EXPEDITING PATIENTS' ACCESS TO MEDICINES:

SOLUTIONS TO SIMULTANEOUS SUBMISSIONS AND APPROVALS

WORKSHOP
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WORKSHOP REPORT

CMR International
INSTITUTE FOR REGULATORY SCIENCE

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EXPEDITING PATIENTS' ACCESS TO MEDICINES: Solutions to Simultaneous Submissions and Approvals

Section 1: Overview and Executive Summary

Background to the Workshop

Major companies engaging in global development programmes are currently trying to reduce the development time in worldwide markets. Ideally, companies are looking for a global development programme that will lead them to simultaneous submissions and approvals. However this is juxtaposed by a perception of approval delays, rising requests for further clinical data, and greater chances of divergent outcomes.

It is hoped that the utilisation of new technologies that have the potential to better define patient populations and the efficacy and safety parameters for new medicines will enable a more predictable regulatory approval process and outcome. Companies and agencies are seeking ways to improve the efficiency and quality of clinical research, including innovative trial designs, use of new technologies/ biomarkers and pharmacogenomics. This Workshop explored how these initiatives are progressing and discovered if they will enable companies to achieve global simultaneous submissions and approval to ultimately expedite patients' access to new medicines.

Workshop Highlights

The first session of the Workshop, *Global Development and Simultaneous Submission: What Is the Reality?* was chaired by **Professor Hans-Georg Eichler**, *Senior Medical Officer, EMEA.*

Professor Eichler introduced the session by describing the current climate in the pharmaceutical industry as the perfect storm. Regulatory authorities must balance ever-increasing pressures for expedited access to medicines and the need for incentives for innovation against requirements for comprehensive safety assessments and cost-effectiveness data, all within shortened regulatory review times. At the same time, increased industry research and development is resulting in reduced productivity. The most feasible method for increasing the overall productivity of the pharmaceutical development and review process, Professor Eichler explained, is the reduction of regulatory heterogeneity, which was the focus of the current Workshop.

Dr Franz Pichler, *Portfolio Manager, CMR International Institute for Regulatory Science* detailed the results of the Institute's research showing the interrelation and statistical trends for global regulatory review timing and submission strategies and their effect on simultaneous approval. This research compiled publicly available data for 731 new active substances approved between 1997 and 2008 by EMEA, FDA, PMDA, Health Canada, Swissmedic, and TGA.

Using the framework of a pilot parallel review project between Health Canada and TGA, **Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada*, discussed the advantages, disadvantages and issues for consideration for simultaneous and sequential filing and Health Canada's plans for next steps in the examination of parallel regulatory review.

Robin Evers, *Vice President, Head of Global Regulatory Affairs, Europe, Middle East & Africa, Wyeth Europa* provided a commentary that progressed from the challenges of initiating global clinical trials to the growing importance of post-approval requirements. Mr Evers also discussed the positive example of the recent global approval of methylnaltrexone bromide for opioid-induced constipation, showing that multiple multinational requirements can be met with global solutions, resulting in remarkable labelling consistency.

Dr Paul Huckle, *Senior Vice-President Global Regulatory Affairs, GlaxoSmithKline*, presented an updated summary of instances of regulatory review divergence between the US and Europe from January 1995 until March 2009 and suggested some reasons for and solutions to these divergences. Among the potential solutions, the early and frequent engagement in dialogue with regulatory authorities has been consistently shown to be one of the most important factors in consistent approvals across agencies.

A Case Study of Tedisamil: An Industry Viewpoint placed a spotlight on a recent instance of divergent opinions between agencies in Europe and the US. **Tracy Baskerville**, *Head, Global Regulatory Affairs, Liaison, Cardio-Metabolic, Solvay Pharmaceuticals* described the medicine's extensive development plan, place in the

therapeutic continuum, points of regulatory concern and lessons learned and questions raised in risk management in light of a divergent regulatory decision.

In a regulatory counterpoint presentation, **Dr Murray Lumpkin**, *Deputy Commissioner, International Programs, FDA* provided data for medicines with recent concurrent review in the EU and US to show that the incidence of divergence in opinion and approval is not as common as may be generally perceived. He also proposed that receiving a single approval (or rejection) to a simultaneous global application for a new medicine may not be in the best interest of all stakeholders.

Syndicate Discussions and Recommendations

Two Syndicate groups were charged with deriving recommendations from the discussion of assigned topics. The first topic was *what are the potential barriers and solutions to simultaneous submission and approval?*

Syndicate 1 chose to define simultaneous submission by the content rather than by the timeframe of the submission and arrived at the following definition: *A simultaneous submission is one in which the data set submitted has not changed nor has there been time for new data to be generated.*

Recommendations from Topic 1

- Seek/Engage in scientific advice as much/as frequently as possible, potentially in parallel, with open discussions regarding plans for a simultaneous submission.
- Formalise a standardised benefit-risk assessment methodology (ie, framework and appropriate models) in ICH Regions.
- Commission work to identify true intrinsic and extrinsic differences in clinical data (ie, science versus cultural based).
- Seek out creative means to enable data sharing and communication through IT solutions.

The second topic was *reasons for divergent opinions based on same data, same timeframe and same dossier and how to mitigate the risk.*

Syndicate 2 noted that in addition to the most obvious and extreme divergence of regulatory approval and non-approval, other examples of disparity included receiving a broad versus a narrow indication, the types and numbers of claims in labelling and the information required before versus after approval (post-marketing commitments). There may also be divergences in process such as the requirement for risk management plans, the types of risk-minimisation tools required and the amount of necessary safety and other information required in labelling. To avoid divergence in these regulatory outcomes, Syndicate 2 also included the development of a benefit-risk framework in its recommendations.

Recommendations from Topic 2

- Survey regulatory authorities and industry on their experience with pros and cons of different methods of obtaining regulatory guidance from more than one regulatory authority. Identify best practices.
- Establish agreed frameworks for benefit-risk assessments.
- Develop a Global Tool Box for risk management plans.
- Evaluate the impact of local requirements on approval.

The final session of the Workshop, *Solutions to Enable Simultaneous Submission, Approval and Outcomes and the Role of Innovative Clinical Development* was chaired by **Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*.

The use of new technologies, new clinical trial designs and simulation and modelling were some of the strategies put forward by **Damian O'Connell**, *Executive Director, Clinical Group Head, Pfizer Clinical R&D* to improve success rates for clinical trials and ultimately to expedite patient access to needed medicines.

Alison Lawton, *Senior VP, Global Market Access, Genzyme Corporation* discussed a case study of biomarker-based patient identification and its effect on labelling, concluding with a comprehensive representation of the current influence of this technology on the development of medicines.

Eric Abadie, *Chair, CHMP, EMEA*, provided the European regulators' perspective on the issues and challenges presented by the use of new technology, including issues surrounding post-hoc analysis of incomplete data sets and the authoritative validation of testing methods.

A positive outlook for the regulatory environment was stressed by **Dr Leonie Hunt**, *Head, Office of Prescription Medicines, TGA,* in her outline of the issues surrounding the use of new technologies, including the gains made, challenges faced and way forward for all stakeholders.

Professor Trevor Jones, *Member of the Scientific Committee, Innovative Medicines Initiative (IMI)* provided the background for the development of the IMI, the largest public-private partnership in medicine. The IMI seeks to promote medical innovation in Europe and eliminate bottlenecks in the R&D process through innovative research projects.

In the final presentation, **Dr Alberto Grignolo**, *Corporate Vice President, Global Strategy and Services, PAREXEL Consulting, Member, CTTI Executive Committee*, detailed the work of a US public-private partnership, the Clinical Trials Transformation Initiative (CTTI), in which the FDA Office of Critical Path Programs and Duke University joined together with other healthcare stakeholders to identify practices that through broad adoption will increase the efficiency and quality of clinical trials.

Section 2: Syndicate Discussions

Workshop participants formed two syndicate groups to discuss the following topics:

Topic 1: Potential barriers and solutions to simultaneous submission and approval by Western and Japanese agencies

Topic 2: Reasons for divergent opinions based on same data, same timeframe and same dossier and methods to mitigate the risk of divergence

The Chairpersons and Rapporteurs for the two groups follow:

Syndicate 1	Chair:	**Prof Sir Alasdair Breckenridge**, *Chairman, MHRA, UK*
	Rapporteur:	**Dr Kathryn Broderick**, *Associate Director, Eli Lilly and Company, USA*
Syndicate 2	Chair:	**Prof Tomas Salmonson**, *Vice Chair, CHMP, EMEA*
	Rapporteur:	**Dr Victor Raczkowski**, *Vice President, US Regulatory Affairs, Solvay Pharmaceuticals Inc, USA*

Syndicate 1

Background

The objective for Syndicate 1 was to consider topic 1 and identify the potential barriers and solutions to simultaneous submissions to and approval by western and Japanese agencies. The key question for consideration was *what are the critical success factors, key information sets and decisions needed to enable a company to develop a new medicine globally and to undertake simultaneous submission?*

It was recognised that barriers that impede a company's ability to submit their dossier simultaneously to the major agencies may differ depending on the agencies to which dossiers are being submitted, but as a start, the group was asked to consider submission to USA, EU, Japan, Canada, Australia and Switzerland. It was further suggested that to contextualise the discussion for this Syndicate discussion, the group agree on a definition of simultaneous submission. This could be based on a time frame or be descriptive.

The following barriers were provided as beginning points for discussion:

Barriers for simultaneous submission

- Lack of harmonisation of technical requirements
- Differing expectations by agencies in terms of data, study designs, analysis undertaken and regulatory endpoints
- Difficulty in using global data to develop a single dossier
- Company strategy
- Submission logistics and internal company resources
- Lack of suitability of the strategy for all compounds

Barriers for simultaneous approval

- Differing processes and systems in place in agencies
- Managing the questions raised and interactions between agencies during simultaneous review

Outcome of Discussions

Syndicate 1 chose to define simultaneous submission by the content of the submission rather than by its timeframe and arrived at the following definition: *A simultaneous submission is one in which the data set submitted has not changed nor has there been time for new data to be generated.*

Before considering barriers and solutions, the Syndicate agreed that for each new medicine being developed, the Sponsor must answer the fundamental question of whether a simultaneous submission is a suitable goal, that is, is it the right process for a particular submission? Indeed, for some medicines, simultaneous submission may be unrealistic, but for those medicines for which it is thought to be a desirable and achievable goal, the following barriers were identified.

Barriers for Sponsors

- The company structure and decision-making framework may not be coordinated

well enough to allow for simultaneous submissions.

- Because of different clinical practices or regulatory guidelines, a global data set may not serve for all the target countries.
- Owing to the multiple rounds of review that are often necessary, companies may be unwilling to wait for the amount of time necessary to achieve global alignment of advice from all Agencies of interest.
- There may not be sufficient funds, or the opportunity may not be deemed as having sufficient capacity for return on investment to underwrite the cost of the development program to achieve simultaneous submission.
- Because review and queries from Sponsors for a new medicine should be handled by the same core group of regulatory Agency personnel, the capacity of internal expert resources to handle queries from multiple Sponsors could present a significant barrier.
- Although a basic requirement, the time required for translations may be an impediment.
- There are often regional differences that impact other modules of the Common Technical Document (CTD) than module 1, which is designed to accommodate regional differences.

Barriers for Regulatory Agencies

- Differences in the availability and use of technology, such as that necessary for electronic CTD submission or secure channels for electronic communication can impede simultaneous submissions.
- Other issues of communication challenge include extreme time zone differences and language barriers.
- Review management processes, procedures and schedules differ across agencies.
- Lack of clarity on population definition can have a negative impact on simultaneous submissions; that is, are differences between acceptable populations intrinsic to the results of genetic heterogeneity or do they represent extrinsic factors such as regional medical practice, product use, or clinical trial ethics, recruitment, conduct and data analysis?
- Differences exist in the acceptability of surrogate endpoints or biomarkers across global agencies.

Potential Solutions

- One of biggest advantages available to Sponsors and Agencies is their ability to seek or to provide scientific advice as early and as frequently as possible, potentially in parallel, with stated intent for a simultaneous submission.
- Sponsors aiming for simultaneous submission will have to factor in the potentially extended timing necessary for global scientific alignment.
- Although the objective of global submission with one data package is often implied, there is value to the Sponsor in being completely transparent in their intentions to regulatory agencies early in development.
- In cases of lack of clarity or potential for multiple interpretations in scientific advice, Sponsors must seek follow-up.
- Both Sponsors and Agencies will benefit from a standardised benefit-risk assessment methodology that relies on a transparent framework and appropriate models.
- Agencies and companies must agree on the true intrinsic and extrinsic differences of the treatment populations.
- Agencies should enhance opportunities for data sharing and communication through IT advancement whenever possible.

Recommendations

1. Determine each medicine's suitability as a candidate for simultaneous submission.
2. Use processes already in place to gain clarity: seek and engage in scientific advice as frequently as possible, potentially in parallel, with open discussions regarding plans for a simultaneous submission.
3. Continue ongoing work to formalise a standardised benefit-risk methodology.
4. Commission work to identify true intrinsic and extrinsic population differences.
5. Seek out creative means to enable data sharing and communication through information technology solutions.

Finally, two important questions associated with simultaneous submission arose during the Syndicate session, and were addressed during the general Workshop discussion: Whose interest is being served? and What is the role of Health Technology Assessment?

General Workshop Discussion

Whose interest is being served?

- We need to question whether simultaneous submission is for the ultimate good of the patient. It may be that it is not a universally applicable process.
- Patients' timely access to medicines underlies all this discussion, and there are parts of the world where medicines are not available until approvals have occurred in primary markets. However, there are examples of medicines for which simultaneous submissions for expedited availability would not necessarily be appropriate; for example, so-called lifestyle drugs.
- National or regional guideline differences can also impact a medicine's potential for simultaneous submission. Guidelines provide for example, for both osteoporosis prevention and treatment in the United States, but only treatment in Europe. In oncology, overall survival data are required for approval in Japan but not in Europe. In contrast, homogeneous guidelines for type 1 or 2 diabetes medicines make them fit for simultaneous submission.

What is the role of HTAs?

HTA requirements

- Enforcement of risk management plans for some EU member states has been complicated by seeming insurmountable difficulties in enrolling the required number of patients not just for regulatory purposes, but for HTA agency determinations as well. That is, HTA bodies can issue requirements for clinical testing of a number of patients beyond that which would be expected to address a clinical trial endpoint.
- Significant variances in HTA requirements across national boundaries often centre on needs for comparators for cost-effectiveness models. The payors are interested in value questions: what is going to be replaced on the market, will it be frequently used and will it drive up the cost of healthcare? Direct, head-to-head comparisons reflective of regional standards of care and medical practice are frequently required and defy harmonisation efforts. These requirements underscore the need for early regulatory advice as to specific regional requirements for both regulators and HTAs.

Evolving pricing model

- It was remarked that a model is desirable in which product pricing is linked to evolving therapeutic expectations as opposed to trying to develop a health economics model to support a price that's set after the clinical development process. In this latter instance it is highly probable that economists will develop a sensitivity model that will arrive at results different from those intended. A pharmacoeconomic model grounded in the changes in expectations for a molecule that occur during development is bound to be far less controversial.
- The large number of national or regional variables such as the costs of physicians and ancillary healthcare, supplies, transport and general standard of care also factor in cost equations. The way forward is to better define the rules around the common analyses.

Information technology

- The difficulty of developing information technology that is compatible amongst agencies and companies should not be underestimated. Parallel review with its attendant need for constant ongoing dialogue is complicated by the need for internal firewalls and other security measures for agencies and companies. Extreme differences in time zones represent another communications hurdle. Discussions of these issues are now taking place among regulatory agencies in Singapore, Canada, Switzerland and Australia.

Syndicate 2

Background

- The objectives for Syndicate 2 were to identify why divergent regulatory review outcomes occur and to recommend ways companies can mitigate the risk of obtaining these outcomes. Several slides from Dr Huckle's presentation at the Workshop were used as the basis to propose reasons for divergent outcomes for discussion. These reasons included:
- Clinical development programme: design and types of clinical trial
  - Number of pivotal trials, applicability of foreign data or endpoints
  - Failure to address regional or national differences

- Type of regulatory review process, procedures and decision-making
  - Timelines and timing of the decision
  - Extent of review: bottom up versus top down
  - Agency focus or areas of specific interest to particular agencies
  - Decision making (EU approach by committee versus FDA divisional decision)
  - Benefit-risk approach/framework
- Pre-review discussions with regulatory agencies
- Lack of sharing of development plans to the agency during execution or use by companies of scientific advice from agencies
- Other factors
  - Cultural and regional variations in medical practice
  - Recent experience of the Agency in the therapy area
  - Ability of the Agency to impose and monitor post-approval conditions

Outcome of Discussions

Several assumptions were built into this Syndicate discussion. First, a *simultaneous submission* was defined as one in which the applicant submits the same data, in the same timeframe, to different regulatory authorities. It was also assumed that the applicant seeks a similar outcome (approval) from each of the regulatory authorities: at about the same time, for the same indication(s), with the same claim(s), labelling and post-marketing requirements and with reimbursement decisions that are predictable, reasonable, timely, and which have been made efficiently.

In consideration of possibilities for regulatory divergence, the most obvious and extreme is that between approval and non-approval. Other examples of disparity exist, however, including receiving a broad versus a narrow indication, the types and numbers of claims in labelling and the information required before versus after approval. There may also be divergences in process such as the requirement for and scope of risk management plans, the types of risk-minimisation tools required, the amount of necessary safety information in labelling such as contraindications, boxed warnings, and their prominence and the types and amounts of other information required in labelling (for example, clinical trial descriptions and nonclinical information).

Reasons for divergence

The myriad of potential causes underlying regulatory divergence include differences in societal values, sophistication of the local healthcare systems, technologic capabilities and living standards and ways in which key decision issues are prioritised and agency resources used. Countries and regions may differ in the stringency of requirements for the design and conduct of clinical and preclinical studies, and different evidentiary standards (ie, placebo-controlled vs active comparator studies; emphasis of primary vs secondary endpoints) will result in disparate interpretation of the results. At the most basic level, laws and regulations for medicines and the ability to monitor and enforce those regulations differ geographically.

The lack of a standard framework for benefit-risk assessment may mean that some reviewers are using quantitative whilst others use qualitative methodology to judge the same therapy. Furthermore, agencies' comfort level with uncertainty in risk or in benefit varies widely.

Recommendations

1. Develop effective and efficient processes by which regulatory authorities will strive to harmonise their views on the adequacy of a sponsor's development plan and provide feedback; not just to obtain timely marketing authorisation for the indication being sought, but also to support a timely and favourable Health Technology Assessment. If harmonisation is not achieved, each Regulatory Authority can provide the essential, major and minor elements of development plan necessary to support approval, providing the sponsor with clarity on requirements and allowing more informed integrated developmental decision-making.

Gathering informative data for Recommendation 1:

- Survey Regulatory Authorities and pharmaceutical companies on their experience and lessons learned regarding the different methods of obtaining regulatory guidance from more than one regulatory authority: through joint, serial, or parallel advice from Regulatory Authorities.

- Evaluate the Joint Scientific Advice process for lessons learned; results should provide a foundation for best practices.

In a discussion of their perceptions of joint advice currently in use, Syndicate 2 identified the following needs:

- Simplification of logistics
- A regulatory process owner
- Faster process
- Commitment from industry and regulatory agencies to make the system workable

2. Establish agreed frameworks for benefit-risk assessments to improve the underlying science supporting benefit-risk decisions; improve both the process by which benefit-risk decision-making is conducted and the reliability, predictability, and quality of benefit-risk decisions; create greater alignment and clearer communication among stakeholders in understanding benefit-risk decisions and in how benefit-risk decisions are made.

Gathering informative data for Recommendation 2: Develop a survey for Regulatory Authorities and for Industry to gather specific data on which factors most influence the ultimate benefit-risk evaluation. Include the following fields to assess multiple dimensions of benefit-risk assessments:

- Evidentiary standards
- Societal values
- Decision-making processes
- Comfort with uncertainty (in risk or in benefit)
- Frameworks for benefit-risk assessment

3. Develop a Global Tool Box for risk management plans. Tools actually selected and used to mitigate risk may be highly dependent on the health system, societal values, and other factors in the region or country of interest.

Gathering informative data for Recommendation 3: Evaluate which tools can be used most effectively in each region/country. Perform a survey among regulators and industry to evaluate best practices for use of tools in different regions/countries.

4. Evaluate the impact of local requirements on regulatory approval. Assess the degree to which, if at all, local requirements such as bridging studies have had an impact on approval in different regions/countries.

Gathering informative data for Recommendation 4: Perform a survey of regulatory authorities and industry to obtain data on impact of specific local requirements, exploring societal values, scientific validity and other factors.

5. Develop and harmonise guidelines for evaluation of new therapies for specific diseases. Differences in diagnosis and treatment or standard of care can have an impact on regulatory decisions. For example, because they do not typically undergo invasive cardiac procedures, patients in Eastern Europe may be considered as a differentiated patient population who have distinguishable results in cardiovascular clinical trials.

   Identifying the specific factors that can support or limit homogeneity from one country or region to another will allow for more rational pharmaceutical development.

General Workshop Discussion

Is parallel advice really wanted?

It was remarked that although the opportunity for simultaneous EU and US advice has been available for some time, few companies have availed themselves of the process. This may reflect a perception of the tendency of agencies, who when required to harmonise, harmonise more stringently rather than less.

One Sponsor reported that it was recently strongly recommended by a regulatory agency that her company not seek parallel advice because of the amount of additional work that it would require and the diminishing returns likely to accrue.

After receiving divergent advice

An open forum in which regulatory agencies could discuss divergent opinions was proposed.

In veterinary medicine, regulators have obviated logistic problems associated with assembling all parties for simultaneous review by using a triangular review process in which industry

presents an application to both agencies, then the agencies meet together separately from the sponsor and report the results.

The consensus among Workshop participants, however, was that this model was not translatable to human medicines. In light of the significant investments as well as the potential for important societal impact, open and frank discussions amongst all parties are required.

Divergent decisions: a proposal

"Clusters" of therapeutic expertise exist within the context of the FDA and EMEA bilateral relationship, with these experts maintaining close interagency contact and awareness. The clusters function as a peer-review and peer-interactive system for the regulators in both agencies in the clusters. These clusters may offer enhanced opportunity for parallel advice to sponsors. Although the clusters presently offer the opportunity for discussions before development decisions are made, a suggestion proposed at the Workshop will be considered for action by both Agencies to structure the interagency consultation that currently exists into a process through which companies receiving divergent opinions on product development issues from the FDA and EMEA could request a tripartite discussion of the decisions.

Soon after this Workshop was convened in March 2009, an article was published detailing the efforts of the Simultaneous Global Development Committee of The Pharmaceutical Research and Manufacturers of America (PhRMA; Saillot JR and Paxton M. *Drug Info J.* 2009;43:3.) This group is working to identify the barriers to global pharmaceutical development and to make specific recommendations to overcome those barriers. Outreach to regulatory authorities has also been initiated, beginning with Agencies in the East Asian region.

WORKSHOP PROGRAMME

Session 1: Global Development and Simultaneous Submission: What is the reality?	
Chairman's welcome and introduction	**Professor Hans-Georg Eichler**, *Senior Medical Officer, EMEA, UK*
Regulatory approval, submission strategies and roll out time to major markets 1997-2007: What do the data tell us about changes over time?	**Dr Franz Pichler**, *Portfolio Manager, CMR International Institute for Regulatory Science, UK*
Advantages and disadvantages to agencies of simultaneous or sequential submissions of a dossier by companies to an agency: An agency viewpoint	**Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada*
Internal and external barriers: What are the barriers which impede simultaneous submission and possible solutions?	**Robin Evers**, *Vice President and Head of Global Regulatory Affairs for Europe, Middle East & Africa, Wyeth Europa, UK*
Divergent regulatory opinions: An update	**Dr Paul Huckle**, *Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA*
Case study of tedisamil: an industry viewpoint	**Tracy Baskerville**, *Head, Global Regulatory Affairs, Liaison, Cardio-Metabolic, Solvay Pharmaceuticals, France*
How to mitigate against divergent outcomes: an FDA Viewpoint **One submission – One answer?**	**Dr Murray Lumpkin**, *Associate Commissioner, International and Special Programs, FDA USA*
Session 2: Solutions to Enable Simultaneous Submission, Approval and Outcomes and the Role of Innovative Clinical Development	
Chairman's welcome and introduction	**Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*
Innovative clinical development: What new science opportunities are there and which areas do companies believe have the most promise?	**Dr Damian O'Connell**, *Executive Director, Clinical Group Head, Pfizer Clinical R&D, UK*
Genomics, Biomarkers and surrogate endpoints: Are these the key to improving regulatory decision-making based on clinical trials? **Industry Perspective** **European Regulatory Perspective** **TGA Viewpoint**	 **Alison Lawton**, *Head of Global Regulatory Affairs, Genzyme Corporation, USA* **Dr Eric Abadie**, *Chair, CHMP, EMEA, UK* **Dr Leonie Hunt**, *Head, Office of Prescription Medicines, TGA, Australia*
Improving efficacy data: update on the IMI initiative **Clinical Trials Transformation Initiative**	**Professor Trevor Jones CBE**, *Member of the Scientific Committee, IMI, UK* **Dr Alberto Grignolo**, *Corporate Vice President, Global Strategy and Services PAREXEL Consulting, USA*

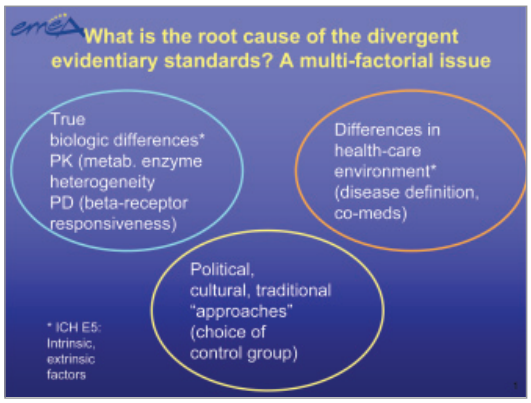
SECTION 3: WORKSHOP PRESENTATIONS

Session 1: Global development and simultaneous submission: What is the reality?

Chairman's introduction

Professor Hans-Georg Eichler

Senior Medical Officer, EMEA, UK



Professor Eichler introduced the session by describing the current climate in the pharmaceutical industry as the "perfect storm." Regulatory authorities must balance ever-increasing pressures for expedited access to medicines and the need for incentives for innovation against requirements for comprehensive safety assessments, all within shortened regulatory review times. At the same time, increased industry research and development time and costs are resulting in reduced productivity as evidenced by the decreasing number of new molecular entities being developed for submission. The most feasible method of increasing productivity and improving registration predictability, Professor Eichler explained, is the reduction of regulatory heterogeneity, which was the focus of the current Workshop.

It is true that regulatory decisions, which are based on both data and the values of the reviewing agency, are often divergent. In deconstructing the divergences, however, it is important to understand whether they are based on real differences in a benefit-risk threshold, which would indicate a failed drug, or on evidentiary standards, which may indicate a failed pharmaceutical development programme.

The reasons for divergent evidentiary standards fall into several categories. The first two, are the well-accepted differences detailed in ICH E5 Guideline: intrinsic differences in population biology, such as beta-receptor responsiveness, and extrinsic differences in healthcare environments such as the infrastructure to deliver quality healthcare. The third cause is what Professor Eichler called differences in cultural or political "approach." He provided an example of two regulatory groups, which despite exhaustive mutual consultation, continued to maintain differing schools of thought as to whether a development programme should employ placebo or active controls. It is these differences in approaches that the industry is challenged to address.

Professor Eichler concluded that although the slow pace of global harmonisation may seem to outstrip the significant strides that have been made, this should be regarded as opportunity for improvement.

Regulatory approval, submission strategies and roll out time to major markets

1997-2008: What do the data tell us about changes over time?

Dr Franz Pichler

Portfolio Manager, CMR International Institute for Regulatory Science, UK

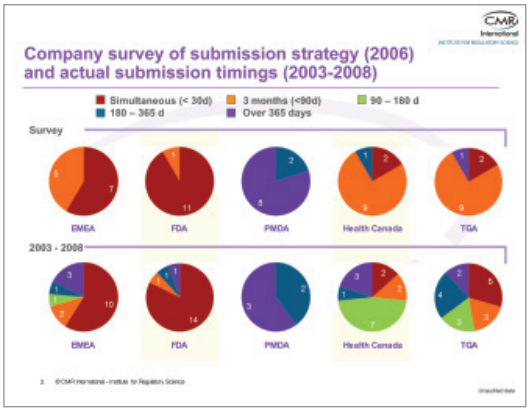
Regulatory Approval Times

In the ideal world, compounds would be submitted simultaneously to different agencies, reviewed within the same, short length of time and approved simultaneously. In the real world, however, there are differences in timing for all three of these parameters.

In the last three years, the number of new active substances (NAS) that were approved has spiked in the EMEA and PMDA. Whilst the PMDA increase may because of improvements in information now available for that agency, the EMEA increases are thought to be accurate and may be reflective of submissions through centralised procedures. FDA and Health Canada both approved fewer medicines in this time period, whereas approval rates for Swissmedic and TGA were variable.

The median NAS approval time by year is trending to 1 to 1.5 years, although considerable difference can be found among agencies. FDA and Health Canada decreased both time to approval and the variability around approval timing. Swissmedic, on the other hand, experienced a slight trend upward in time to approval. Factors that were examined with the potential for causing variability in timing were expedited status, compound type, therapy area, and company size.

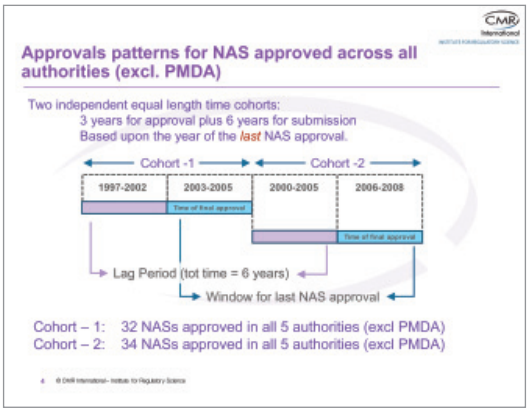
Expedited review: There were substantial differences between agencies in the proportion of expedited to standard approvals in 2003-2008. For example, approximately 50% of approved compounds were subject to expedited review at the FDA, compared with 7% receiving this designation at the EMEA. When examining median approval times by review type, a sizeable difference can be observed between times for compounds granted expedited review and those subject to standard review at the FDA and Swissmedic, whereas some agencies have small overall approval time differences.



Compound type: For most agencies, the rate of approval for chemical versus biotechnology entities is similar but biotechnology product review times were generally found to be shorter than those for chemical entities at the PMDA.

Therapeutic areas: Median approval times for products in the top six therapeutic areas were found to be consistent at the EMEA and TGA, but highly variable at the FDA, PMDA and Swissmedic. At least for the FDA, this variability may be more reflective of the proportion of NAS given expedited status rather than their therapy designation. At the PMDA, anti-infective therapies were approved in a similar time frame as that of other agencies.

Company size: At most of the agencies, the median approval times for compounds submitted by the top 15 companies (as designated by the size of research and development spending) were slightly shorter, which may be reflective of company experience and the resulting quality of dossiers.



In general, review times are getting shorter at the FDA and Health Canada, remaining stable at the EMEA and TGA, slowing at Swissmedic and are variable at PMDA.

Company Submission Strategies

The results of review of data for actual dossier submissions revealed a three-tier strategy, with first submissions to FDA and EMEA followed by a second-tier of submission to Health Canada, SwissMedic and TGA. Within this second tier, compounds with priority designation were generally submitted within 90 days after first submission, and those with standard designation, within 180 days. Although there is a long lag until third-tier submission to PMDA, the gap has recently been reduced from a median of 2.9 to 1.2 years after first submission.

Simultaneous Approvals

Conducting a pairwise comparison of all compounds submitted to agencies within the tiers showed that although the first-tier FDA and EMEA were subject to simultaneous or near simultaneous submission (within less than 90 days) over half the time, simultaneous or near simultaneous approval occurred at a rate of only 13%. Comparisons of tier two submission pairs demonstrated similar results, with simultaneous submission achieved between 19% and 23%.

Summary

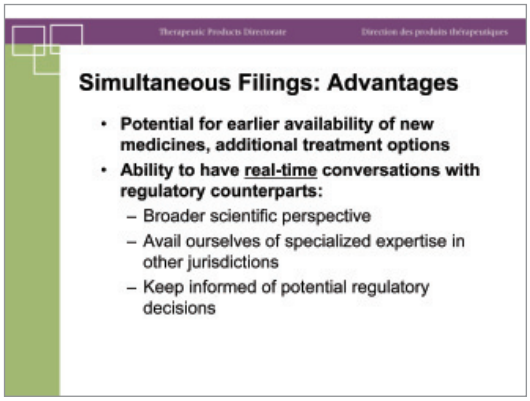
Dr Pichler summarised the research by informing the Workshop that regulatory approval times in general were becoming more consistent and that expedited review status is a primary driver of variability in approval times; that companies typically employed a three-tier global submission strategy; and that while simultaneous approvals are currently possible within tiers, they currently occur at a low rate of frequency.

Simultaneous or sequential filings: an agency perspective

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Health Canada

Using the framework of a pilot parallel review project between Health Canada and TGA, Dr Sharma discussed the advantages, disadvantages, and issues for consideration of simultaneous and sequential filing and informed the Workshop of Health Canada's plans for next steps in this process. Dr Sharma began by commenting that Canada's recent experience as the agency issuing a first-in-world label for two different products underscored the fact that an agency's perspective on simultaneous submission may depend on where that agency fits into a company's overall development programme.



Simultaneous filing advantages

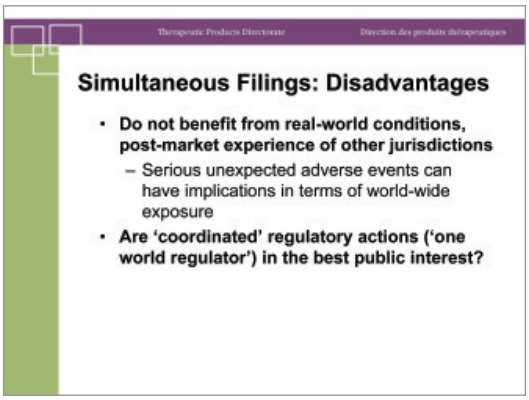
The advantages to the simultaneous filing of product dossiers are obvious from a patient or healthcare provider perspective, that is, there is at least the potential for earlier availability of new medicines and additional treatment options. From the regulators' perspective, simultaneous review brings the ability to have real-time discussions with regulatory counterparts, as opposed to finding time to have discussion when a review may have moved on. It may also result in a broader scientific perspective, the opportunity to make use of specialised expertise in other jurisdictions and a way to keep informed of potential regulatory decisions. This last advantage is particularly important in a world with heightened scrutiny and interconnectivity. Simultaneous filing can also bring the potential benefit of a shared work process.

Experience

As the result of a Biologics and Genetic Therapies Directorate (BGTD) 2003 proposal, a Memorandum of Understanding for a pilot project of parallel review between Health Canada and the Therapeutic Goods Administration (TGA) of Australia was signed in 2004, in which each authority was to carry out a separate but parallel review of a new medicine application according to its own processes and timelines and render its own regulatory decision. It was agreed that there would be shared expertise and information regarding review practices, shared documentation issued and received from the sponsor, and shared review reports. The candidate submission was filed in November of 2007 and each authority was to conduct its own post hoc evaluation of the project. This pilot was regarded as a mechanism for building confidence in another agency through the understanding of that agency's regulatory expertise and processes. Additionally, it was hoped that the project would enhance the working relationship between agencies and identify lessons learned and best practices for future collaboration.

Outcomes

In June 2008, the BGTD issued a negative decision for the application, whilst the TGA rendered a positive decision in July. Upon the review of additional requested information, however, the BGTD did recommend the product for use in February 2009. It was determined that the difference in initial assessment between the authorities was largely the result of different regulatory parameters and philosophies.



Key findings from evaluation

The results of the evaluation of the simultaneous review process, which was conducted by an external consultant, indicated that both agencies found the experience to be valuable. It was determined that there was effective communication between the regulators and sponsor, but inter-agency communication was often complicated because of substantial time zone differences. Differences in regulatory requirements and decision-making processes provided opportunities for inter-agency learning and confidence building. In fact, the most significant project benefit noted was the increased knowledge of regulatory and decision-making processes in the other jurisdiction. It was felt, however, that there was an enhanced burden for the sponsor due to differences in submission requirements between jurisdictions and the need to address simultaneous response times; this was complicated by the lack of a secure portal for the exchange of large pieces of information. The next steps will be to develop a strategic framework to guide future policy development, strategic decision-making, and regulatory priorities.

Simultaneous review disadvantages

Dr Sharma told the Workshop that agencies who engage in simultaneous dossier review may not benefit from real-world data or the post-market experience of other agencies. It must be considered whether coordinated regulatory actions are in the best public interest or whether there are benefits to multiple sequential scientific assessments (and potentially more robust data), and sovereign decisions based on the particular needs of a population.

Considerations for parallel review

Companies and agencies seeking to achieve simultaneous submission and review must determine if regulatory management processes are comparable and consider how to manage region-specific requirements, whether these are intrinsic or value based. Additional questions to be answered include how to manage different regulatory decisions and different sponsor marketing strategies. Establishing platforms for the secure exchange of large amounts of data is critical and a plan for communication across time zones and readiness for electronic applications must be determined. Finally, it should be recognised that parallel reviews are resource-intensive for both the agencies and sponsor and given the pressure to meet domestic timelines, a decision to make short-term investments for potential long-term gains can be difficult.

Considerations for sequential filings

Sequential dossier filings allow regulators to benefit from the collection of real-world data in a primary approval country and the post-market experience of other jurisdictions theoretically may speed subsequent review processes. Agencies can capitalise on scientific expertise available in other jurisdictions and multiple assessments can optimise scientific decisions. There is also the opportunity for use of foreign reviews, provided there is comparability of data packages, documented procedures that guide how foreign reviews will be used within the domestic regulatory framework, and access to unedited reviews and documentation as the source of the information that forms the basis of the review.

Conclusions

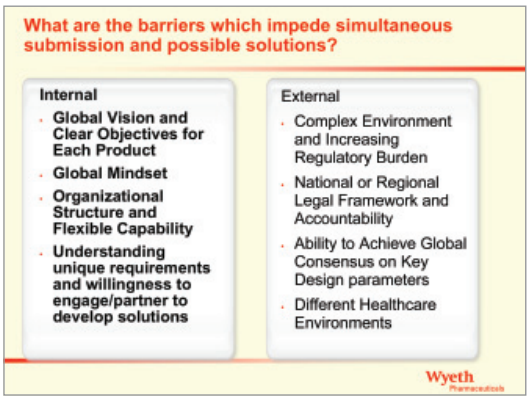
Dr Sharma concluded by remarking that it would be ideal for all regulatory authorities to see full complete data packages as early as possible. Whether that leads to earlier access to medicines, however, remains to be seen. It may be that the heterogeneities in the regulatory system provide the best opportunities for harmonising the review process.

Internal and external barriers

What are the barriers which impede simultaneous submission and possible solutions?

Robin Evers

Vice President, Head of Global Regulatory Affairs, Europe, Middle East & Africa, Wyeth Europa, UK



Interior and exterior barriers

One of the most important internal requirements within a Sponsor's organisation to support a simultaneous submission is a global vision for the product at the outset of its development, complete with clear objectives. Also key are the global mindset and experience of the development team and its ability to leverage the company's framework and capabilities. Finally, it is crucial that companies understand unique issues that may emerge through interactions with regulatory agencies and experts and possess the willingness to engage in the development of solutions to these barriers, including the evolution of the development plan to address those issues.

Increasingly complex regulatory environments are a real and recognised external barrier to global submissions. Other factors include the challenge to develop global consensus on key trial design factors within widely differing environments for the administration of healthcare. Ultimately, clinical trial and product licensing decisions are dependent on the national and regional legal frameworks of each authority.

Key steps requiring global regulatory alignment

Before the initiation of clinical trials, there must be a reconciliation of divergent data requirements from all target agencies as well as agreement to often complex procedures and timelines. Agreement on data requirements for confirmatory studies is required, and can take from several months to 1.5 years to finalise, with a successive cycle of protocol assessments or scientific advice. Finally, global dossier requirements, approval procedures and ancillary document requirements must be established.

Challenges to clinical trial initiation

In considering whether regulatory complexities have impeded the initiation of clinical trials, Mr Evers noted that a shift in the location of global clinical trials has recently taken place, with the percentage taking place in the UK dropping from 6% in 2002 to 2% in 2007. This statistic may reflect the increased burden of harmonised procedures, or a requirement to accrue regional data for necessary sub-studies or parallel trials. However, this movement of trial populations may also be the result of reluctance of academic institutions to participate in early clinical trials and the relative unwillingness of Western Europeans to enrol in trials.

In seeking to establish benchmarks for the initiation of clinical trials, Wyeth has established a list of critical internal success factors, such as the early identification of study sites and detailed knowledge of country requirements; and external factors through which initiation can be complicated, such as the ability to find investigator and agency agreement

on study and data requirements, widely varying implementation and study conduct timelines, and the need for specific local requirements such as repeat analytical testing or differences in regulatory guidelines.

The need for companies to develop internal process efficiencies to expedite pharmaceutical development was highlighted recently when Wyeth evaluated one of its own clinical trial programmes for a phase 3 drug in which 40% of countries submitted clinical trial applications within 60 days of Investigational Medicinal Product Dossier (IMPD) submission, compared with 100% of countries for another phase 3 drug. As one solution to this issue, Wyeth developed the Clinical Trial Application Tool Kit, a web portal to manage information and to ensure the effective supply of information and mobilisation of resources to clinical groups designing protocols, to regional regulatory groups facilitating submissions, to affiliate groups working with local ethics committees and to clinical trials supply groups managing the efforts of all key contributors.

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Guidelines

Differing content and availability of formal agency clinical trial guidelines also have an effect on global medicine development. Acceptance of placebo-controlled studies (or the reliance on active-controlled studies), alignment on primary and secondary endpoints, and an agreement on the statistical analysis plan must be achieved. Additionally, guidelines frequently progress into more advanced versions after a pharmaceutical development programme is initiated, requiring planning updates.

Divergent requirements from emerging markets have also added to regulatory complexity and need to be addressed as part of an overall global development plan. Submissions in Brazil, for example entail a certificate of pharmaceutical product (CPP) from first-wave countries and Russia requires local authorised testing methods to characterise vaccines and biotechnologies.

What about post-approval?

Global lifecycle management of medicines has emerged as a challenge equal in complexity to that of the initial submission and approval, requiring a continued commitment of resources to ensure appropriate product use. Required changes to labelling must meet varied regional requirements: the FDA requires immediate implementation of safety changes despite complex requirements; whilst labelling changes at EMEA can take multiple rounds of review lasting from 30 days to 2 years, and at the PMDA, approval times can take 30 days to 1 year.

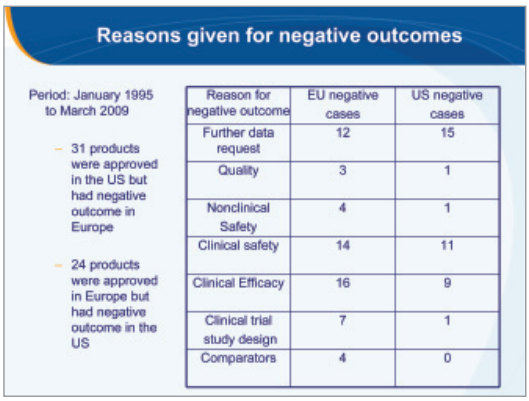
Conclusions

Mr Evers concluded by providing the positive example of the recent global approval of methylnaltrexone bromide for opioid-induced constipation. The key factors in facilitating this medicine's global approval were addressing an unmet medical need, extensive interaction with local agencies prior to submission, and global team(s) working in parallel. This example demonstrates that multinational requirements can be met with global solutions, resulting in a remarkable consistency in labelling and the need for industry and regulators to juggle far fewer priorities.

Divergent regulatory opinions: An update

Dr Paul Huckle

Senior Vice President Global Regulatory Affairs, GlaxoSmithKline, USA



Divergent FDA and EMEA opinions

Popular newspaper headlines from even a short period of time provide many specific examples of divergent regulatory decisions on new medicine applications and show that any news about pharmaceuticals is considered big news. Although the advantage of this wealth of information is that it makes broad patterns in data easy to discern, precise details surrounding medicine approval or rejection decisions may only be available to those with comprehensive knowledge of the submissions.

In the period from January 1995 until March 2009, the EU rejected 31 applications that the US approved, whilst the US rejected 24 applications that the EU approved. Submissions made at significantly different time points were excluded from this analysis, because it was assumed that filings may not have been identical. Opinions that were rendered at significantly different time points were likewise not included.

Failed submissions were defined as those that were rejected by agencies or in some cases withdrawn by sponsors. This category also includes several medicines, which although designated as "approvable" by agencies, still have ongoing, unusually protracted periods of review. Within that same time period, in addition to the obvious divergence of regulatory approval or rejection, a number of products received regulatory approval for differing indications.

The most common reasons given for rejection were deficits in clinical safety or clinical efficacy and the need for further supportive data. Dr Huckle observed that some products were rejected for more than one cause.

Reasons for divergence

The causes for divergent opinions from the EMEA and FDA included differences in opinion regarding the suitability of the development plan, encompassing such issues as the number of required pivotal studies, the use of placebo versus comparator studies, and the acceptability and applicability of "foreign" data as a key component of the submission.

The dissimilar regulatory processes of the two agencies, that is, the fixed timing, committee-based EU approach versus the US multiple-review-cycle, single-decision style may have also influenced the divergent opinions. For example, a higher priority, focus, and higher rates of approval were found in the review of certain therapeutic classes of medicine in the US.

Differences in the scope of a product's labelling often occurred, including approvals for broad versus second- or third-line use, the use by specialist versus generalist prescribers and early disease intervention versus late-stage more clinically informed use.

Other reasons for divergent outcomes highlighted by Dr Huckle were whether products were given orphan drug status versus those intended for broad general use; the agency experience in reviewing the particular therapeutic area; and the ability of the agency to require rigorous post-approval risk mitigation commitments.

Early and regular communication to the agencies of details regarding the product's development programme and the use of scientific advice or special protocol assessment emerged as significant positive factors that facilitated product approval. It was observed that late-stage filing of already completed programmes, as might occur following product acquisition by a sponsor, significantly reduced the chances of engaging the agency in pre-submission dialogue and increased the chance of divergent outcomes.

Synchronicity of filing was examined and simultaneous submission was found to be a contributor to positive and matching US and EU outcomes. Dr Huckle noted that the larger the window from the first to the next submission, the greater the potential impact of changing standards and emerging post-marketing data on the subsequent submission decisions.

Potential solutions

Dr Huckle ended his presentation by suggesting several solutions to mitigate divergent regulatory outcomes. First, the early and frequent engagement in dialogue with regulatory authorities consistently has been shown to be one of the most important factors in minimising divergent approval decisions. In addition, specific agency requirements must be addressed in a robust development program with no gaps or inconsistencies.

These data show that companies should seek priority review or accelerated approval whenever possible, as these typically result in favourable consistent reviews. It is recognised, however, that these results may be based more on the fact that priority status is usually granted to those treatments potentially fulfilling unmet medical needs, and post-approval commitments may be significant for these products.

Because variability in standards and methods of measurements understandably produces variability in results, the establishment of and adherence to regulatory and treatment guidelines and a standardised benefit-risk approach to global clinical development and submission reduces the likelihood of divergent outcomes.

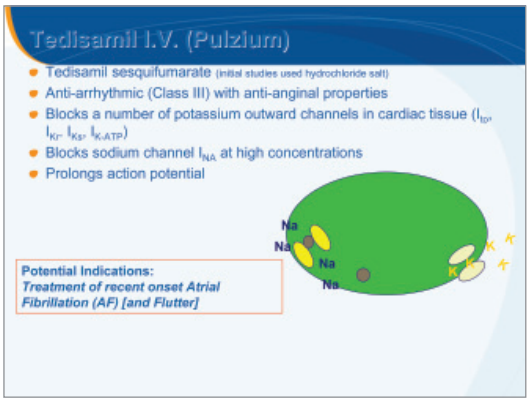
These data show that companies should seek priority review or accelerated approval whenever possible, as these typically result in favourable consistent reviews. It is recognised, however, that these results may be based more on the fact that priority status is usually granted to those treatments potentially fulfilling unmet medical needs, and post-approval commitments may be significant for these products.

Finally, to receive consistent results, the same data package should be submitted to all authorities. Although this last factor may seem obvious, companies sometimes seek different approval targets for negotiation in filings (eg, different dosages, indications). It has been observed, however, that these discrepant filings more frequently result in discrepant reviews and outcomes.

Case study of tedisamil: an industry viewpoint

Tracy Baskerville

Head, Global Regulatory Affairs, Liaison, Cardio-Metabolic, Solvay Pharmaceuticals, France



Tedisamil: divergent regulatory decisions

Tedisamil sesquifumarate is a treatment for atrial fibrillation that was approved in the EU via decentralised procedure, in UK, Sweden, and Spain, but was considered not approvable by the US FDA in December 2007 following a unanimous negative Advisory Committee recommendation.

The agent is a class III anti-arrhythmic with anti-anginal properties. It blocks a number of potassium outward channels in cardiac tissue, and a specific sodium channel at high concentrations and prolongs action potential. The proposed indication for both jurisdictions was the rapid conversion of recent onset (~48 hours) atrial fibrillation to normal sinus rhythm (NSR).

Phase 3 trials were initiated in 2002, and 397 patients were treated at 0.32 mg/kg, the recommended dose. The original application proposed gender-specific dosing regimens, but this was ultimately rejected as too complex, even in a hospital setting, and a single dosage was proposed as part of the revised label application. Ten studies provided a programme of comprehensive evaluation. Torsades de Pointe (a ventricular tachycardia [VT]) remains a potential serious event in particular in patients with elevated QTc or receiving supra-therapeutic doses. It should be highlighted that the benefit/risk as measured by conversion to normal sinus rhythm/torsades was greatest at a different dose level for women than it was for men.

Position of tedisamil in medical landscape

Treatment options for the correction of cardiac arrhythmia include direct current cardioversion (DCC) and oral and intravenous anti-arrhythmic medicines. It was the sponsor's belief that because atrial fibrillation therapy must be individualised, a new treatment option such as tedisamil would be a valuable addition to the treatment armamentarium. Moreover, administration of tedisamil in a hospital setting where patients are monitored by telemetry would mitigate some of the risk associated with torsade. Oral medications are not optimal for rapid cardioversion because of the delayed onset, and tedisamil would be best used when rapid cardioversion is necessary or when contraindications to other anti-arrhythmics exist. DCC is highly effective but is not optimal for rapid cardioversion in haemodynamically stable patients where fasting and anaesthesia are required. It takes time to prepare the patient and is associated with risks such as unsynchronised shocks, bradycardia, and anaesthetic complications. Other intravenous anti-arrhythmics carry known risk of VT, including propafenone, flecainide and ibutilide.

EU issues to be overcome

The EU review resulted in several issues that needed to be resolved by the sponsor. Concerns for what was regarded as a complex gender-based dosing regimen were solved by changing to one recommended dosage for males and females. In response to questions of safety, prediction of persons at risk, risks associated with concomitant β-blocker use and defining appropriate monitoring periods, label revisions were undertaken and Solvay committed to a detailed risk management plan including an observational study of safety in the post-approval setting.

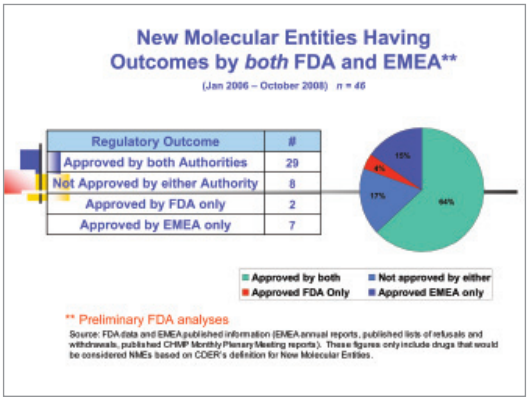
Summary

	US	EU
Complex dosage administration	✓	✓ Resolved adopting one dose for males & females
Safety profile	✓	✓ resolvable
Non-Pharmaco-therapy Comparator	✓	Less of an issue
Gender differences	✓	✓ resolvable
	Non-approval	Approval

The FDA letter of non-approval, however, stated that issues surrounding the drug's safety profile, its complex dosage administration, gender differences, and the need to compare the drug's activity to a non-pharmacotherapy comparator were major impediments to approval. One death occurred during the programme which gave the FDA some cause for concern. Based on an analysis by Solvay's outside experts, the patient would have experienced the same serious adverse event regardless of whether cardioverted by medications (such as tedisamil) or by DCC (electric shock) because of likely sick-heart syndrome. Therefore, in the opinion of the sponsor, the death did not tip the benefit/risk balance away from tedisamil toward DCC (or use of other pharmacologic cardioversion). The incidence of serious adverse events such as Torsade de Pointe was low and well characterised given the wide dosage range studied in the clinic; however, the FDA asserted that this could be extrapolated to a much higher rate of risk in a larger real-world population.

The comparison of tedisamil to DCC, which as a device does not have a rigorously compiled record of clinical trial safety, was considered problematic by the sponsor, which raised the question of whether there will be an increased expectation to compare pharmacologic to non-pharmacologic therapies. Furthermore, it was agreed that the requirement for a nonpharmacologic comparator would have been better communicated very early in the development process.

In summary, divergent results can occur even when similar data sets are provided to two agencies. Early, clear and consistent communication with the agencies may reduce the risk of divergent regulatory decisions.



How to mitigate against divergent outcomes: an FDA viewpoint

One Submission – One Answer?

Dr Murray Lumpkin

Deputy Commissioner, International Programs, FDA USA

Harmonisation or Homogenisation?

Comparing both product development oversight and marketing application review processes and procedures across political and geographic boundaries is of interest to regulators, who tend to use this approach as a form of peer review and as an effective method to leverage limited resources. For industry, an examination of clinical development plans rather than the review process is likely to have the greatest impact on the mitigation of divergent outcomes.

However, a single global decision for new drug submissions may not be in the best interest of industry or public health, nor even be achievable, given the diversity and the realities of the world in which we live and in which product marketing decisions have to be made by both industry and regulators.

Similar to harmonisation in music, harmonisation in regulatory review adds complementary robust depth when compared to the relatively flat and

shallow effect of a unified homogenous group effort. Cacophony, on the other hand, is not wanted in music or in regulatory affairs. There have been great strides in harmonisation of technical requirements and in content and format due to efforts of the ICH, but what we don't have and are likely to never have is unity in decision-making, because of the many different factors that come into play.

For industry, an examination of clinical development plans rather than the review process is likely to have the greatest impact on the mitigation of divergent outcomes.

Is the EMEA faster and less conservative?

It seems as though public perception of global regulatory review has come full circle in the last 20 years. In 1989, many considered FDA guilty of a perceived "drug lag," in the USA, but by 1999, the European review was considered to be slower than that in the United States as a result of several factors including:

- Fundamental differences in study design requirements
  - Non-acceptance of unvalidated surrogates
  - Dissimilarities in recognition of sensitivity, specificity and utility of diagnostic standards
  - Requirement for active comparators

Now in 2009, the media reports that the US is lagging behind in performance again, but is this supported by data? The FDA and EMEA authorisation procedures and processes are very different, but often work in parallel, with more and more of the new chemical entities being submitted to both agencies within a 6- to 12-month window.

In some therapeutic areas such as oncology, paediatrics and vaccines, there is a great deal of interaction and ongoing discussion of individual applications among "clusters" of technical reviewers across the two agencies.

In a comparison of three years of recent data of outcomes for 83 new molecular entities (NMEs) for the FDA and 92 for the EMEA* (Jan 2006 – October 2008), there was essentially the same proportion approved (67% for the EMEA vs 64% for the FDA).

Looking at a subset of 46 of these NME reviews (those having outcomes by both FDA and EMEA)*, 2 were approved by the FDA only and 6 (7 with one later withdrawal) were approved by the EMEA only, a difference of just 4 compounds. We would argue that such numbers do not indicate a significant divergence – either in time to decision or outcome of decision.

Despite there being no formal harmonisation of the decision-making processes between FDA and EMEA, recent outcomes of the review processes in these agencies indicate that there are striking consistencies with respect to the proportion of new products approved, and relatively small divergences of opinions between these independent agencies. The geographic, political and other influencing factors often touted as critical influences of regional decision-making may not play as important a role as does the scientific analysis of a product's benefits and risks and the perception of a given region's tolerance of the known risk with respect to the demonstrated benefit. Such differences in risk tolerance are not fundamentally differences in science; but rather differences in culture. Despite these factors that engender regional differences, they do not appear to act as a significant barrier to expediting patient access to new therapies.

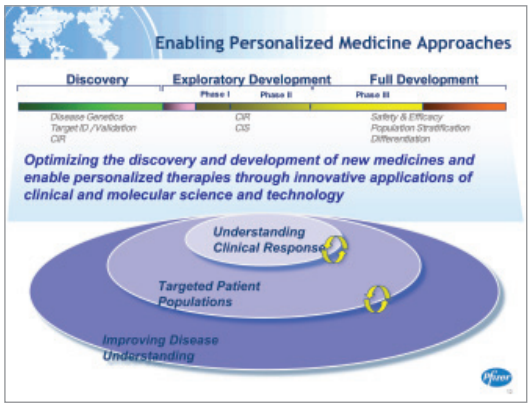
**FDA figures do not include resubmissions of NDAs that were first acted on prior to 2006. Approval outcomes include approval following NDA resubmission to FDA or revised opinion following re-examination by CHMP during this timeframe. Source: FDA data and EMEA published information (EMEA annual reports, published lists of refusals and withdrawals, published CHMP monthly plenary meeting reports). These figures only include drugs that would be considered NMEs based on CDER's definition for new molecular entities.*

Session 2: Solutions to enable simultaneous submission, approval and outcomes and the role of innovative clinical development

Chair: Professor Robert Peterson

Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada

Innovative clinical development: What new science opportunities are there and which areas do companies believe have the most promise?



Dr Damian O'Connell

Executive Director, Clinical Group Head, Pfizer Clinical R&D, UK

Enhanced Clinical Trial Design

Finding ways to maximise productivity continues to challenge the pharmaceutical industry. Thirty percent or more of compounds in phase 3 development ultimately fail to receive approval, and these late-stage failures contribute to high pharmaceutical development costs. Confidence in and knowledge about a compound's mechanism of action, safety, and differentiation should be captured much earlier in the pharmaceutical development process.

In the learn-and-confirm paradigm adopted by some pharmaceutical companies, if smaller leaner phase 2 studies to test viability fail, they do so early and at low costs. Later phase 2 trials, which confirm activity, characterise dose-response and contribute to an understanding of PK/PD, can include planned futility analyses for inactive doses and endpoint validation. Finally, for compounds that progress to phase 3, trials can be simple, streamlined and focussed, with an extremely low rate of failure.

Use of simulation and modelling is critical in optimising clinical trial design, and Pfizer is at the fore in using these methods to quantify drug mechanisms and safety and the differentiation that need to be achieved, while potentially accelerating the time to trials without increasing risk to patients or the risk of clinical failure.

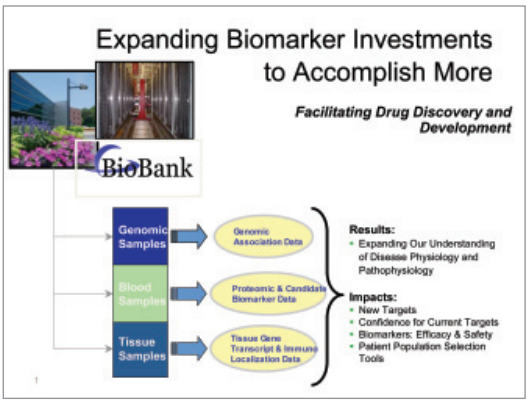
Biomarkers and genomics

Pfizer has also invested heavily in an infrastructure for biomarker research and development. The state-of-the-art Pfizer BioBank is an active sample repository that enables research into the understanding of disease and drug response, and the discovery, development and validation of biomarkers. The BioBank consists of the DNA and bio-fluids bank and a separate tissue bank, linked by a common tracking system. This investment enables an increased understanding of disease pathophysiology that helps to identify new targets and to increase confidence in existing targets.

Biomarkers can be used as tools to demonstrate compound efficacy and safety as well as to select the most likely responder patient populations. Biomarkers have assumed centre stage in many clinical trial designs, as advances in imaging and other technology have provided improvements in the type and quality of data available. The development of global

standards for approving and analysing biomarkers, imaging protocols and surrogates remains a critical need.

We have progressed from the cataloguing of the human genome to the more recent research in genetic variation, driving home the need to study patients to understand the nature of the genetic basis of disease. The use of genomics may result in an enhanced predictability of response and the reduction of risk in the individualised treatment of chronic disease.



Personalised medicine

Pharmaceutical research is gradually shifting from the so-called "blockbuster approach," which was used in an attempt to identify multiple potential targets, to smaller focussed efforts to validate specific disease targets. Optimising patient selection through genomic characterisation could increase a therapy's efficacy, providing the targeted evidence base that is key to improving the probability of technical and regulatory success. Whilst the use of diagnostics will potentially reduce the pool of treatable patients, better efficacy in this selected cohort may improve reimbursement/access, pricing and compliance. Improved efficacy or enhanced safety among a well-characterised target cohort could also potentially result in the use of smaller, less costly clinical trials. It is also feasible that a personalised approach could bring medicines to market quicker, based on smaller studies and faster approval.

Conclusions

Dr O'Connell concluded by saying that these types of novel approaches are important to the delivery of new medicines that address unmet needs. Leveraging these novel approaches will require greater alignment and coordination of multiple activities across discovery and development.

Science and technology are advancing to make personalised medicines a reality. Regulatory and policy issues will require close partnership between agencies and sponsors, especially as these relate to agreements concerning new diagnostic and assessment methods. Proactive coordination and partnership with payors and healthcare practitioners will likewise be required to unlock the full potential of new medicines.

Question

As the strategy of patient selection results in reduced numbers of participants in individual trials, does safety become the trade off?

Response

Choosing a targeted population reduces drug exposure to a group of patients, for whom it will be of no clinical value, potentially resulting in a better therapeutic index. Even though there may be smaller participant numbers, it's a question of building targeted evidence that supports an ongoing regulatory dialogue.

Question

Isn't our current knowledge base too limited for the personalised approach?

Response

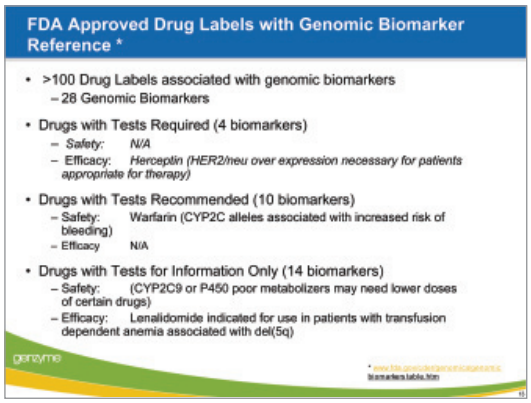
It is already been implemented successfully in some therapeutic areas such as oncology. We are moving beyond drug registries into disease treatment registries. Disease learning is an ongoing investment process and we need to leverage those learnings to benefit from the advantages of targeted personalised therapies.

Genomics, biomarkers and surrogate endpoints:

Are these the key to improving regulatory decision-making based on clinical trials?

Alison Lawton

Senior VP, Global Market Access, Genzyme Corporation, USA



Ms Lawton began her presentation by providing basic definitions. **A biomarker** is a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacologic responses to a therapeutic intervention. **A genomic biomarker** is a measurable DNA or RNA characteristic that is an indicator of normal biologic or pathogenic processes and/or response to therapeutic or other intervention (ICH E15). **A surrogate endpoint** is a biomarker intended to substitute for a clinical endpoint, and is expected to predict clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.

The FDA, EMEA and PMDA have all cited the identification and validation of biomarkers as important steps throughout all phases of pharmaceutical development to address issues with lagging research and development productivity. In a number of priority diseases (eg, oncology), surrogate endpoints such as imaging- based response, relative response, time to progression and progression-free survival versus overall survival are accepted, albeit with some regional differences in approach. However, new contradictory data have now caused some previously validated surrogate endpoints such as haemoglobin A1c in diabetes to come under question.

The FDA allows the use of surrogate endpoints when the effect is reasonably likely to predict clinical benefit, and Genzyme has had significant regulatory success using surrogate endpoints in the clinical testing of orphan therapies for which no alternative therapy exists. The EMEA grants conditional approval to compounds using surrogate endpoints if they can demonstrate a positive benefit-risk balance based on preliminary evidence from an ultimately comprehensive development programme.

As was discussed earlier by Dr O'Connell, trial and error research is being replaced with personalised medicine in which patients undergo detailed genomic testing to determine the therapy most likely to have a safe and efficacious response. This new paradigm has already shown a positive impact on differentiated haematologic cancers for which the 5-year survival rate two decades ago was approximately zero and today approaches 70%.

FDA labelling and genomic biomarkers

The FDA website contains a list of more than 100 examples of labelling associated with 28 different genomic biomarkers. Of these, only 4 biomarkers are associated with therapies for which biomarker testing is required for efficacy, 10 biomarkers are associated with therapies for which testing is recommended for safety, and 14 biomarkers associated with drugs for which testing for safety or efficacy is for information only.

There are still only limited examples of the use of genomic biomarkers to guide development programmes or to identify the optimal patient population to be studied and enrolled in pivotal therapeutic trials. More often, biomarkers are identified to improve the efficacy or safety profiles of already marketed therapies.

Biomarker identification and labelling: a case study

In a case study of the impact of later-stage genomic biomarker identification on labelling, in September 2006, the FDA granted accelerated approval of Vectibix (panitumumab) for the treatment of EGFR-expressing metastatic colorectal carcinoma (mCRC), whilst in May 2007, the CHMP, unconvinced of a clinical benefit, recommended against approval.

Numerous retrospective studies later suggested the mechanism of action for Vectibix may be dependent on the lack of a K-Ras mutation. In November 2007, the CHMP recommended approval based on the "ability to select patients with mCRC who are likely to benefit from Vectibix monotherapy treatment" and in December of that year the EMEA approved Vectibix monotherapy for patients with EGFR expressing mCRC with non-mutated (wild-type) K-Ras. In June 2008, the CHMP also recommended use of Erbitux (cetuximab), a therapy with the same mechanism of action in mCRC patients, only if they have wild-type K-Ras.

Although US physicians are now beginning to use K-Ras gene tests regularly in their practice, payors began to discuss requiring testing for treatment and the FDA Oncologic Drugs Advisory Committee was convened to discuss conditions under which a retrospective analysis would be appropriate for biomarker analysis to support a labelling update; the US label still has not yet been updated to include K-Ras testing as a condition of patient selection.

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Outlook

There is a mutual recognition in Europe and the United States of the need to identify and validate biomarkers in high-priority diseases to expedite early drug development and to identify the optimum patient cohort. A consistent acceptance of surrogate endpoints (as part of an accelerated/ conditional approval process) is more likely in life -threatening diseases with high unmet medical need affecting small populations. However, the current HTA-influenced environment is driving toward a benefit-risk assessment of medicines with more outcome/ evidence-based endpoints, and the accumulated wealth of genomic information needs translation into real-world solutions for human disease. Opportunities for characterising a drug's profile may vary, depending on the stage of development when genomic markers are identified.

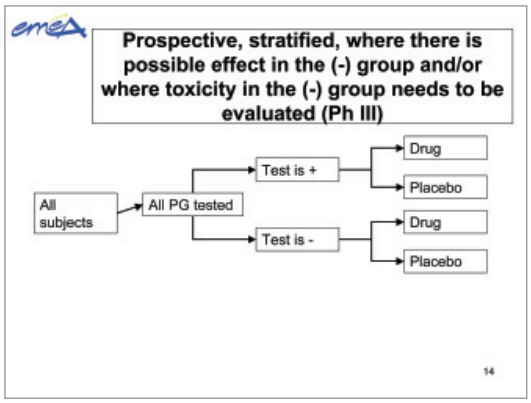
Differences in the regulatory requirements for diagnostics will continue to result in divergent regulatory decisions with the EMEA having no legal authority over the regulation of diagnostics and the FDA having a requirement for a well-controlled study to determine specificity and sensitivity of a biomarker.

There remain many opportunities for optimising the use of genomic biomarkers and surrogate endpoints to have a positive impact on patients' access to medicines.

Genomic biomarkers and surrogates: key to improve regulatory decision-making

Dr Eric Abadie

Chair, CHMP, EMEA, Phamacogenetic Working Party, UK



Biomarker validation

Mr Abadie initiated his presentation with a discussion of biomarker classification and validation. Measured before therapy, biomarkers are considered **predictive or prognostic**, whereas those used to measure response after therapy are considered to be of **pharmacodynamic** interest. In order for a biomarker to be validated as a surrogate of the effect of therapy, there must be a qualitative correlation between it and a specific outcome. This type of correlation can typically be supported by ample data, but the quantitative correlation that is drawn from clinical trials, and which is also a requirement for surrogacy, has been more difficult to establish.

There are multiple potential issues of concern to regulators that surround the use of biomarkers in phase 3 trials. These relate to the multifactorial nature of some diseases, the heterogeneous risk levels of the treated population, the confounding effects of multiple therapies, the extrapolability of results to other medicines with the same or differing mechanisms of action, and the requirement for direct rather than surrogate indications of safety.

Several challenges exist for beginning a programme of pharmacogenetic evaluation at the time of marketing authorisation. Where there is a treatment effect in both patients with positive and negative pharmacogenetic findings, a benefit-risk evaluation is necessary before approving or restricting therapy for that population. Granting marketing authorisation to medicines with a genomic test may require that the utility of the test be validated, but extreme caution must be exercised in making such a test mandatory, as the EMEA does not have the authority to approve these tests.

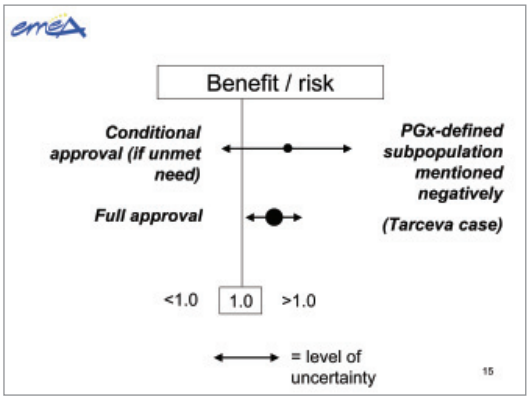
CHMP pharmacogenetic oncology experience

Pharmacogenetic biomarkers have had a major impact in oncology. Between January 2000 and December 2008, 33 new oncology products were approved in Europe and 9 (27%) indicated for patients with specific genetic biomarkers. Four drugs were approved for leukaemia: Glivec (imatinib), for c-kit+ gastrointestinal stromal tumour [and for Ph+ chronic myelogenous leumkaemia (CML)]; Tasigna (nisotinib) for imatinib-resistant Ph+ CML; Sprycel (dasatinib) for imatinib-resistant Ph+ CML; Trisenox (arsenic trioxide) for promyelocytic leukaemia/RARα gene+ [or t(15;17) translocation] acute promyelocytic leukaemia. Five therapies had indications for solid tumours: Herceptin (trastuzumab) for Her2+ breast cancer (BC); Erbitux (cetuximab) for epidermal growth factor receptor (EGFR)+ metastatic colorectal cancer (CRC) after failure of irinotecan (immunohistochemistry: at least one cell is +); K-Ras wild-type metastatic CRC; Tarceva (erlotinib) for advanced non-small cell lung cancer (no clinically relevant effects demonstrated for patients with EGFR- tumours; ie, ≤ 10% of cells)*; Vectibix (panitumumab) for EGFR+, non-mutated K-Ras metastatic, previously treated CRC –(conditional marketing approval [MA]); Tyverb (lapatinib) in combination with capecitabine for Her2+ BC after failure of taxanes and trastuzumab –(conditional MA).

Although post-hoc analyses can be part of the regulatory review of medicines with specific activities or contraindications associated with pharmacogenetic variations, ideally, efficacy and safety analyses should be

performed on treatment results from patients who have been prospectively stratified into groups with positive or negative genomic findings, where all patients are included in the trial and in the analysis of its results. Patients who have been designated as responders or non-responders to therapy can be further divided into groups with positive or negative genomic findings. However, this type of analysis may be problematic in instances in which genomic data has not been collected for all patients. Alternatively, analyses can be made for patients who have been prospectively tested and treated based on positive genomic findings, whilst those who tested negatively may have been excluded from treatment.

For diseases with unmet need, if insufficient pharmacogenetic data are available to construct a complete benefit-risk evaluation for all patients, a conditional approval that does not include a pharmacogenetically defined population can be granted, as was the case for Tarceva (erlotinib), for which pharmacogentic data were only obtained for 55% of the patients in the pivotal trial and for which the EMEA statement concluded ". . there is not enough justification for or data on its use in patients whose tumours are EGFR-negative."[1]



Testing methods

Although the EMEA has no jurisdiction over the approval of genetic testing methods, it is required for regulatory purposes that a test has been validated in pivotal clinical trials, be widely available, and fulfil the EU requirements for diagnostic tests/agents.[2] Rarely, it may be necessary to specify the platform/test/kit to be used. Genetic test requirements are described variously in the summary of product characteristics. For example:

- HERCEPTIN Her^2/EGFR testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures
- ERBITUX It is recommended that the detection of EGFR expression be performed by an experienced laboratory using a validated test method
- VECTIBIX Detection of non-mutated K-Ras expression should be performed by an experienced laboratory using a validated test method

Pharmacogenomics and adverse reactions

Genetic testing can also be used as a tool to identify patients at risk for serious drug-associated adverse events as was successfully accomplished with Ziagen (abacavir), for which pivotal studies revealed that the carriage of the HLA-B*5701 allele greatly increased the risk of a hypersensitivity reaction. Specific warnings were incorporated into the SPC.

Conclusions

The use of biomarkers in clinical research should begin during the preliminary phases of pharmaceutical development. Use of surrogate biomarkers in phase 3, however, presents issues of validation, interpretation and safety; and outcomes based on these markers are not likely to be accepted by health technology assessment agencies.

Industry is encouraged to rethink pharmacogenetic development approaches through the identification of new pathways and phenotypes. Regulatory support should likewise move forward with scientific advice in support of new development methods and scientific opinion for the qualification of these novel methodologies to expedite approvals for the most appropriate target population.

1. European public assessment report available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/tarceva/061805en1.pdf; accessed April 2009.

2. Reflection paper on EMEA pharmacogenetic experience in oncology available at http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf; accessed April 2009.

Improving regulatory decision making — genomics, biomarkers and surrogate endpoints

Dr Leonie Hunt

Head Office of Prescription Medicines TGA , Australia

Dr Hunt began by discussing the regulators' need to balance the seemingly conflicting interests of patient needs: the need to have timely access to new therapies and the need for protection from those medicines that may do more harm than good.

The goals of industry and regulatory agencies, however, are aligned: both wish to measure outcome in terms of benefit and risk for patients in both the short and long term. Both groups would also like to use that knowledge to improve outcomes by predicting which patients may best respond to treatment and to monitor their effective progress, while withholding treatment from those who would derive little benefit or who would be at risk for associated adverse events. Finally, both groups have time constraints on their decision-making. Additional stakeholders, in the form of Health Technology Assessment (HTA) agencies have emerged with particular prominence, and they too want to ensure that the right patient is receiving the right medicine. What the HTAs are ultimately buying is not medicine, but health outcomes, and improved health outcomes are the reason for the development of medicine.

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Clinical trials to derive the evidence necessary to ensure these improved health outcomes are attained may be complicated by various factors, such as excessive length of trial time or a very large study size required for a valid analysis. There may also be unknown differences in potential risks and benefits to an intended patient group or ethical constraints against research that would measure final outcomes, such as may occur in oncology trials.

Tools are needed to assist companies, regulators, healthcare providers and payors in their efforts to deliver improved health outcomes. To be useful, however, these tools need to be valid, reproducible, accessible and timely. Potential tools include genomic markers, biomarkers and surrogate endpoints. Some of the tools have already been in use for many years. Hypertension, for example, has been a predictor of cardiovascular mortality for over two decades. The goal of antihypertensive medications is not to reduce blood pressure, but to provide the improved health outcome of the reduction of risk of heart attack and other cardiovascular diseases.

Despite tremendous growth in knowledge and understanding there are still limitations on what we know about the identification and application of biomarkers in the pharmaceutical approval process. There have been some recent issues surrounding the matching of a biomarker to a final outcome or health benefit; for example, the recent controversy regarding the predictive value of haemoglobin A1c as a reliable long-term indicator of likelihood for diabetes and diabetes sequelae. Other factors such as body weight are now recognised as factors that may carry more importance in influencing outcomes.

Although perhaps not yet fully realised, new methods for identifying target patients and for measuring response have been developed; for example, effective Her2 receptor treatment for genomic marker-positive patients with breast cancer. It is vital that these new tools be prospectively

validated, rather than result from post-hoc validation. HTA agencies will require clinical trial results that link surrogate markers to health outcomes. The scientific community needs to monitor these health outcomes in the long term and assess the value of the newer biomarker as more is learned, continuously reassessing the value of older markers.

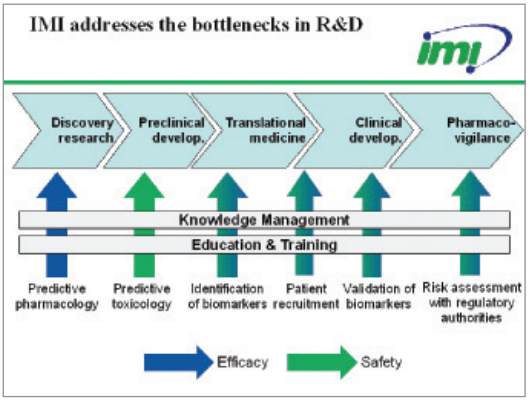
Conclusions

This is an evolving area of science, and expectations of early gains were quite high on all sides and perhaps somewhat unrealistic. Reflection, however, will reveal the extent of the gains that have been made, and the tremendous potential for great advances in timeliness and reliability of measurement of outcomes leading to better decision-making for all stakeholders involved in patient care. The issues and the challenges surrounding the rapidly evolving science and practice of genomic-based medicine belong to all stakeholders and will require engagement to recognise, investigate and address.

Improving efficacy data: Update on the IMI initiative

Professor Trevor Jones, CBE

Member of the Scientific Committee, IMI, UK



The Innovative Medicines Initiative (IMI), a unique and innovative collaboration, was established by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Commission. As outlined by Professor Jones, the drivers for the development of the IMI were the desire to shorten the timelines and enhance the predictability of pharmaceutical development, to implement the wealth of opportunities represented by the advance in genomics, to increase cooperation between healthcare stakeholders and to enhance European competiveness in the development and regulation of novel therapies.

PredTox

Predictive Toxicolgy (PredTox) a pilot consortium venture, was initiated in October 2005 under the auspices of EU InnoMed, an integrated project funded by the European Commission Sixth framework Programme (FP6). PredTox is an association of 16 companies, 14 universities, and 8 small- and mid-size enterprises (SMEs) from across Europe participating in 3 years of intense collaboration. The goals of the collaboration were to assess the value of combining results from genomics technologies together with the results from more conventional toxicology methods to develop a more informed product safety profile earlier in the development process.

The PredTox initiative identified 14 drugs that had failed in development because of preclinical liver or kidney toxicity. These were then subjected to newer innovative in vivo/in vitro screens and compared with 2 reference compounds with well-characterised toxicity profiles, gentamycin and troglitazone. Each of the 16 compounds was administered at 2 dosages levels and at 3 time points. The results were reviewed by 3 independent expert groups. The research resulted in the identification of several distinct new biomarkers for hepatic and renal toxicity, the publication of which is subject to finalising intellectual property negotiations.

IMI

The consortium's strategic research agenda was set by 350 participants, 35% from universities, hospitals and public research, 30% from pharmaceutical and imaging companies,13% from SMEs, 7% from regulatory authorities, 5% from the European Commission, 3% from patient organisations, and 7% from other groups. A programme of predictive pharmacology, predictive toxicology, identification and validation of biomarkers, patient recruitment, and benefit-risk assessment within five disease areas (cancer, brain disorders, inflammatory diseases, metabolic diseases and infectious diseases) was agreed upon by all stakeholders.

Funding from the European Commission for IMI goes to patients, academia and SMEs. Regulators in the consortium contribute expertise, whilst pharmaceutical companies contribute in-kind. As part of the patient-centred research programme, IMI will set up an information sharing platform to integrate medical information from hospitals and companies. Patients and companies will mutually benefit from the collaboration, the companies from an enhanced patient recruitment and data-gathering ability and patients from better treatment option information and opportunities.

The first call for research projects was launched in April 2008. The call comprised 18 topics: 6 in safety, 7 in efficacy and 5 in education and training. There was an average of 7 expressions of interest per topic for a total of 134 by 130 applicants. Forty-eight percent of applications were from academia, 41% from the pharmaceutical industry, 7% from SMEs and 2% each from regulatory agencies and patients. After several stages of consortium and peer review, the Board approved 14 project proposals for research in March 2009. Two were rejected and 2 are awaiting further review after a non-consensus decision by reviewers. Approved projects will enter into a negotiation to complete project and grant agreements and projects are anticipated to start Q3/4 2009. A second call for proposals will address new areas of research and will most likely be launched in late June 2009.

The expected long-term benefits of IMI for society as a whole include faster pharmaceutical approval times through better collaboration with the regulatory authorities, fewer post-marketing withdrawals through better pharmacovigilance tools, fewer patients required in pivotal trials through optimised trial design, validation of new assessment methods such as biomarkers, more skilled professionals in biomedical research and more cost-efficient R&D.

Conclusions

Multiple benefits accrue from IMI participation for its various stakeholders. In addition to unique opportunities for collaboration, all parties have access to precompetitive knowledge, experience the stimulation of creativity and enhanced learning and the generation of innovative solutions. Member states can leverage their national research infrastructure through good EU coordination and may experience an increase in jobs and education and training in the biomedical arena. An increase in the European science base helps countries retain and attract scientific talent, resulting in a healthier and economically stable society.

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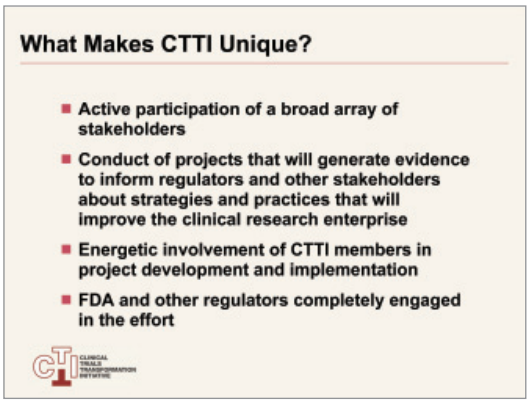
Clinical Trials Transformation Initiative (CTTI)

Dr Alberto Grignolo

Corporate Vice President, Global Strategy and Services, PAREXEL Consulting, Member, CTTI Executive Committee, USA



The FDA Office of Critical Path Programs and Duke University recently joined together as founding members of a public-private partnership: The Clinical Trials Transformation Initiative (CTTI).

Dr Grignolo explained that many and diverse stakeholders are involved in this initiative, including government, industry, academia, patient advocates, clinical investigators, and others to conduct projects in support of the mission to identify practices that will increase the quality and efficiency of clinical trials. *Quality* in this instance is defined as the ability to effectively answer the intended question about the benefits and risks of a medical product or procedure, while assuring protection of human subjects. Although CTTI will concentrate initially on the design and conduct of clinical trials in the United States, it seeks to identify practice improvements that can be applied internationally.

Active projects

Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials: Many sponsors employ monitoring methods that are heavily reliant on multiple site visits, with a focus on source data verification and study documentation, which can be time-consuming and costly; furthermore, the intensity, focus, and methods of monitoring vary considerably among trials. Additionally, information on how to determine adequate and appropriate monitoring in a particular trial may be limited. CTTI will therefore develop a white paper that will promote effective and efficient monitoring in the conduct of clinical trials. First, current monitoring practices will be reviewed and the factors that drive their adoption examined. Next, key quality assurance objectives within clinical trials will be defined, and finally, a qualitative assessment of the effectiveness of current practices in meeting key quality assurance objectives across a spectrum of trial types will be conducted.

Improving Serious Adverse Event (SAE) Reporting to IND Investigators: Current US FDA regulations (21 CFR 312.32) require IND sponsors to notify investigators of all unexpected SAEs associated with a drug during its investigational phase. Individual expedited reports, however, often lack context and detail, and meaningful interpretation of SAEs across indications and regimens is difficult. The result is significant investigator investment of time and effort for little-to-no gain in understanding more completely an investigational product's benefit-risk profile. This project will generate empirical evidence on resource use and the value of current practices, and develop a proposal for possible modification and improvement. First, the current range of sponsor practices will be documented; next, investigator time and perceived value of current practice to inform sites about new adverse events will be quantified and comparisons made with current alternative practices; finally, an expert group will be convened to assess and integrate the findings and make recommendations to optimise SAE reporting and ultimately, patient protection.

Both projects are expected to generate results within approximately one year.