in a timely fashion.
- The lack of competition from other therapies may not be reassuring. Competition helps generate a knowledge base, both amongst the companies and for the regulators. Interaction with regulatory colleagues allows companies to have generic information about development programs and the likelihood of success with a particular compound.

Proof-of-concept (POC) stage

- At this stage, defining the TPP is very important. A company should stay focused on the TPP; if not, problems could arise.
- A good safety profile is always important, even with manageable side effects. If the side effects are potentially as lethal as the disease itself, then they can be mitigated through monitoring of those side effects. This is a key area: drugs should not continue in development if technology does not exist to effectively monitor and define the side effect profile.
- A good therapeutic index is important. If it is a mild disease, the drug is expected to have a fairly high therapeutic index. In contrast, for a serious disease, the therapeutic index may be narrower because there are no alternatives. Also, subpopulations may be identified in the future that will have a better therapeutic index than the general population.
- Interaction with the agencies and KOL advice is important at this stage. In a lethal disease state for which the program is going to be accelerated, companies will be encouraged move forward (with fewer data) with support from the agencies.
- This stage is often focused on a single-centre study that is very carefully controlled with very specific patient types. Moving forward, efficacy generally diminishes as development moves into a multicentre setting. Scalability is a reality check: if there is an erosion of safety and efficacy, how does this affect the TPP?
- Special protocol assessment (SPA) for a major program helps improve predictability from key regulators. The hard questions should be asked. In Europe, the equivalent of a SPA does not exist, but there are other measures for developing collaborative confidence.

Phase 3

- The labelling discussion is more important than the TPP. It is critical at this stage to be developing realistic labelling.
- Safety at this stage represents an acceptance of the product's profile. Good risk management creates predictability and creates confidence. The stakeholders should know: "yes, patients will have side effects, but they can be reasonably managed."
- Recruitment into trials may be a predictor: while recruitment is necessary to meet companies' milestones, a lack of recruitment could indicate an underlying problem (eg, competition, lack interest amongst both the KOLs and the patients).
- Investigator-initiated trials (IITs) in some of the more serious diseases may be important to a company. Some elements for the development of a compound might be outside the company-sponsored studies, but helpful information (eg, biomarkers, endpoints) can be obtained from IITs. This offers the option of incorporating additional data from external sources to supplement but not replace the core package.
- In Europe and increasingly in the US, agencies are looking for incremental HECON outcome benefits and incremental improvement for mild diseases through new therapies in which some financial benefit needs to be shown over the existing therapeutic options. For serious diseases, a positive HECON outcome needs to be demonstrated, but it does not have to be an incremental improvement because no alternative treatment options exist.
- Companies need to be compliant with good manufacturing practices (GMP), good clinical practices (GCP), and chemical manufacturing and control (CMC) standards and should prepared for audits of their dossiers and sites. Data from IITs need to be defensible.

Submission, post-marketing

- At this stage, a realistic benefit-risk assessment is needed before filing and, ideally, this has been developed earlier during the development phase.
- Realistic labelling is required.
- KOL advocacy is important in developing the argumentation around the benefits of the new compound.
- Agency interactions will improve the predictability of the regulatory expectations.
- Sponsors must be prepared for long-term commitments. About 70% of marketing authorising applications now are associated with some post-licensing commitment.

Company culture

- Both company culture and characteristics are factors that influence the way forward. For example, if the Sponsor is a small biotech company, their willingness to "kill" their only compound is a very difficult choice. The company circumstances will influence how a company will predict its future. The company that is developing many compounds will have more options than a small company with a single drug.

Making the review of new medicines more predictable

Companies should focus on the pivotal issues when seeking scientific advice. Interaction with agencies (eg, scientific advice) improves the regulatory outcome.

Objective: This syndicate group focused on identifying avoidable errors in compiling and submitting applications and the ways in which interactions between Sponsors and regulatory agencies can help the review process, including retrospective analysis of successes and failures in review procedures.

Ideally, a standardised framework for BR assessment would result in a more predictable outcome. Companies should be transparent on contentious issues and focus their discussions on key issues during interactions with the agencies.

Interactions with agencies

- A fundamental issue is the management of expectations. By soliciting and following scientific advice, companies increase their chances of attaining success.
- In the EU, it is possible for Sponsors to participate in the leadership role in the review process. Interactions can help guide the selection of the best qualified candidates for rapporteur and co-rapporteur.
- It is redundant to duplicate certain aspects of the drug development process for each regulatory jurisdiction. Thus, companies should explore creative methods to implement a standardised, global regulatory approach.
- Companies could focus on a therapeutic area in which there is confidence in the review process within an agency or region (eg, paediatric oncology).
- Harmonisation of expectations amongst the agencies is challenging and has been slow to evolve.

Challenges

- Joint versus parallel scientific advice: Is joint advice even feasible in the current environment?
- Sequential versus parallel strategies: Is there any benefit of having a common briefing document presented without the presence of the sponsor? It might be more expedient for the various jurisdictions to have a dynamic dialogue that includes the sponsor.
- Can agencies agree on a common platform for the assessment of benefit-risk? Inter-agency discussions could be expanded to pilot further harmonisation.

Scientific advice

- Companies need to be transparent and focus on the key issues in pre-submission meetings and when seeking scientific advice.
- From the perspective of the reviewer, companies that focus on noncritical issues during these meetings waste time.
- Recognise that jurisdictional bias cannot be eliminated.
- There are advantages and disadvantages to binding versus nonbinding advice. Amongst the different regulatory agencies, some adhere to bound advice, whilst others are more informal. Those with nonbinding advice may offer more frequent opportunities for interactions.
- Scientific advice has a different role in smaller jurisdictions. Smaller agencies (eg, TGA) are

not resourced to provide the kind of scope and advice that is received from EMEA or the FDA.

- National EU advice tends to be more informal, but is no less invaluable.

Considerations

- A standardised framework for BR assessment will provide a more predictable regulatory review outcome.
- Greater transparency on contentious issues: A misunderstanding may arise if companies believe the agencies are looking for ways to reject the application.
- Consider the use of teleconferences and video conferences instead of face-to-face meetings. These types of communications are increasingly being used as a way of interacting with remote authorities.
- Utilise meetings to gather agreement on novel trial designs (eg, adaptive designs).
- Consider stronger and continuous communication links between agencies. Ideally, scientific advice should be a long-term dialogue through the entire drug development process.
- Instead of a summary of product characteristics (SPC)-focused approval model, consider a benefit-risk model or equation offering more versatility and thus, more value.
- For major issues, share the advice discrepancies in advance and promote cross-agency dialogue and resolution.
- Commit to regularly scheduled meetings.
- There is a wide range in the quality of submissions. A well-organised, easy-to-navigate, thoughtful dossier is not the norm, and there needs to be work done to help those companies who are struggling with quality submissions.

WORKSHOP PROGRAMME

Session 1: improving Predictability - Why are compounds failing in late-stage development and review?	
Chairman's welcome and introduction	**Dr Peter Honig**, *Senior Vice President and Head of WRAPS-GSDO, Merck & Co Inc, USA*
Why do potential winners fail?	**Dr Robert Ruffolo**, *Former Executive Vice President for Research and Development, Wyeth Pharmaceuticals, USA*
Success rates and time to failure – what is the current picture?	**Dr Neil McAuslane**, *Director, CMR International Institute for Regulatory Science*
Managing technical risk in late phase development – Can it be done? How?	**Dr Eiry Roberts**, *Vice President, Transitional Phase Development, Eli Lilly and Company, USA*
What is the role of preclinical studies in predicting safety in man: Can these be improved?	**Dr William Mattes**, *Director of Toxicology, The Critical Path Institute, USA*
What can be learned from experience of late-stage failures: Torcetrapib: A case study	**Dr Charles Shear**, *Vice President and Therapeutic Area Clinical Lead, Pfizer, USA*
Session 2: Predicting Winners: Can certainty be built into development and review?	
Chairman's welcome and introduction	**Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK*
Are today's regulatory submissions flawed? **A regulator's viewpoint**	**Dr Janet Woodcock**, *Deputy Commissioner, FDA, USA Industry Speaker*
An industry viewpoint	**Dr Paul Huckle**, *Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA*
Improving regulatory outcome – What needs to be done in development	**Prof Tomas Salmonson**, *CHMP (EMEA) Member (Vice Chairman), Medical Products Agency, Sweden*
Outcome of a pilot study to evaluate a scorecard approach where companies and agencies rate the submission and review	**Andrea Mallia-Milanes**, *Research Fellow, CMR International Institute for Regulatory Science*
Improving the quality of development and review **An agency perspective**	**Dr Leonie Hunt Director**, *Assistant Secretary Office of Prescription Medicines, Therapeutic Goods Administration, Australia*
Utilisation of feedback loops and dialogue as a way of improving the quality of the development and review process **An industry perspective**	**Michael Doherty**, *Global Head of Pharma Regulatory Affairs, F-Hoffmann-La Roche Ltd, Switzerland*
Session 3: Syndicate Discussions	
Chairman	**Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK*

SECTION 3: SUMMARY OF PRESENTATIONS

Session 1: Improving Predictability: Why Are Compounds Failing In Late-Stage Development And Review?

Why do potential winners fail?

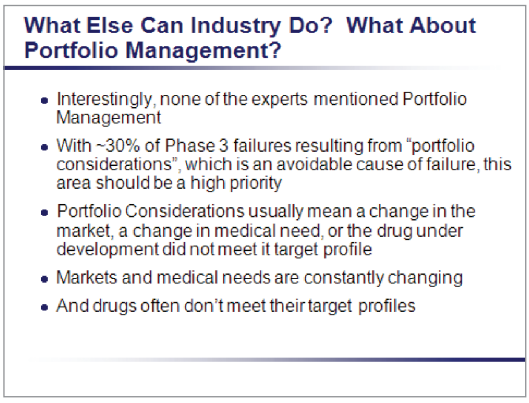
Dr Robert Ruffolo

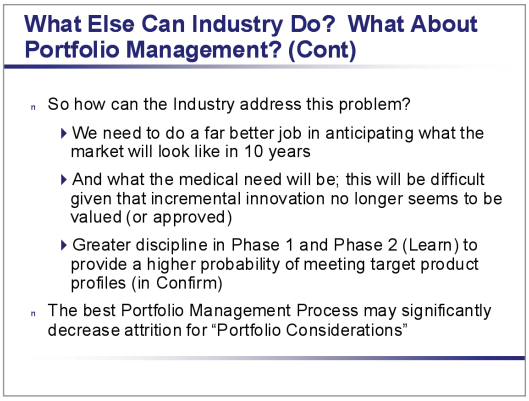
Former President for Research & Development, Wyeth Pharmaceuticals, USA

Dr Ruffolo presented data that indicated that the current model of drug discovery and development followed by the international pharmaceutical industry is unsustainable. A confluence of factors have come together to make drug development more challenging than in any time in the past. Pharmaceutical companies are now focussing on difficult therapeutic areas. The top two therapeutic areas in research and development (R&D) are oncology and neurosciences, which are two areas that have the highest attrition rates and have lengthy development times. There is no single reason that explains why potential winners fail. Over the years, an increasing number of stakeholders have become involved in the development process, with some whose benefit of involvement is questionable. Furthermore, the success rates of clinical trials are decreasing and are predicted to worsen. The focus of a company's portfolio and the way the portfolio is managed are avoidable causes of the failure of potential winners. Product liability has affected the industry's decision to underwrite some types of clinical trials and research. The lack of harmonisation amongst the global regulators has slowed cross-national agreements about common assessment requirements for drug approval.

The evolution of science and medicine is leading to greater challenges in the R&D pipeline. Innovative drugs come with new risks; novel drugs tend to have high study attrition rates, longer development timelines, and higher costs. Genomic targets have been slow to be clinically developed; improved diagnostics and targeted treatments have therefore, developed more slowly than anticipated. R&D productivity is decreasing and R&D costs are rising due to a variety of factors (eg, clinical trial size, increased number of trials per new drug application [NDA], increased patients per trial, regulatory demands). The industry as a whole is focussing on diseases that are more difficult to treat (eg, Alzheimer's disease). Clinical trials have become longer and more complex. Often, patient recruitment is the rate-limiting step and the primary cause of developmental delay. Long-term outcome studies have become increasingly required by regulators, which increases the expense and the length of clinical trials.

To combat these difficulties, the industry must work toward streamlining development times, have in place mechanisms to improve patient recruitment capabilities, participate in collaboration consortia with global regulatory agencies and consider new ways of improving the use of outsourcing (eg, find new places for clinical trials). The industry could develop more efficient clinical trial designs and better characterise dose-response earlier during development.





The regulatory environment has changed. The current environment is one of an unrealistic safety expectation by the public and perhaps also by the regulators. Dr Ruffolo hypothesised that the external oversight of the FDA by Congress has caused changes in policy that may be detrimental to patients. There has been an increased focus on safety surveillance: a 900% increase in adverse event (AE) reporting in the last decade, and a 400% increase in labelling changes. Dr Ruffolo questioned whether the FDA has changed its standards for new drug approvals.

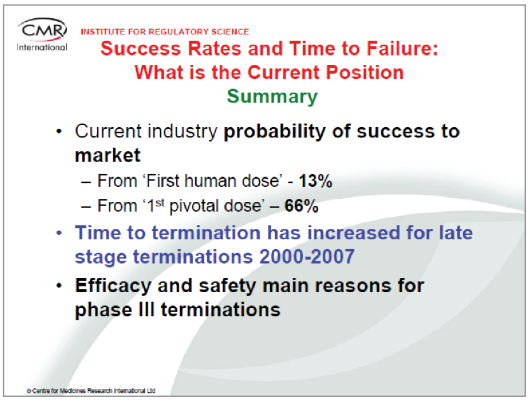
There is increased caution when approving a new drug if another drug in that class is already on the market. It appears that the long-standing requirement by regulators that new drugs be "safe and effective" has evolved to become "safer and/or more effective" when a second drug in the same class is under review. New stakeholders have joined in the new drug approval assessment discussion. The practice of medicine has long involved industry, regulators, physicians and patients. Increasingly, payors, members of Congress, industry watchdogs, media and whistle-blowers have their say in influencing drug approvals. The question remains whether these stakeholders have made changes to the regulatory environment that will ultimately be detrimental to the patient. It remains the challenge for industry, regulators and other stakeholders to facilitate a common discussion that ultimately results in the rapid identification, streamlined development, common approval and ready availability of beneficial new therapies that improve the public health.

Success rates and time to failure:

What is the current position?

Dr Neil McAuslane

Director, CMR International Institute for Regulatory Science



Dr McAuslane discussed the productivity challenges, trends in success rates, characteristics of success rates to be considered, time to termination, and reasons for termination of new drugs in development. The number of new molecular entities (NMEs) launched into the world market has been steadily decreasing over a 10-year timeframe whilst global R&D expenditures have been rising.

The current industry probability of success (ie, of reaching the market) of an active substance at the time of first human dosing is 13%. Based on industry-level success rates, companies will require 7 to 8 projects coming into phase 1 to produce 1 new approved medicine. The therapeutic area is considered the characteristic with the greatest influence on success rates. When examining the success of a portfolio, it is important to consider the company's mix of products across therapeutic areas.

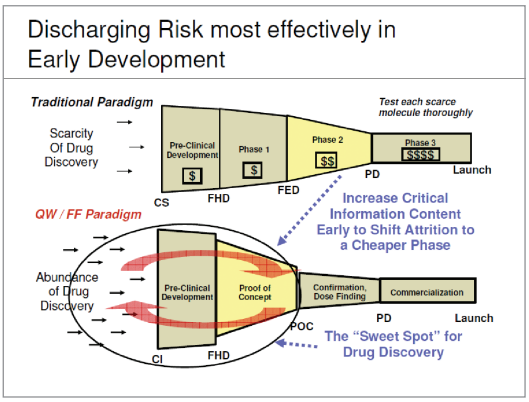
There has been no change in median time to terminating a development program from first human dose during the 2000-2007 timeframe. However, median time to termination has increased for compounds reaching phase 3; it was 2.7 years during 2000-2001, and 3.3 years during 2006-2007. The majority of terminations across all phases were due to the expected approvability of the product (80%) with commercial (20%) reasons accounting for the balance. A lack of expected efficacy and a poor safety profile are the main reasons for phase 3 terminations. During 2004-2007 there was a proportional increase in terminations due to a lack of efficacy and "strategic reasons" compared to the findings during 2000-2003.

Managing Technical Risk in Late-Phase Development:

Can it be done? How?

Dr Eiry Roberts

Vice President, Transitional Phase Development, Eli Lilly and Company, USA



Dr Roberts described the current state of phase 3 success rates, the types of risk reduction companies can undertake to improve the development success rate, the tools available to understand risk profiles, and the management of portfolio risk.

Some late-stage failures at Lilly were discussed. These involved three internal and two licensed compounds that failed because of an insufficient margin of safety or insufficient efficacy.

Several key actions can be taken by companies to alter their overall exposure to drug development risks. Companies should become experts in these areas:

- Disease: decide which diseases, technologies and collaborations to pursue.
- Understanding the variability of biology and physiology: have a good understanding/prior knowledge of the target population so as to better detect signals of benefit and risk.
- Patients: have an understanding of factors that influence patients' well-being and decision-making (genetic, environmental, economic).
- Therapies: understand all other therapeutic options that exist for the patients.
- Regulatory: understand the regulatory path to successful value generation.

Efficiency diagrams can be used to illustrate the amount of technical uncertainty that can be resolved over time (including at what cost). In addition, these diagrams from separate projects can be compared to determine which projects are more or less efficient in resolving their uncertainty.

CHORUS is a Lilly initiative to drive the resolution of significant uncertainty from candidate selection to proof of concept. This program is in its fourth year of activity. The projects that fit best into the CHORUS paradigm are those that involve a significant amount of uncertainty at the point of proof of concept.

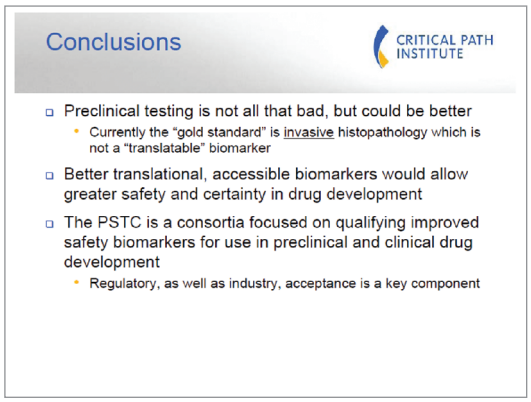
When technical risk cannot be mitigated, risk-sharing business models can be used to optimise the development path (eg, using a fully integrated pharmaceutical NETwork [FIPNET] to overcome risk points).

What is the role of preclinical studies in predicting safety in man:

Can these be improved?

Dr William Mattes

Director of Toxicology, The Critical Path Institute, USA



Dr Mattes discussed past and present preclinical safety assessment models, the current tools and their limitations, the role of biomarkers in preclinical studies, and the Predictive Safety Testing Consortium (PSTC). In the US, prior to the Federal Food, Drugs, and Cosmetic Act of 1938, drugs were sold without testing for safety with sometimes devastating outcomes (eg, elixir sulphanilamide, which contained diethylene glycol resulting in the deaths of more than 100 people).

Dr Mattes presented the results published by Olsen et al 2000, which examined toxicity of pharmaceuticals in humans and animals. The authors found that 70% of human toxicities (HTs) were predicted by preclinical toxicology, and that most of the toxicity signals were detected in early clinical development. In addition, certain types of HTs (liver, renal) were more damaging to the continuation of development programs than other HTs. However, for those serious HTs, the preclinical results might have been ambiguous, leading to the advancement of the drug into the clinical phases. In today's environment, those pharmaceuticals that have ambiguous signals of toxicity during preclinical testing will either be advanced into development or dropped; the difficulty is predicting those that will actually demonstrate toxicities in the clinic compared with those that should not have been dropped from development because their safety profile in man would have been acceptable for clinical use.

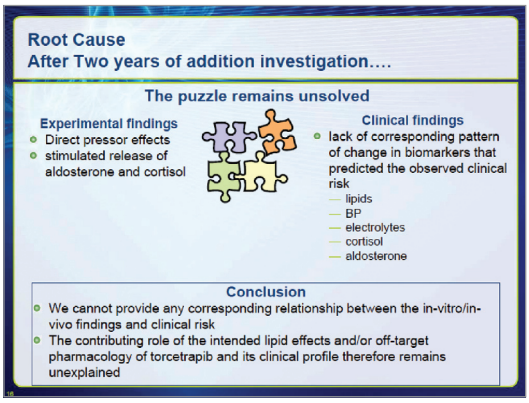
In the current approach to safety, some commonly used biomarkers are dated and limited in their predictive value; for example, serum creatinine is often assessed but most measures are not sensitive enough to detect the development of early kidney damage. Therefore, new qualified safety biomarkers are needed to improve the predictive value of preclinical testing. The PSTC is focused on using combined resources and expertise to identify and qualify more accurate biomarkers. In the second quarter of 2008, the FDA and EMEA confirmed their joint review and acceptance of seven new urine laboratory tests that provide early signals of renal damage. The use of these renal biomarkers in clinical trials will be considered on a case-by-case basis to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.

What can be learnt from experience of late-stage failures:

Case studies

Dr Charles Shear

Vice President & Development Team Lead, Pfizer, USA



Dr Shear presented a case study of the failure of torcetrapib, a drug in late-stage development.. Torcetrapib is a potent and selective inhibitor of cholesterol ester transfer protein (CETP), has linear pharmacokinetics in the clinical range, is extensively metabolised, and has a difficult-to-characterise long terminal elimination profile. In phase 2 studies, torcetrapib, when administered with atorvastatin, demonstrated a beneficial effect on lipid profiles, raising HDL-C and reducing LDL-C levels. Therefore, the working hypothesis became: optimal cholesterol control can be obtained with the administration of atorvastatin (decreases LDL-C) and torcetrapib (increases HDL-C). Across ten studies, a phase 2 integrated blood pressure (BP) analysis revealed a 2.22-mmHg systolic BP (SBP) elevation with the 60-mg once-daily dose. There were no leads as to the mechanism of action associated with this blood pressure increase. The ILLUMINATE trial was then terminated prematurely because of the statistically significant number of deaths and cardiovascular events in the group treated with torcetrapib.

After 2 years of investigation of the root cause, no relationship was found between the in vitro/in vivo findings of cardiovascular toxicity and clinical risk observed in the controlled trials in man. The process for target selection and the criteria used to determine when to progress a candidate to the next phase of development have consequently changed since the development of torcetrapib. Despite these process improvements, late-stage failures will continue to occur as part of any drug development program.

Are today's regulatory submissions flawed?

A regulator's viewpoint

Dr Janet Woodcock

Director, Center for Drug Evaluation and Research, FDA, USA

Dr Woodcock addressed whether US regulators have become more conservative and less predictable in their reviews of registration dossiers. It seems that industry would be satisfied if more conservatism was coupled with greater review predictability. However, the US FDA is viewed by industry as being less predictable according to three indicators. First, well- publicised turn-downs: in these cases, the Sponsors were confident about the positive reception of their compounds, yet the FDA withheld their approval. This suggested that the Sponsor's prediction of success was inconsistent with that of the regulator. These events have been touted as evidence that the FDA is not predictable in its review practices. Second,

discordance with other regulators: how could regulators from other parts of the world, when presented with the same data set, come to different conclusions about a drug's safety and efficacy? And finally, there is the perception that the agency is issuing an increasing number of "approvable letters." Also, there is a view that there is an increase in review cycle time. Many come to the conclusion that all of these items indicate greater conservatism and less predictability.

Fewer approvals?

The problem with objective data on this issue is that the FDA is working with small numbers of annual approvals of new molecular entities (NMEs). Historically, the rate of approvals compared with submissions has remained within a consistent range. The percentage of submissions that are ultimately approved by the FDA has not changed. Furthermore, the FDA does not have a lower rate of acceptance of priority or standard applications.

The industry is filing more priority NMEs, and there has been a higher approval rate for these than in the past. This trend on the part of industry reflects the healthcare focus on value. Also, the FDA is seeing fewer drugs in the same class. For the standard submission of the Nth drug in class, it may appear as though there was a slightly lower approval rate. However, due to small numbers, this may not be true. There is no evidence of a change in FDA evaluation process or outcome, although it might seem that way from the industry's perspective. There is no evidence that the overall success rate for approval has dropped. Despite what critics say, the FDA wants the industry to know that the target is for regulators to be able to review high-quality submissions. The FDA would then be in a position to approve more drugs on the first review cycle and a higher percentage of the submissions overall. Currently, the industry is not seeing a good return on their development investment and this is sometimes blamed on the regulators. The FDA is undertaking rigorous analysis of objective evidence to determine whether the agency has become more conservative in its reviews, and the agency expects to publish the results.

Lately, the FDA has been missing Prescription Drug User Fee Act (PDUFA) response times owing to the new burdens of the FDA Amendments Act, which has encumbered the new drug evaluation staff and other disciplines supporting it. In response, the FDA has hired more than 600 people into the Center for Drug Evaluation and Research (CDER) this year. This hiring effort took a huge resource toll in many ways. The good news is that CDER is becoming staffed more appropriately; however, typically new hires require a year or more of training to become fully effective. The FDA Amendments Act requires new procedures for Risk Evaluation and Mitigation Strategies (REMS). Each REMS must currently be reviewed centrally by CDER and by FDA lawyers for consistency and concordance with the law. These reviews have resulted in some delays, but do not affect whether the drug is approved or not.

Discordance with other regulators?

Another concern focuses on drugs that are approved in Europe and elsewhere but not by the FDA. The question is: what leads to these divergent outcomes? After close examination, most of these drugs (where there has been discordance) have been associated with specific safety issues. Mostly, there are concerns about potential life-harming side effects with no additional efficacy benefit over existing therapies. The other regulators were aware of these liabilities, but they have balanced the factors in a way that led to a different decision. The FDA is not willing to

introduce drugs with additional liabilities into the market unless they have some advantage over existing therapies. Regulators in other jurisdictions could offer different opinions based on their benefit-risk assessment, the available alternatives for that indication and their definition of safety standards.

Everyone is wiser today than 20 to 30 years ago on a variety of safety issues (eg, QT prolongation observed in various drug classes, central nervous system [CNS] consequences, cardiovascular side effects). Drugs targeting the CNS and those not directed to the CNS can have a risk of suicidality and other CNS consequences (eg, abnormal thoughts). Suicidality causes a public uproar because of the sentiments attached. This is complicated by the observation that the media cannot adequately convey the subtle but important differences between the concepts of suicidal thoughts versus suicides. Studies are now designed to identify the subtle differences in these adverse events to better characterise the BR profile of new drugs. Another issue is the cardiovascular side effects of drugs not directed against cardiovascular conditions (eg, Vioxx®, Avandia®). The FDA focuses on the overall impact of outcomes, not only on how the drug treats the target condition. One could say that the FDA is, therefore, taking a more conservative approach, but others could say the FDA is being more savvy in its overall approach to BR assessment.

Regulators need to be candid about their expectations of a drug's review; this will help provide a sense of predictability to the outcome. Industry must identify potential safety issues with a drug that is directed at one disease/organ system, but that causes harm to another organ system. If the studies and analyses are not designed to detect these unique signals, then the development program will fail in its ability to characterise the drug's profile. This is not conservatism; it is good medicine and good science.

More approvables? Fewer first-cycle approvals?

The last concern centres on the goal of approving more rather than fewer first-cycle applications. The FDA has examined this issue recently; there is no objective evidence or emerging trend suggesting that the percentage of first-cycle approvals has decreased. However, there is an improving record on priority approvals, of which a high proportion of applications are reaching the market.

Dr Woodcock expressed hope that "science will get us out of this box." Progress is being made with the Critical Path Initiative. Liabilities exist with every new drug and there is room for improvement to identify and explain to the end users how to interpret or even avoid these limitations

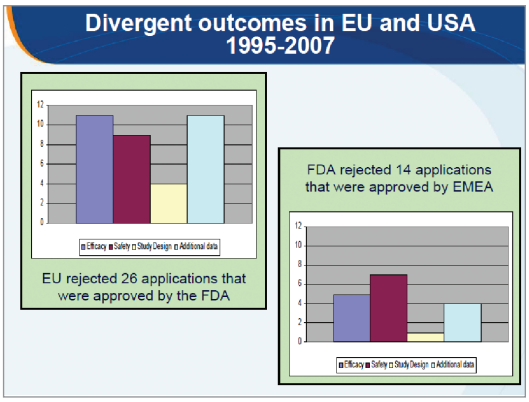
In summary, Dr Woodcock noted that one can interpret the changes perceived in the approval process as a reflection of "increased conservatism." However, there is no objective evidence that there is a trend for a slow-down of approvals based on this "conservatism." The US regulators are looking very closely to the use of more formal benefit-risk analyses to improve the transparency of their decision making process.

Are today's regulatory submissions flawed?

An industry viewpoint

Dr Paul Huckle

Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA



Dr Huckle presented publicly available data about drug applications submitted to the EMEA and USFDA from 1995 to the end of 2007. (Only applications that had been submitted to both regions in a similar timeframe were considered, as these are most likely to represent cases in which the agencies are reviewing the same data package). A variety of therapeutic areas and companies were included.

During this period, EMEA rejected 26 applications that were approved by the FDA, and the FDA rejected 14 applications that were approved by EMEA. The top reasons for rejection by the EMEA for applications were efficacy issues and a lack of additional data required to make a fully informed decision. This lack of additional data may be due to the applications being more US- than EU-focussed in their content. The FDA rejected applications primarily due to safety or efficacy issues. He noted that the BR analysis was not likely to be viewed or interpreted consistently across the different jurisdictions.

Dr Huckle reviewed several examples in which the application was rejected in the US but approved in the EU, and vice versa. It appears that a decade ago, medicines were more likely to obtain approval in the US than in the EU, a situation that now appears to have reversed.

Dr Huckle listed several potential reasons for the divergence in approvals between the FDA and EMEA. One reason could be differences in the agency's acceptance of specific types of studies (eg, non-inferiority studies, number of pivotal studies, placebo vs comparator studies, comparator choice). The impact of the regulatory process could also affect outcomes. In the EU, there is a fixed time point for review versus in the US, where there is a procedure allowing multiple review cycles and extended review times. Another difference is the committee approach in the EU, where consensus positions are sought, versus the approach in the US, where the FDA provides division-based decision.

The analysis suggests different success rates across divisions and therapeutic classes. Some therapeutic areas may be given a higher priority or focus in some jurisdictions. For example, data from the EMEA suggest that therapies such as anti-infective agents are more likely to obtain approval than respiratory or hormone therapies.

Differences in scope of the final label may exist between regions. The content of the label is based on more than a simple review and approval decision; rather, the label must reflect regional uses of the therapy and reflect the agency's assessment of BR (for example, a new product may be approved for second- or third-line treatment versus a broad-label claim).

A product that relies on a novel mechanism of action for the treatment of a life-threatening disease may see speedier approval time. From EMEA data, companies that had developed orphan drugs sought scientific advice frequently, but nevertheless, less than 50% of the orphan drugs applications were approved in 2007.

Exposing the regulators to details of the development program during

scientific advice or special protocol assessment might positively affect review outcomes. From a recent performance report from EMEA, of those applicants who received scientific advice and followed it, only 7% had objections, whilst amongst those who asked for scientific advice but did not follow it, 59% resulted in major objections.

Sponsors may fail to address important regional or national differences in regulatory requirements. Sponsors need to be aware of changing standards and expectations; for example, regional requirements describing the proportion of local subjects and/or local studies in a dossier. The outcome may also depend on the size of the sponsor. One report places success rates as follows: 20% for small-, 38% for medium-, and 50% for large-sized companies. Smaller companies may be less successful because of their lack of experience and fewer resources in creating quality dossiers.

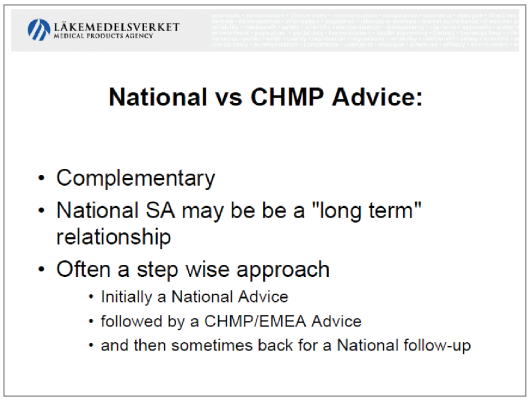
In summary, sponsors should utilise all opportunities to engage in dialogue with the agencies. The sponsor should seek scientific advice and follow it to address agency needs. Sponsors should promote the establishment of regulatory review guidelines; clarity in this area will improve review outcomes. Ideally, a standardised BR approach would result in a more detailed and systematised review process.

Improving Regulatory Outcome

What needs to be done in development

Prof Tomas Salmonson

CHMP (EMEA) Member (Vice Chairman), Medical Products Agency, Sweden



Among the most helpful strategies for predicating the outcome of a regulatory review is seeking and following scientific advice. In Europe, there are two ways to obtain scientific advice (SA) in Europe: either through CHMP/EMEA or through the national agencies. The advice provided through these routes is complementary. National SA may be considered as the basis for a long-term agency relationship. Often, sponsors follow a step-wise approach with the national advice being sought initially, then CHMP/EMEA advice, and then sometimes back to national for follow-up.

Key features of the advice are that it is typically in the form of an oral, informal discussion. If there is further clarification needed after the meeting, it is handled via e-mail or telephone. While no formal minutes are prepared, the sponsors' minutes may be reviewed by the agency.

Prof Salmonson offered some advice when interacting with the Swedish Medical Products Agency (MPA): be sure to include an adequate level of detail in the briefing materials; identify questions and provide the sponsor's viewpoint; make the questions specific and avoid asking generalities such as "Is this documentation sufficient for approval?" Expect that the briefing materials have been read before the meeting.

The meeting is not the time to convince regulators that this is an approvable drug. Rather, successful meetings begin with a short, concise presentation, serve as a forum for a dialogue with the assessors, and focus on identifying potential problems. Sponsors should therefore, strongly consider the advice and, if needed, schedule a return meeting. Sponsors should have a united front in their presentation; the clinical leader and regulatory affairs representatives should have the same focus.

Utilisation of feedback loops and dialogue as a way of improving the quality of development and review process

Outcome of a pilot study to evaluate a scorecard approach where companies and agencies rate the submission and review

Andrea Mallia-Milanes

Research Fellow, CMR International Institute for Regulatory Science

Ms Mallia-Milanes presented an overview of a pilot study, which was carried out in April 2008, to test the usefulness of scorecards in assessing the quality of dossier submissions and the review of those applications. The pilot study was a development from the feasibility project that was carried out in 2006.

The pilot study was carried out retrospectively and had several objectives: to learn more about the potential outcomes of a larger study; to test the updated scorecards in terms of appropriateness and content validity; to identify potential problems that may occur using this proposed method; and to utilise the information obtained from the study in order to design an appropriate prospective study. Three agencies and seven companies participated in the study. The sample used in the pilot study was made up of eight products. These products were submitted to the three authorities for review between 2004 and 2007. Companies were asked to rate the agency's review process and agencies were asked to give scores on the quality of the dossier and the interactions with the sponsor.

Results of the scorecards completed by the companies on the quality of the regulatory review

For the majority of the reviews, the companies rated positively the agencies' consistency and their adherence to their own guidelines. It was also indicated that there were no deviations or unexpected steps. The companies were less satisfied when approval requirements were more stringent and when there were differing views between staff of the agency.

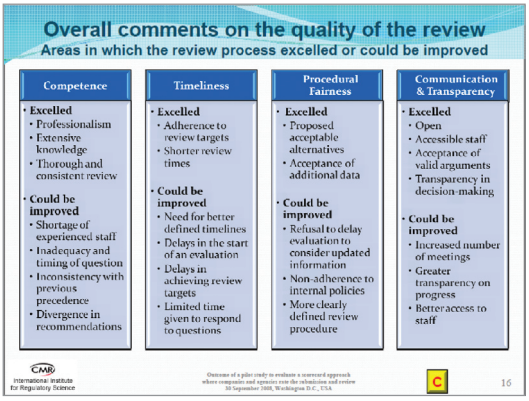
With regard to the agencies' professional and scientific knowledge, companies felt that for the majority of the applications, the agencies had the required knowledge and experience in the therapeutic area of the reviewed product. In most cases, the questions asked by the agency were also relevant and clear, and companies were satisfied with the timeframes given to respond to the questions raised. Positive ratings were given when deadlines were reasonable and when there was a certain amount of flexibility. Slightly lower ratings were given for the relevance of questions, for example, when the agency's overview contained inaccurate conclusions and when there were differing views between agency staff.

In addition, the scorecard also had a number of closed questions on the appropriateness of the questions asked. For most of the applications, the companies felt that the questions asked by the agencies were appropriate and were not based on misinterpretation of the dossier. Moreover, in many cases the questions were well communicated and no meeting was required.

Another area through which the companies were asked to assess the

quality of the review process was through the assessment of the product information (SPC, PL and labelling). The companies felt that this part of the review process was fair, consistent and driven by science and that the product information reflected the data that were submitted. However, the results also showed a certain amount of concern from the companies in terms of transparency and openness of the decision-making process. Less positive ratings were given when dialogue and the access to reviewers were limited, when no detailed assessment report was given and when text amendments were imposed without clear rationale.

The agencies actively pursued communication with the companies. Positive ratings were given when applicants were kept informed on the progress of reviews, when communication was clear and timely, as well as when all forms of communication were used. More attention, however, could be given to make agencies' staff more accessible and to increase the level of transparency. Lower ratings were given when communication was limited and no information was provided on status of the product evaluation.



Results of the scorecards completed by the agencies on the quality of the dossier application

The three agencies gave similar high scores on the application format, presentation, clarity of language used and completeness of the data sets of the applications. There were very few "satisfactory" scores and no "poor" ratings. Lower ratings were given when studies were not described clearly or navigation was poor and links were insufficient to move easily through the application.

Ratings showed that the quality of the dossier applications was within expected standards. Overall, the application summaries were considered detailed, factual and complete and provided a concise discussion and interpretation of findings. Lower ratings were given when the extent to which summaries were linked to other parts of the dossier was poor, and when major issues were inadequately addressed.

All the agencies considered the companies to have the required knowledge and experience (scientific competence) in the therapeutic area of the reviewed product. High ratings were given, with the competency of the majority of companies considered to be "good."

With respect to the quality of the submitted SPC, PL and labelling, the ratings were mostly "good" or "satisfactory." The agencies indicated that certain amendments needed to be made to bring the submissions in line. For example, amendments were needed to bring the PL in line with the SPC.

Another way of measuring the quality of a submission is by assessing the completeness and quality of the prescribing information. Mixed results were reported by the agencies.

Positive ratings were given for the companies' accessibility and professionalism. Lower ratings were given for the companies' level of transparency and their level of communication during pre-submission meetings. For a considerable number of applications, no pre-submission meetings were held. Agencies commented positively when the company contact was readily available to discuss the submission and to address any agency concerns.

For the agencies' overall assessment of the dossiers, there were no

"excellent" ratings. A mix of "good" and "satisfactory" ratings were given for each part of the dossier.

Overall, participation in the pilot programme was very encouraging and interest in this initiative has been high. The participants responded positively to the study and without reserve to requests for ratings. The results showed that significant cross-comparisons can be generated through the standard scorecards.

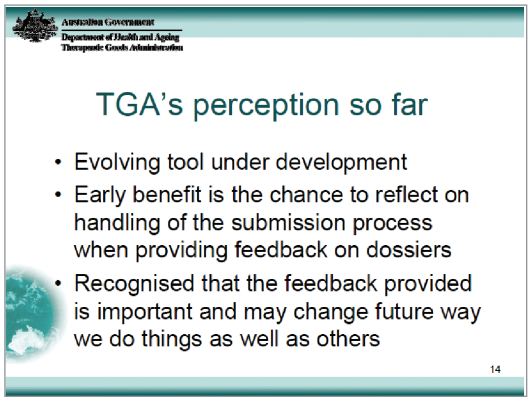
It is planned that a prospective study using a slightly modified scorecard will be undertaken during 2009. Member companies of the Institute will be invited to participate. The number of agencies could also be expanded to include the FDA, EMEA and key agencies from the emerging markets.

Improving the quality of development and review

An agency perspective

Dr Leonie Hunt

Director, Assistant Secretary Office of Prescription Medicines, Therapeutic Goods Administration, Australia



Dr Leonie Hunt discussed regulation, review practices, and the TGA perspective of their participation in the CMR Scorecard pilot project.

Regulation

The purpose of regulation is to ensure that medicines meet standards of quality, safety, and efficacy. However, these medicines need to be made available in a timely manner. Therefore, regulation and regulatory practices are not intended to be barriers to the availability of medicines that are of good quality, safe, and efficacious, but to facilitate such access whilst preventing access to products that do not meet established criteria.

To measure the effectiveness of regulation, emphasis has often been on performance measures based on time taken to approve products, the numbers of products approved, or numbers of recalled or withdrawn products. However, these measures describe only part of the scenario. There are other parameters that although not easy to quantify, play an important role in the decision to approve or keep a product on the market:

- What is the quality of the information underlying a regulatory decision?
- Did the review process help or hinder a correct decision being made in a timely manner?
- What could have been done better during the review process?

Review Practice

Agencies want and need good review practices (GRPs) as part of their decision-making processes: transparency, consistency, integrity, scientific validity, and clinical relevance form important elements of these practices. Of importance to agencies is whether their review systems are working or whether they need to be improved. To ensure effective GRPs, agencies can compare themselves with benchmarks from other agencies, develop peer

review processes within and external to the agency, implement quality management systems (QMS), and develop specific feedback mechanisms. A difficulty is that no one measure reveals if all of the GRP objectives are being met, since both qualitative and quantitative measures are required.

In the same way that no agency works in isolation, no company works in isolation. Each needs to do their best to interact and provide a professional deliverable, be it the dossier or the review process. Each will have different but important insights that can be shared through direct dialogue. It is an important tool, but direct dialogue is more likely to address a major or isolated aberrant issue than to result in improving an overall process. Therefore, a more comprehensive tool is needed to convey the various dimensions required for a complete open dialog about the strengths and weaknesses of a dossier and its review.

Scorecard Project

TGA has participated in both the first pilot and the most recent Scorecard Project. This project has the potential to facilitate qualitative feedback amongst agencies and companies so that systems on both sides can be optimised.

TGA perceived the scorecard to be an evolving tool under development. One early benefit from participating in this project was the chance to reflect on the submission process when providing feedback on dossiers. TGA recognised that the feedback provided was important and may change the ways the agency approaches specific tasks during the review stage.

The Scorecard Project requires that an agency be willing to be open and transparent in giving feedback, be willing to listen to feedback on the agency, and be prepared to act to change what is not working.

In a finalised scorecard system, TGA would like a greater number of products involved, which would help identify performance patterns. The TGA would participate in an electronic data collection tool, which would encourage use among the reviewers.

Utilisation of feedback loops and dialogue as a way of improving the quality of the development and review process

An industry perspective

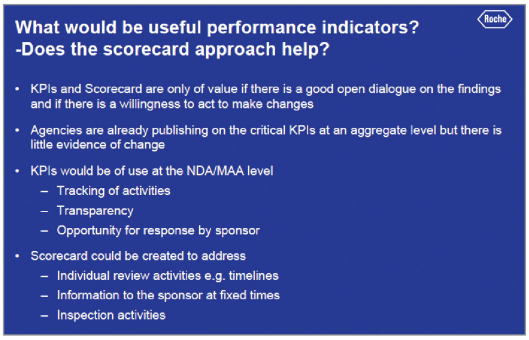
Michael Doherty

Global Head of Pharma Regulatory Affairs, F-Hoffmann-La Roche Ltd, Switzerland

Mr Doherty outlined how predictability plays a role in the R&D and review processes.

Scientific predictability

Sponsors must understand the current medical and review environment to fully characterise a product's BR profile. To this end, sponsors must demonstrate a willingness to establish early on the most appropriate population for the product, be able to communicate safety issues to



stakeholders, and if possible, drive the biomarker strategy (ie, as response predictors, to identify patient exclusion factors, as diagnostics). Similarly, agencies must collaborate with sponsors on ways to streamline and make the development and review process more predictable; this might centre on agreeing on novel study protocols that use adaptive design. Also, agencies should be flexible on the acceptance of clinically relevant endpoints (eg, non-inferiority progression-free survival [PFS] for replacement strategy in oncology, prevention of onset of diabetes through weight loss, patient-reported outcomes [PROs] in neuropsychiatry). Overall, the sponsor must understand the risks involved in their clinical development program and regulatory strategy and be willing to dialogue with the agencies on the key issues to limit misinterpretations or unexpected outcomes.

As an example, Mr Doherty described how PROs and other clinical outcomes that measure functioning in patients with neuropsychiatric illnesses represent valuable clinical insights for prescribers. While these measurements are used to provide evidence for the regulatory review and to justify reimbursement for the medicine, these data are rarely reflected in the prescribing information and are often used in different ways depending on the country or agency. For example, the Progressive Deterioration Scale (PDS), a measure of activities of daily living in Alzheimer's disease, is often described in the EU label, but not in the US. However, Personal and Social Performance (PSP), a measure of functioning in schizophrenia, is used in both EU and US package inserts (PIs). As a way to increase predictability, a collaboration of scientists from academia, industry, and agencies has been set up to determine which PROs can be used as validated endpoints across regulatory jurisdictions.

Acceptance of a clinical benefit for an oncology product differs between agencies. In the EU and countries such as Switzerland and Australia, PFS prolongation in certain disease settings (eg, first-line treatment of metastatic breast cancer [mBC], gastric cancer) supported by data showing a lack of detrimental effect on overall survival and quality of life, is generally considered clinically relevant, and is accepted as the basis for approval. In Canada and countries such as Chinese Taipei, demonstration of an overall survival advantage across disease settings (including first-line mBC) is expected for approval.

In December 2007, the Oncologic Drugs Advisory Committee (ODAC) discussed whether PFS can be considered a direct measure of clinical benefit; whilst many ODAC members supported this concept, it was not put to a vote to reach a formal consensus. Sponsors continue to be told by the FDA that PFS-advantage alone will not suffice for full approval. Providing a consistent approach to an endpoint analysis such as this can greatly contribute to the transparency of dossier review and the predictability of the review outcome.

Value of regulatory advice

Regulatory advice in the form of scientific or technical advice, is influenced by the differing perspectives between agencies or rapporteurs. Personal scientific agendas can influence advisory or scientific advisory groups (SAG). A lack of transparency of the advice and review process results in unexpected deficiency letters at a late stage, action dates that pass without completion of the review, and project managers often not being able to give sound consistent advice to sponsors.

Future state

Therefore, it has become crucial to identify:

- How do we improve dialogue in order to increase predictability of development and review outcomes?
- What would be useful performance indicators to assess the review process?
- Does the Institute's scorecard approach help?

The lack of predictability is a function of a variety of confounding factors, including the different approaches to dossier assessment taken by each authority, the timing and quality of interactions with sponsor, the agency's interpretation of the validity of key endpoints, and the overall communication flow between the agency and the sponsor.

To address these issues, several actions could be taken. Regarding different position of different authorities, providing parallel scientific advice and establishing early on overall acceptance criteria that can be built into a global development and statistical plan would be useful. Post-submission meetings and an obligation to provide the sponsor with monthly updates (eg, feedback on a regular basis) would help in maintaining transparent interactions with the sponsor. For interpretation of validity of endpoints, increased regulatory, industry and academic collaboration on the underlying science, and the creation of guidelines for the use of endpoints and biomarkers will be critical for success. Agencies should create a regular communications plan or internet-based tracking process for each submission; then sponsors could provide data in real time if identified as missing.

Scorecards and KPIs

The assessment of Key Performance Indicators (KPIs) and the use of scorecards are of value only if there is an open dialogue on the findings and if there is a willingness to act to make changes. Agencies are already sharing information on their critical KPIs at an aggregate level, but there is little evidence of wholesale change based on these preliminary findings.. Perhaps the best use of a scorecard could be for exchange of performance data between sponsor and authority on a specific filing. This would create a good two-way feedback mechanism which would not involve any confidentiality issues.