

Post-Approval Commitments and Conditional Authorisations

**Report of the Workshop organised by the
CMR International Institute for Regulatory Science
at the
Woodlands Park Hotel, Cobham, Surrey, UK
12-13 May 2005**

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CMR
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POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS

CMR INTERNATIONAL INSTITUTE WORKSHOP

12-13 May 2005, Woodlands Park Hotel Cobham, Surrey, UK

WORKSHOP REPORT

Margaret Cone, Neil McAuslane and Mayu Hirako

SECTION 1: OVERVIEW

The Workshop Topic

When a marketing approval is issued for a new medicine there are always certain statutory conditions and commitments, such as post-marketing surveillance of adverse drug reactions (ADRs) and labeling requirements that are applied routinely. The discussions at the Workshop convened by the CMR International Institute for Regulatory Science, in May 2005, however, focused on the post-approval commitments (PACs) that are applied selectively and agreed on a case-by case basis, at the time of authorisation.

Such PACs often require special studies to be carried out to confirm and supplement aspects of the technical data, such as the use of biomarkers and surrogate endpoints. The related subject was discussed of issuing 'conditional authorisations', which allow urgently needed medicines to be made available to patients early, but restrict full marketing until specific obligations have been fulfilled.

Different approaches

Speakers from FDA, EMEA and PMDA gave an overview of the different practices in the USA, EU and Japan.

Under FDA procedures certain PACs are required by law or regulation (e.g., following accelerated review) whilst others are mutually agreed between the company and regulators during the review process.

In the EU the legislation is undergoing changes that will modify and clarify the requirements for conditional authorisations and the procedures for accelerated assessments, where approval is almost inevitably associated with 'specific obligations' to carry out further studies.

In Japan there are conditional authorisations and PACs but the picture is somewhat different in that there is a routine request for companies to collect information on all patients using the new medicine, for a fixed period or until a specified number of cases have been collected ('complete count survey').

In presentations made at the Workshop by senior executives from industry, concerns were expressed about resource implications, lack of clear criteria for assigning PACs and discussion at a very late stage in the review process. Regulators were disturbed about commitments that were not fulfilled in a timely manner, and the official action that should be taken. It was apparent, however, that there was consensus that PACs provide a valuable means of expediting early authorisation and quicker access to important and needed new medicines.

Company survey

A survey was carried out by the Institute, in preparation for the Workshop which documented companies observations on the increased workload attributed to PACs and concerns about the usefulness of some of the studies that had been requested. Nonetheless companies recognised that they were a 'valued regulatory tool that enables faster access to medicines by patients in a *real-world* setting'.

Syndicate discussions

The break-out groups, or Syndicates, at the Workshop were asked to discuss improvements to current procedures related to PACs and conditional authorisations and to look toward future changes that might streamline drug development and make new therapies more rapidly available to patients. The following were included in the recommendations:

- The importance of early discussion between companies and authorities to avoid PACs becoming a last-minute issue in the late stages of review;
- The need for improved international cooperation between agencies to harmonise requirements for additional studies when reviewing the same product;
- Proposals for a Workshop to examine the potential role of large-scale population-based databases of electronic health records (EHRs) as a source of post-marketing information on medicines;
- The need for constructive approaches to the on-going problem of communicating with, and educating patients, politicians, the media and healthcare providers on the issues related to risk and benefit for medicines.

Workshop Report

This report is presented in three sections:

Section 1: Overview

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

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

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

The CMR International Institute for Regulatory Science has been established as a not-for-profit division of the Centre for Medicines Research International Ltd in order to continue its work in the regulatory and policy arena, and to maintain the well-established links that the Centre has with regulatory authorities around the world. The Institute operates autonomously, with its own dedicated management, and funding that is provided by income from a membership scheme. The Institute for Regulatory Science has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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Workshop Organisation

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Report prepared by Margaret Cone

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SECTION 2: OUTCOME

Session 4 of the Workshop, during which the syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Associate Head of Pediatrics, Dept of Pediatrics, British Columbia's Children's Hospital, Canada*.

The Workshop participants formed four Syndicate groups to discuss the issues arising from the Workshop and to make recommendations. The Chairpersons and Rapporteurs for the four groups were:

Syndicate 1	<i>Chair:</i>	Dr Patrick Le Courtois , <i>Head of Unit, Pre-Authorisation of Medicines for Human Use, European Medicines Agency</i>
	<i>Rapporteur:</i>	Dr Simon Larkin , <i>Director, Drug Development – Europe, Kyowa Hakko UK Ltd</i>
Syndicate 2	<i>Chair:</i>	Dr Stewart Geary , <i>Deputy Director, Corporate Regulatory Compliance and Quality Assurance, Eisai Co Ltd., Japan</i>
	<i>Rapporteur:</i>	Dr David Lyons , <i>Senior Medical Officer, Irish Medicines Board</i>
Syndicate 3	<i>Chair:</i>	Prof Samuel Vožeh , <i>Head Business Unit Prescription Medicines, Veterinary Medicines and Pharmacovigilance, Swissmedic, Switzerland</i>
	<i>Rapporteur:</i>	Dr Paul Huckle , <i>Senior Vice President, European and International Regulatory Affairs, GlaxoSmithKline, UK</i>
Syndicate 4	<i>Chair:</i>	Dr George Butler , <i>Vice President, Customer Partnerships, AstraZeneca Pharmaceuticals, USA</i>
	<i>Rapporteur:</i>	Prof Thomas Kühler , <i>Director of Operations, Medical Products Agency, Sweden</i>

SCOPE OF THE WORKSHOP

The main focus of the Workshop was post-authorisation commitments (PACs) and conditional authorisations, although the scope of discussions at the meeting included a wide range of related issues. During the presentations (reported in Section 3) the following points on terminology and procedures were clarified for the three ICH regions:

USA: Agreements made at the time of authorisation for companies to carry out specific Phase IV studies are known as **post-marketing commitments (PMCs)** and also (historically) 'Phase IV commitments'. Certain PMCs are often required for products approved under the *accelerated approval rule* ('fast-track' approvals), particularly if the approval was based on a surrogate marker for efficacy and additional data are needed to confirm clinical benefit. Others are mutually agreed between FDA and the applicant and documented in the approval letter.

EU: The type of PACs that may be attached to any application are known as **follow-up measures**. Under the new EU legislation revised procedures will be implemented for **conditional marketing authorisations** which may be granted following an accelerated review. The PACs attached to such authorisations are designated as **specific obligations** and will need to be reviewed annually until the obligations are fulfilled and a normal authorisation is granted. There are also authorisations granted under **exceptional circumstances** (e.g., for orphan medicines), which have 'specific obligations' attached, but may never reach full authorisation status.

Japan: All new drug authorisations are subject to a **post-authorisation observational trial** in a fixed number of patients over a specified period and **early post-marketing phase vigilance (EPPVs)** with special requirements for reporting adverse drug reactions (ADRs). **Conditional authorisations** are used to put limitations on the use of a new product, for example restricting it to specified medical institutions for a given period after approval.

BACKGROUND TO THE SYNDICATE DISCUSSIONS

This Workshop was held against a background of increased obligations being placed on companies to carry out further studies under post-authorisation commitments. It was convened in response to requests to quantify the perceived trend and examine current regulatory practices and policies when attaching conditions to the grant of an authorisation. Whilst PACs can have significant resource implications for industry their appropriate use is supported by companies since they can mean that products can be authorised at an earlier stage, especially following an accelerated review process. On the other hand, there are concerns that discussions on the need for post-marketing studies often start at too late a stage in the regulatory review process with a result that companies may feel pressurised into making commitments to studies without sufficient time to study the feasibility and resource implications.

Regulatory concerns relate to the absence of adequate documentation, in the marketing application dossier, of proposals for post-authorisation studies and risk management plans. There are also concerns about the apparently high number of agreements that are not fulfilled within agreed timelines.

The Syndicates were asked to look at current practices and discuss changes that would improve the value that can be obtained from PACs and conditional authorisations. They were also asked to make recommendations for future changes that could expedite patient access to important new medicines whilst ensuring that safety is not compromised.

The discussions focused mainly on clinical PACs as these are the most burdensome and qualitatively demanding, but it was recognised that requirements for further non-clinical and pharmaceutical (CMC) data can also be onerous, by volume alone.

SUMMARY OF RECOMMENDATIONS

Main Recommendations

- **Early dialogue is essential:** The post-approval commitments (PACs) and other conditions for further studies attached to a marketing authorisation need to be discussed at a much earlier stage in the product development and application review process than at present;
- International cooperation is needed to minimise duplication and redundancy: There is a need to exchange information between agencies about the commitments to post-authorisation studies that are made in different countries and regions in order to harmonise requests, whenever feasible, and reduce inefficiencies resulting from slightly different PAC demands;
- Improved use of electronic health records (EHRs) should be promoted : A Workshop should be convened to examine the potential role of large-scale population-based databases of medical information as a source of post-marketing information on medicines;
- Conditional authorisations could hold the key to earlier access to medicines: The range of products considered for early release under conditional approvals should, in future, be extended to a wider range of products, e.g., for progressive chronic diseases. More controlled product launches and the development of robust surveillance systems, linked to EHRs, could provide improved safety safeguards.

- **Post-approval plans should be** set out clearly in the regulatory dossier: Companies should routinely include a statement on their risk management plans and proposed post-authorisation studies when making a marketing application. It is recommended that the ICH Common Technical Dossier (CTD) format should be amended to accommodate this;
- **Greater transparency would improve confidence in early authorisations:** The adoption of an international 'Work in progress' symbol or icon should be considered as a means of alerting physicians and patients that a new medicine is subject to on-going studies as a condition of its authorisation;
- **Better education on medicines and risk is needed:** Further action is needed to educate the public, including patients, politicians, the media and healthcare providers, about the assessment of benefit and risk in relation to medicines. A future Workshop could address the topic.
- **Clearer criteria and processes should be established for requesting PACs:** Regulatory agencies should develop internal guidelines or procedures to establish clear and consistent criteria to guide requests for PACs as well as the appropriate timing and processes for interactions with sponsors.

Critical factors and 'best practices' for PACs

- PACs should be 'value adding' to the body of knowledge and not requested on a 'nice to know' basis;
- PACs should not be intended to reveal new safety issues (which is the role of pharmacovigilance) but should supplement the information on benefit and risk, gathered in the drug development programme;
- Discussions of PACs, between companies and agencies, should include participants that have the appropriate expertise, e.g., in pharmacoepidemiology, to ensure that the proposals are deliverable;
- If a commitment proves unrealistic or cannot be fulfilled in a timely manner, the sponsor should initiate further discussions with the authorities and not wait to be 'chased' by the agency.

DISCUSSION OF THE RECOMMENDATIONS

1. Early dialogue is essential

Risk management plans and the related PACs should be discussed at a much earlier stage in product development. Often these discussions do not commence until a relatively late stage in the review process when companies can feel pressurised into making commitments that have not been given sufficient consideration and may be impractical or unrealistic.

- Regulatory agencies should adopt procedures and 'good practices' such that PACs, based on clear, scientifically driven criteria, can be discussed in a timely manner during the regulatory review and do not become a last minute issue.
- Risk management plans and PACs should be a routine topic for discussion meetings between companies and regulators at the end of Phase IIb with full disclosure, on the part of companies, of any safety concerns arising from the early studies;
- The discussions should, thereafter, be dynamic and on-going throughout the development process;
- The current EMEA pre-submission meeting (administrative and procedural only) should be expanded to discuss (preferably with the Rapporteurs) specific technical issues related to risk management and PACs;
- There should be more flexibility, allowing agreement 'in principle' to the need for further studies with the details being specified at a later stage, for example following a post-approval 'Scientific Advice' meeting with the agency

2. International cooperation is needed to minimise duplication and redundancy

Situations can arise where companies can be faced with three post authorisation packages from the US EU and Japan. These may overlap in part or not at all. The ideal situation would be where the PACs for submissions made within a short time-frame could be harmonised between the major agencies.

- Discussion of risk management plans and PACs should form part of the discussions held under the confidentiality agreement between EMEA and FDA that allows the exchange of information on products under review;
- The possibility should be explored of arranging joint meetings/videoconferences with agencies to obtain scientific advice after authorisation on PACs that have been agreed in principle (see above). It was, however, recognised that scheduling of such meetings would present logistical problems;
- Divergences in PACs can be expected for applications submitted at different times in a field where the science is moving rapidly, for example HIV treatment

3. Improved use of electronic health records (EHRs)

The full potential of large-scale population-based databases of medical information, as a viable alternative to traditional methods for collecting post-marketing data on the safety and efficacy of medicines has yet to be fully recognised. The international availability and value of EHR databases should be reviewed at a CMR International Institute Workshop and the appropriate use of these data sets should be studied. The workshop could also cover:

- The competencies and training required in order to use and develop existing EHR databases to evaluate pharmaco-epidemiological (PE) data;
- The appropriate methodology for collecting and analysing 'real world' benefit/risk data as a complement to existing spontaneous reporting systems;
- Whether such data address some of the current issues in carrying out PACs.
- Case studies for example using information from established databases to compare two different treatment paradigms for an existing condition.
- Ways of motivating doctors to support the concept of, and contribute to, HER schemes;

It was also suggested agencies should initiate discussions on the question of funding training programmes to develop the PE expertise necessary to develop the potential of record-linked databases:

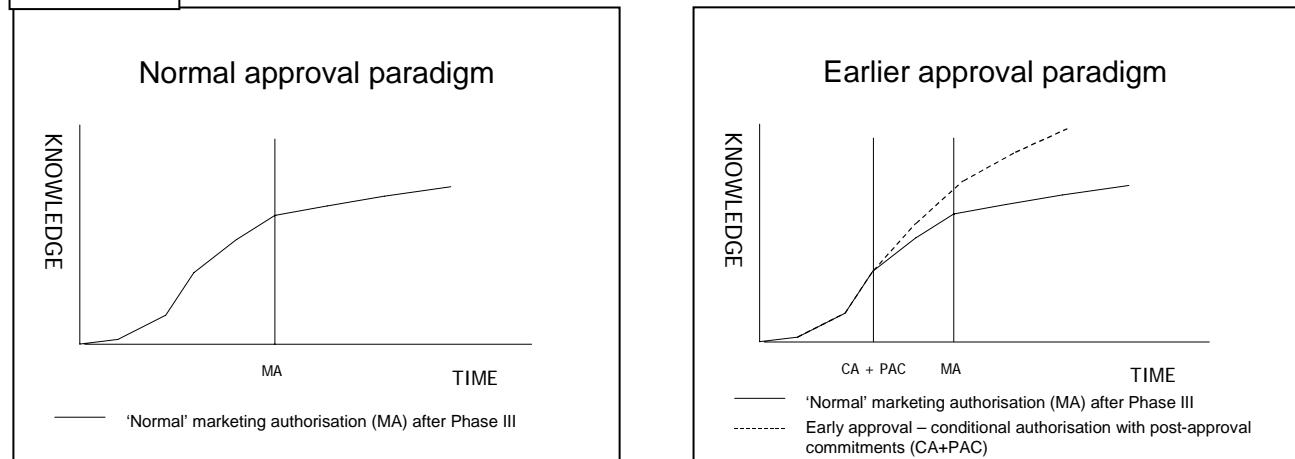
- The initiative should come from regulatory agencies and government but it is acknowledged that funding would need to be supported by industry
- A concept paper on the inception and greater use of PE data should be drawn up, preferably by the agencies

4. Conditional authorisations could hold the key to earlier access to medicines

It was recommended that a target for the future should be a shift in the traditional drug development model which would involve a much broader use of conditional authorisations, with appropriate PACs. This could release products onto the market at an early stage (e.g., without formal Phase III studies) and allow further collection of benefit/risk data to be based on experience in a 'real world' patient population. Early release tends to be restricted to products for the treatment of life-threatening diseases, where there is currently unmet need, and it was felt that the aim should be to extend the facility to medicines for chronic progressive diseases where there is unmet need, such as diabetes and COPD.

The model, shown in *Figure 1* is a schematic illustration of the growth of knowledge on a new compound during development and after the launch of a product, suggesting that an early launch (conditional approval) could result in a greater knowledge-base at the time of full marketing authorisation due to accumulated marketing experience in addition to the continuing development plan.

Figure 1



It was noted that the use of conditional authorisations would allow earlier patient access to important new medicines but was not expected to reduce the overall development time or the amount of data that would be required for new products.

It was also recognised that both companies and regulators might be 'nervous' about the release of products where there is a 'gap' in the normal Phase III safety data, especially because of limitations in the public understanding of benefits and risk.

- The use of conditional authorisations would not be appropriate when there are known, major, outstanding safety issues;
- Physicians, patients (represented through patient associations) and healthcare providers (the payers) would need to be involved early in the discussions relating to medicines designated for early, conditional authorisation;
- The EU model of reviewing conditional authorisations on an annual basis might not be practical if such approvals become more widely used;
- Proposals for more widespread use of conditional authorisations is closely linked to the development of safety monitoring through EHRs (see above) as it will be necessary to strengthen the current ability to detect safety signals in marketed products;
- The limitations on use attached to a conditional authorisation should make it possible to limit 'explosive' product launches and make it possible to manage better the early marketing of new medicines.

5. Post-approval plans should be set out clearly in the regulatory dossier

The need for communication about PACs is two-way and there was concern that companies are not being sufficiently pro-active in discussing risk management and the need for further studies in regulatory dossiers.

One way to address this would be to amend the ICH *Common Technical Document* format for applications to include a specific section on 'post-approval plans' in which the company could set out its proposals for risk management and on-going studies in the post-authorisation period.

- This would allow discussion of post approval plans to be addressed formally from the outset of the assessment rather than arising at a late stage in the discussion;

- The discussion in the application could include proposals for any public statements that might be made once the product is authorised.

In relation to the regulatory dossier, there was discussion of the need to move away from the concept that there is a constant need to increase the number of studies and amount of data on safety studies and risk management. What are needed are 'leaner but better' dossiers.

6. Greater transparency would improve confidence in early authorisations

Any move towards increased use of conditional authorisations and PACs, to reduce the delay in making new therapies available to patients, needs to be accompanied by increased transparency. It was recommended that there needs to be a way of informing both physicians and patients that certain new products are still subject to on-going studies. One possibility is an international symbol or icon that would appear in the information about new products that would signal that there was 'work in progress' on the product as a condition of its authorisation. The icon would be accompanied by a reference to an Internet site where further information could be found.

- The analogy was drawn with the 'black triangle' system used in the UK to inform physicians of special safety reporting requirements for new drugs in the first years of marketing;
- It would be important to brief the media on the use and meaning of the symbol;
- The website information would not be expected to give full details of the PACs but would act as an alert and provide sufficient information to help the physician and patient make a better-informed benefit-risk decision;
- The objective would not only be to inform but also to engage the interest of both doctor and patient and thus encourage active feedback into EHR databases and other reporting systems;
- Consideration should be given to allowing companies to include statements in their product literature once additional studies have been successfully completed.

7. Better education on medicines and risk is needed

Concern was expressed about the continuing failure, on the part of both industry and regulators to communicate with other stakeholders about the inherent risks of all medicines and the continual need to balance both benefit and risk. It was suggested that a future Workshop could address the question of best practices in communication by regulators and industry, when providing information to the public and, in particular, the media.

- The Workshop would provide an opportunity to discuss the potential for developing new partnerships with academia;
- The specialised scientific press are often as much to blame as the lay press for negative or unbalanced reporting of pharmaceutical issues;
- The positive role of patient advocacy groups was acknowledged in helping to communicate with patients on therapeutic issues and to motivate participation in clinical trials;
- It was noted that EMEA have a special working party with patient groups and that patients' representatives participate in the Management Board, the Orphan Medicines committee and that they will be involved in the revised scientific advice procedures.

OTHER DISCUSSION POINTS

Penalties for non-compliance

The problem and scale of apparent non-compliance with PACs was recognised but caution was recommended on the question of penalties:

- Hastily agreed PACs may prove to be impractical to fulfil (problems with patient recruitment and the willingness of investigators to participate);
- Conditions can change quickly in certain fields (e.g., HIV treatment) which can make studies redundant or even unethical;
- Withdrawal of an authorisation, except on safety grounds is rarely an option. There will always be patients that have benefited and continue to need the medicine.

Financial and IP implications of earlier marketing

Earlier marketing through the use of conditional approvals and limitations on patient populations could have implications for the benefits gained through data exclusivity and supplementary protection certificates (SPCs).

It was suggested that a financial model should be developed to look at the implications of earlier and more controlled product launches in terms of the earlier revenue stream vs. smaller initial patient populations and the reduction in the data exclusivity period once full marketing is achieved.

On the question of whether increased use of PACs would reduce development times, the conclusion was that it would not. Although earlier marketing – and hence earlier revenue flow – would be achieved some of the workload is shifted to Phase IV and the overall development workload may, in fact, be increased.

POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS

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SECTION 3: SUMMARY REPORT OF THE WORKSHOP PRESENTATIONS

PROGRAMME

SESSION 1: POST-APPROVAL COMMITMENTS – APPROPRIATE REGULATORY TOOL IN TODAY'S ENVIRONMENT OR A REFLECTION OF INADEQUATE DEVELOPMENT?

Chairman:	Professor Sir Alasdair Breckenridge, <i>Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK</i>	Page 1
Limitations in New Drug Applications that lead to Regulators setting Post-Approval Commitments	Dr Armando Oliva, <i>Associate Director for Policy, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration (FDA), USA</i>	1
Do today's post-approval commitments and conditional authorisation systems fulfil a useful role?	Michael Doherty, <i>Head of Global PDR, F Hoffmann-La Roche Ltd, Switzerland</i>	5
What are the expectations and experiences of post-approval commitments or conditional authorisations in Japan?	Dr Osamu Doi, <i>Senior Executive Director, Pharmaceuticals and Medical Device Agency, Japan</i>	10
Current industry perspective on the impact of conditions and commitments attached to authorisations	Dr Mayu Hirako, <i>Senior Analyst, CMR International Institute</i>	15
Key issues for companies in managing post-approval commitments	Dr Edmund P Harrigan, <i>Senior VP, Worldwide Regulatory Affairs and Quality Assurance, Pfizer Inc., USA</i>	19
Are current procedures robust enough to provide adequate safeguards for detecting unforeseen safety issues?	Dr Hugh Tilson, <i>Clinical Professor of Epidemiology and Health Policy, School of Public Health, University of North Carolina, USA</i>	23

SESSION 2: CAN POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS BE USED TO IMPROVE PATIENT ACCESS AND ENSURE LONG TERM SAFETY OF IMPORTANT NEW MEDICINES?

Chairman	Professor Robert Peterson, <i>Associate Head of Pediatrics, Dept of Pediatrics, British Columbia's Children's Hospital, Canada</i>	
Use of early access mechanisms for new medicines – are these a model for the future?	Dr Debra Barker, <i>Regional Medical Director, Novartis Pharmaceuticals Corporation, USA</i>	28
The role of specific obligations and conditional authorisations in supporting innovation? - EU regulatory view point	Dr Francesco Pignatti, <i>Pre-Authorisation of Medicines for Human Use, European Medicines Agency (EMEA)</i>	32
What role should post-approval commitments and conditional authorisations play in a regulatory environment that supports innovation? - Industry Viewpoint	Dr Don Stribling, <i>Vice President and Head of Global Regulatory, AstraZeneca Pharmaceuticals, UK</i>	37

SESSION 3: SYNDICATE DISCUSSIONS

Reported in Section 2 of this report

CHAIRMAN'S INTRODUCTION

Professor Sir Alasdair Breckenridge

Chairman, Medicines and Healthcare Products Regulatory Agency (MHRA), UK

Opening the Workshop, Professor Alasdair Breckenridge suggested that, in the field of regulations, today there can be few more appropriate and controversial topics than post approval commitments and conditional authorisations. When a medicine receives regulatory approval the amount of data available, particularly on clinical safety, is usually quite limited and it is normal for the regulators to enter into discussion with the sponsor and agree a programme of post-marketing safety studies.

One of the difficult issues is that, although both parties may agree with this programme, up to now the regulator has had very limited power to enforce its completion. Professor Breckenridge illustrated this point by reference to a recent well-documented altercation, in the US, over a major product authorised in 1997 with six post-marketing studies agreed, where it was reported that, by 2003, none had been started. In the UK, the MHRA had recently carried out a small survey, as yet unpublished, on the status of post approval commitments (PACs) This found that, since 1990 post-marketing safety studies had been agreed at the time of licensing in 115 instances. By the end of 2004 only one third of these had been completed a third was incomplete and the remainder had not yet been started.

Professor Breckenridge referred to the new European regulations to be implemented in November 2005, which would require applications to be accompanied by a detailed description of the risk management and pharmacovigilance system that the applicant intends to implement. This, he felt, was an important step forward but, as ever, 'the devil was in the detail' and it was not yet clear how the commitments would be monitored and enforced.

He looked forward to the discussions during the Workshop and syndicate sessions that would be addressing some of these difficult issues.

LIMITATIONS IN NEW DRUG APPLICATIONS THAT LEAD TO REGULATORS SETTING POST-APPROVAL COMMITMENTS

Dr Armando Oliva

Associate Director for Policy, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration (FDA), USA

Dr Armando Oliva provided an overview of the way in which post-approval commitments – known in the US as post-marketing commitments (PMCs) – are agreed and followed up under FDA procedures. His presentation discussed the two types of PMCs in the US:

- **Required PMCs**, mandated by law and regulation; and
- **Mutually Agreed-upon PMCs**, agreed between FDA and the applicant.

History and current situation

PMCs have been around a long time, Dr Oliva said, although they were probably better known, in the past, as 'Phase IV commitments'. The landscape changed significantly in the US in 1997, however, when the Food and Drug Administration Modernization Act (FDAMA) was passed by Congress. Among many other new provisions, this Act requires companies to report annually to FDA on their progress in fulfilling post-marketing commitments and, furthermore, FDA was given new responsibilities to make annual reports to Congress and

the public on the status of commitments. The report for FY 2004 could be found on the FDA website¹

Dr Oliva, however, pointed out that FDAMA did not give FDA any authority to *require* applicants to conform to their PMCs. The idea was that making information on compliance publicly available would increase the likelihood that the studies would be performed. FDA has set up a detailed tracking system to follow-up all PMCs and the information is held in a publicly available and searchable database on the FDA web site: (<http://www.fda.gov/cder/pmc>).

Required PMCs

There are three types of Required PMCs:

- Confirmatory studies for products approved under the **accelerated approval rule (Subpart H)**
- Confirmatory studies for products approved under the **Animal Efficacy Rule**
- Paediatric studies required under the **Pediatric Research Equity Act (PREA)** but deferred by FDA during pre-marketing development

Dr Oliva explained each type in more detail.

Accelerated approval rule (Subpart H)

This is part of the Code of Federal Regulations reference 21 CFR 314.510². This regulation applies to those new drugs that are intended to treat serious and life-threatening illnesses and that are approved based on a surrogate endpoint deemed reasonably likely to predict clinical benefit. The purpose is to try to shorten the development time of important new therapeutics. This recognises that, at the time of the conditional approval, not all the necessary information is available but the 'trade-off' is that patients will have access to the new treatment more quickly.

Accelerated Approval Rule: Example

Tenofovir

- Approved under Subpart H for combination therapy against HIV-1 infection
- Surrogate endpoint: 24-week viral load
- PMC: confirmatory studies using a validated surrogate (48-week viral load)
- Status: Ongoing

Information from the FDA database

The regulation goes on to say that the applicant must study the drug further:

- to verify and describe its true clinical benefit;
- to address any uncertainty as to the relation of the surrogate endpoint to clinical benefit.

The confirmatory studies should generally be underway at the time of approval, and Dr Oliva said that reviewers would advise companies to ensure that such studies were in progress in order to secure the conditional approval under the regulation. The regulation also states that the applicant shall carry out these studies with due diligence.

He referred to Tenofovir (see Box) as an example of a product approved under Subpart H.

Animal Efficacy Rule

This is a relatively new rule³ and was developed as part of counter terrorism initiatives. It applies to new drugs intended to ameliorate or prevent serious or life-threatening conditions from toxic biological, chemical, radiological, or nuclear substances. In this setting it allows

¹ Report on the Performance of Drug and Biologic Firms in Conducting Post-marketing Commitment Studies: Availability, Federal Register Vol.70, No.33, Friday, February 18, 2005/Notices: <http://www.fda.gov/OHRMS/DOCKETS/98fr/05-3221.pdf>

² Web reference: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.510>

³ 21 CFR 314.600:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.9>

the agency to approve the product in situations where human studies are not ethical or feasible.

The rule says that post-marketing studies are required:

- To verify and describe the drug's clinical benefit
- To assess its safety when used as indicated

but it also recognises that these confirmatory studies can only be conducted, in practice, if an actual contingency were to arise.

Dr Oliva provided the example (see Box) of pyridostigmine bromide that has been available for many years for the treatment of myasthenia gravis but was approved for new indications under the animal efficacy rule. The company has been asked to provide a protocol that would be followed should a situation ever arise were the data could be collected.

Animal efficacy rule: Example

Pyridostigmine Bromide

- Approved under the Animal Efficacy Rule for the prophylaxis against the lethal effects of soman nerve agent.
- PMC: confirmatory studies in the field when feasible and ethical
- Status: Pending

Information from the FDA database

Pediatric Research Equity Act (PREA)

The third examples of required PMCs are those conducted under the Pediatric Research Equity Act, which was enacted by Congress in December 2003. This amends the Food Drug and Cosmetic Act from which FDA derives its authority. It requires the collection of paediatric data for new drugs and was enacted to address the need for more information about the safe and effective use of drugs in children.

Under PREA, all new marketing applications as well as existing applications that meet certain conditions must contain a paediatric assessment. Dr Oliva explained, however, that FDA can grant a waiver or deferral of such studies.

- Waivers are granted when the study of the drug in children is not appropriate, for example when the disease, such as Alzheimer's does not exist in children.
- Deferrals into the post-marketing stage are allowed when it is agreed that the studies can wait.

Deferral of paediatric studies: Example

Adalimumab

- Approved in adults with moderate to severe rheumatoid arthritis
- PMC: efficacy study in children with juvenile rheumatoid arthritis (required under PREA)
- Status: Pending

Information from the FDA database

The law states that if the drug is ready for approval in adults before the paediatric studies are completed the deferral can and should be granted, the idea being that the absence of paediatric studies should not block the availability of a safe and effective drug for adults.

Dr Oliva expressed the view that the Act gives the agency a substantial degree of leeway and flexibility in deciding when paediatric studies can be deferred and FDA invites the companies to provide reasoned arguments why paediatric studies could be deferred, for example the development of a paediatric formula is not yet available. Again, he provided an example from the FDA database (see box).

Summarising the thinking behind this category of PMCs, Dr Oliva said that if the studies were required *before* approval there would be products that could never be approved (in the case of products for bio-warfare and disasters) and products where there would be an inappropriate delay to the approval of a valuable new medicine.

Agreed-upon Post-marketing Commitments

The second type of commitment, Dr Oliva noted, is where much of the controversy arises. These are studies that are not specifically required under any existing laws or regulations but they are mutually agreed between FDA and the applicant, prior to approval. Under current practices the applicant agrees to the commitments in writing and this triggers an entry into

the FDA database and the start of the tracking and reporting process. The agreement is also documented in the approval letter.

He summarised FDA policy for Agreed-upon PMCs:

- FDA should request a PMC agreement if the results would enhance the safe and/or effective use of the drug (i.e., "need to know")
- FDA should not request a PMC agreement if the results have scientific interest but are unlikely to impact the safe and/or effective use of the drug. (i.e., "nice to know")

Dr Oliva recognised the tremendous amount of leverage that the agency has to obtain one of these agreements prior to approval and FDA are discouraging any tendency, among its reviewers, to request additional studies on a 'nice to know' basis. Controversy and difficulties can, however, arise when determining whether a study is deemed 'need to know'.

He provided an example (see box), again from the anti-HIV drug Tenofovir, of requests for interaction studies that were needed for commonly administered drugs in HIV-positive patients.

**Agreed-upon PMCs: Example
Tenofovir**

- Approved for combination therapy against HIV-1 infection
 - PMC: drug interaction studies with didanosine, methadone, oral contraceptives, adefovir (i.e., commonly co-administered drugs)
- Rationale: enhance safe use of the drug

Inappropriate PMC requests

In conclusion, Dr Oliva provides two (anonymised) examples from the database that, in his opinion, could be regarded as inappropriate:

- A study to compare the efficacy of newly approved drug A, versus a competitor, drug B, currently approved and on the market:
 - Although many might agree that this type of information is 'needed' to make better-informed clinical decisions in prescribing, the FDA lacks the authority to require comparative efficacy studies.
- A study to delineate the renal transport pathway of a drug:
 - It is unclear how the results of such a study will impact the safe and effective use of the new drug.

DISCUSSION

Naming and shaming: Dr Oliva was asked whether the report to Congress was a case of "naming and shaming" in order to identify companies that were not fulfilling their obligations. He replied that, whilst this was the intention, the report to Congress is a very 'high level' one that summarises data on the numbers fulfilled and delayed. The raw data are, however, available in the FDA database on the website.

Unfulfilled commitments: The legal basis for the 'Required PMCs' was raised: Whether it is a legal requirement for FDA to include the commitment in the approval or a legal requirement for the company to carry out the studies. Dr Oliva agreed that this had been the subject of much internal debate. CDER's interpretation is that companies are *required* to conduct these studies and if they fail to do so they are in violation of the statute and can be prosecuted. This, however, raises the question of the penalty for not fulfilling the requirements and lawyers and senior management have always been cautious on the question of removing the product from the market.

Asked if the political climate might change in the light of recent events, Dr Oliva agreed that there was a heightened focus on post-marketing safety. With the development of the new Drug Safety Board and one or two Bills being now in Congress, there was discussion of whether a new authority might be necessary for the post-marketing phase.

'Need to know' studies: A participant pointed out that discussions of additional studies were often carried out within a very short timeframe during which details about the number, size and scope of additional studies are hurriedly determined. Dr Oliva was asked whether it would be better for FDA to specify the 'need to know' scientific question and allow the company to decide how the answer should be delivered. Whilst agreeing, in principle, Dr Oliva stressed that FDA reviewers needed to be involved in discussions of study design as they would later have to decide whether the data were adequate.

Public reporting: There was a comment that the report on the status of outstanding PMCs in the FDA database does not appear to have a separate category for cases where the studies have been completed and submitted but have not yet been reviewed by the agency. These cases are therefore categorised along with the pending cases where obligations have not yet been fulfilled by the company.

DO TODAY'S POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS SERVE A USEFUL PURPOSE?

Michael Doherty

Head of Global PDR, F Hoffmann-La Roche Ltd, Switzerland

Michael Doherty presented an industry viewpoint on the role and usefulness of PACs and conditional authorisations, calling on the experience of Roche, particularly in the US and EU. He explained that he would not be discussing experience in Japan since Roche operations in that country are carried out through their partner company, Chugai.

Mr Doherty had been asked to address the question: 'Are the systems currently in place in the ICH regions adding value to the overall development and risk management plans for new medicines?' The answer, he said, was clearly 'yes' but there was considerable room for improvement in many areas.

Added value of PACs

Risk can be identified very early in the development of a new medicine, allowing post-approval risk management plans to be drawn up in anticipation of the environment into which the product will eventually be released. A critical difference between the US and EU systems, Mr Doherty suggested, is the ability to discuss such risk management plans at an early stage, with FDA. Opportunities to discuss early-identified risks are much more limited in Europe although he was aware that EMEA was focusing on the need for improvements in this area.

PACs also fulfil a role in the evaluation of the type of risk that cannot be assessed in the scale of studies carried out in Phase III. Such risks require a much more epidemiological approach that can only be found in the larger number of patients, after marketing. They are a means of obtaining additional, relevant data that can help in the assessment of benefit-risk, without preventing the approval of the medicine.

Mr Doherty stressed that no added value is obtained from PACs that impose excessive demands that will not improve the label or the benefit-risk. He also rejected the concept of 'checklist' PACs where one company is assigned a PAC because a previous company had been asked to carry it out, rather than through scientific logic.

Current situation: US and EU

Mr Doherty reviewed, briefly, the procedures in the US and Europe that were described in more detail in other presentations⁴. He contrasted the US process, where procedures for

⁴ US procedures: Dr Armando Oliva, CDER, FDA, Section 3 page 1 of this report

EU procedures: Dr Francesco Pignatti, EMEA, Section 3 page 32 of this report

priority review and accelerated approvals (with associated PACs) were well-defined, with the situation in the EU where there are provisions for obtaining an 'accelerated opinion' but the process is not highly accessible or transparent. These fast reviews are not as widely available as the accelerated approval in the US. Furthermore, the company is not informed, until day 120 of the review, whether an accelerated opinion will be given. The accelerated opinion will, however, be replaced by the new provisions for conditional approvals, to be implemented from 20 November 2005, in the centralised process.

Mr Doherty emphasised that US and EU measures to expedite the approval of new medicines were almost always associated with PACs.

Trends in PACs

Mr Doherty presented some statistics on PACs from the US (Box 1). He expressed surprise that the overall levels of PACs were not nearer to 100% as most applications appeared to be associated with some form of PAC. As shown, the type of post-approval studies ranged from simple pharmacokinetic investigations to full Phase III-type studies.

He was also somewhat surprised that the figure for requesting risk management programmes was not considerably higher than 10%. He had also assumed, from his company's experience, that this type of programme – particularly education of prescribers and patients – was growing at a much faster rate than appears from the statistics.

In view of recent events, Mr Doherty also felt that requirements for QT prolongation studies were less frequent than might be expected but commented that these might often be required pre-authorisation.

Box 1

US Post Approval Commitments:

2004 NMEs

- 74% (23/31) of NMEs approved in 2004 had PACs
 - 2003 Cohort: 86% (18/21) had PACs
- Lower rate of PACs in 2004 maybe reflective of products approved
 - Example: 2 products approved were for nutritional adjunct products (Omacor, Nutrestore)
- PACs specified in approval letters for the 2004-approved NMEs range from a simple pharmacokinetic study to randomized and double blind efficacy studies

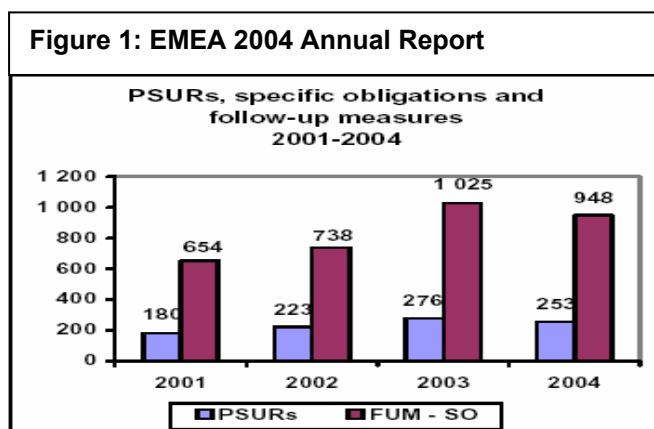
US Trend Analysis of PACs: 2004 NMEs

- Pediatric studies to fulfill the Pediatric Research Equity Act (~30%)
- Formal controlled double blind clinical studies to assess safety and efficacy: (5/21: ~24%)
- Risk Management Programs/Tools (2/21: ~10%)
- QT prolongation studies (2/21: ~10%)
- Other safety studies (2/21: ~10%)
 - Renal Impairment, etc.

Status of Post Approval Commitments in the US

- Number of products with open Phase IV commitments dropped from 570 in 2003 to 191 in 2004
- 13% of Phase IV studies were completed in 2004
 - this is an improvement over the 2003 rate of 8%
- Overall, the FDA's Phase IV Commitment Website initiative has seen improvements in the number of open phase IV commitments

Figure 1: EMEA 2004 Annual Report



Status of commitments

The statistics showing a drop in the number of outstanding commitments was less surprising, Mr Doherty suggested. Companies are now addressing the issue more rigorously and, speaking for Roche, a high-level undertaking had been made in the management of the company to ensure that commitments are tracked and honoured.

Turning to Europe, Mr Doherty referred to data from the EMEA 2004

Annual Report (Figure 1) that shows the increase in the numbers of specific obligations and follow-up measures – EU terminology for PACs. There are large numbers of such obligations, running at about 1,000 per year.

Roche Experience with PACs

Mr Doherty discussed five specific examples from his company's recent experience where, with some exceptions, the commitments were generally of high value.

Example 1, saquinavir, illustrates that even with Type 2 variations – a smaller line extension-type application, PACs will still be applied. In this case there was a requirement for some further drug-drug interaction (DDI) studies which revealed a major interaction with HIV triple-therapy, resulting in hepatitis in some individuals. Roche reacted with an urgent amendment to the product literature and a global 'Dear Doctor' letter that was dispatched the day after speaking to the *Rapporteur*.

Example 2: Fuzeon

- Exceptional Circumstances Approval EU. Accelerated Approval USA
- Specific obligations and follow-up measures mainly related to follow on clinical data (longer duration of use), paediatrics and increasing the understanding of the safety profile with additional preclinical and clinical studies.
- US PACs similar to EU.
- Overall PACs justified and related to clinical findings or requirements to provide longer term clinical data as understood from available guidance.

Example 1: saquinavir

- Type 2 variation to include ritonavir boosted regimen on the label
- EU & US PACs included extensive DDI studies, final reports, follow up data and safety data
- DDI study with Rifampicin showed major interaction of triple therapy
- Resulted in urgent SPC amendment and Dear Dr Letter.

Example 2, Fuzeon, was the first of the fusion inhibitors preventing the HIV virus from fusing with, and entering the cell. This obtained approval under 'exceptional circumstances' in the EU, with an accelerated opinion and was also given accelerated approval in the US. It was a case where the EU and US applications were running in parallel and it was possible to talk to the agencies more or less at the same time. The PACs were the same for the EU and US and were felt, by the company, to be sound and justifiable. Mr Doherty pointed to this as an example of how the system should work.

Example 3, Tarceva, an anti-cancer drug, is a first-in-class HER 1/EGFR (epidermal growth factor receptor) inhibitor that has only been approved in the US, following a priority review. The PAC to carry out a study on expression of the EGF receptor and mutations of the receptor did not come out of Roche data but was related to a publication on Iressa (gefitinib) which suggested an association between EGFR mutations and response in a very small number of patients. Roche data did not show this, but the study had to be carried out, although the label was not affected.

Example 4: Pegasys

- Having demonstrated that 24 weeks therapy is as efficacious as 48 weeks in genotype 2/3 patients, FDA insisted that we look at 16 weeks also.
- 1500 patients, marginal gain

Example 3: Tarceva

- US fast track (priority) review
- PACs included 2 phase 3 studies (one following platinum based therapy and one to look at impact of EGFR expression) and 4 commitments on PK.
- Substantial commitments of global applicability

In the case of Example 4, Pegasys, an alpha interferon, Mr Doherty questioned whether the PAC was of great value. Approval was granted on the basis of demonstrating the efficacy of 24 week therapy and the company was asked to look at 16 weeks. Such studies, he commented, represent a major commitment of resources.

Example 5: Avastin

- Approved through Centralised Procedure in January 2005.
- Follow-up measures requested by the CHMP mainly related to follow on clinical data and pharmaceutical aspects.
- Over 25% of follow-up measures have been fulfilled within 3 months of approval.
- The majority of ongoing commitments are related to long-term clinical follow-up data.

Example 5, the anti-cancer product Avestin was, on the other hand, an example where the PACs assigned by the EU Committee for Human Medicinal Products (CHMP) were felt to be reasonable and justified. Over 25% of the immediate clinical and pharmaceutical follow-up data could be provided within 3 months whilst the majority of the remainder related to long-term clinical studies.

Mr Doherty provided statistics for Roche's on-going PACs at the end of 2004 for the EU, US and rest of the world, which totalled 200 and represent a substantial burden of work.

Conditional approvals

In the decade 1994-2004, Roche had experience of four priority reviews in the US, all of which were completed within PDUFA time-frames. Mr Doherty commented that he believed that priority review in the US is 'as fast as you can go'. The questions and interactions relating to PACs are often in the last three weeks of the review and it is almost impossible to carry out a meaningful feasibility determination within that timeframe. This can result in making commitments to studies that do not, later, prove to be achievable because investigators are reluctant to repeat the study or because science in the area has moved on. He felt strongly that, once the outstanding questions had been identified, there should be greater flexibility in determining the details of how the answers should be obtained.

In the EU, Roche have had experience of two authorisations granted under 'exceptional circumstances', both for HIV products. Mr Doherty noted that new regulations for 'conditional authorisations' would be implemented in November 2005 but felt that greater clarification is needed on the types of product that would qualify for accelerated approval, which, he felt, should be much broader than at present.

He also expressed concern about the procedures for an annual review of conditional authorisations and the associated PACs and felt that it was important to avoid a situation where new requirements were added at each review. The additional studies required to convert from a conditional to a full authorisation should be finalised at the time of the CHMP opinion. They should be based on a benefit-risk assessment for the proposed indications and not be seen as an opportunity for the CHMP to 'drive the entire lifecycle of the product'.

Current and future value of PACs

The primary and most important function of PACs is that they can facilitate early approval of new medicines and provide an opportunity to have the scientific questions answered in the longer term. Mr Doherty also believed that a sound programme of follow-up studies engenders a culture, within companies, of a continual obligation to manage products and their risks.

Looking to the future, Mr Doherty stressed the need for an earlier understanding of risk, leading to dialogue with reviewers at the end of Phase II on future management of risk. Whilst this is currently encouraged in the US, similar facilities are not available within the EU systems.

The US system allows for a continuum of advice and interaction with the FDA, with the same assessment team working with the company throughout the IND process to submission of the NDA and determination of post-approval commitments. Mr Doherty expressed concern that the new clinical trials directive in the EU offers no such continuum, with the process for clinical trial assessment being separated from marketing authorisation procedures and the associated scientific advice. He hoped that the EU 'Road Map' discussions would be addressing this critical issue.

Summary

In conclusion, Mr Doherty summarised the following points for ensuring that PACs continue to serve a key role in providing valuable post marketing data, thus enabling approval while the commitment is ongoing:

- Critical long-term data should be agreed at end of Phase II, and ongoing at time of review;
- PACs need to be targeted and focused to be of value;
- Conditional approval in the EU will facilitate availability of medicines;
- Accelerated approval in the EU must be developed for a wider array of indications;
- Scientific advice enhancements will improve the process.

DISCUSSION

Scientific advice in the EU: Thomas Lönngren, Executive Director, EMEA, was invited to comment on the concerns expressed about the opportunities to obtain Scientific Advice relating to PACs in the EU. He confirmed that there was agreement that the Scientific Advice procedures would be revised and that a consultation document would be issued in time for revisions to enter into force at the time of the implementation of the new EU pharmaceutical legislation in November 2005. One proposal is for the scope of Scientific Advice to be broadened to include advice on risk management plans.

Resource implications of PACs: Mr Doherty was asked if the cost of post approval commitments had been measured in terms of FTEs and percentage of the R&D budget. He replied that the information had not been readily available but his personal estimate, based on the number and scope of commitments was that it could be equal or greater than the whole drug development programme of 2 or 3 NCEs.

Inappropriate PACs: Asked how often the company was requested to undertake studies that, in their opinion, would not produce any benefit to either the use or labeling of the drug, Mr Doherty felt that the large majority of PACs had some added value. Exceptions had been highlighted in the presentation but, in most cases, it had been possible to negotiate with the agencies to ensure that the additional work was of value.

Major Studies as PACs: Mr Doherty was asked about one of the post-marketing commitments for a formal double-blind clinical trial to assess safety and efficacy, which would surely have been required before an authorisation was agreed. He explained that this was an example where the commitment was focused on the life-cycle of the product in a broader area than the actual authorisation. For example, an application might be submitted on a broad patient population but, through the negotiations, the indications are narrowed down to a smaller population. The agency, however, might feel that the product will be more widely used once on the market and would ask for additional confirmatory studies.

EXPECTATIONS AND EXPERIENCES OF POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS IN JAPAN

Dr Osamu Doi

Senior Executive Director, Pharmaceuticals and Medical Device Agency, Japan

In his opening remarks, Dr Osamu Doi said that, as one of the founders of ICH, he had long been emphasising the importance of faster development of innovative new drugs and advocating that such medicines be made available to patients of the world with a minimum of delay. When one looks at recent global events surrounding the safety of medicines, however, it is clear that the emphasis is primarily on safety, rather than on maintaining the balance between safety and efficacy. Consequent delays in the development and review of medicines appear inevitable and Dr Doi expressed his concern that the tendency to require massive long-term clinical studies to be conducted in the drug development phase may become yet stronger. Against this global background, it was particularly timely that the CMR International Institute should examine the topic of post-approval commitments and conditional authorisations.

Requirements in Japan

Complete count survey

In Japan there is a requirement for a 'Complete Count Survey' (Box 1) that has several purposes but is, primarily, to identify rare ADRs which cannot be detected during the drug development phase. In some cases the survey may be designed to focus on a particular ADR, seen in the clinical trials, where the frequency needs to be verified.

The Survey is also conducted to study the impact that the drug may have in specific patient populations, such as paediatric patients, patients with the loss of hepatic or renal function, or the elderly, after the drug is marketed. It is often difficult to study such effects during the development phase.

When a product is authorised for marketing on the basis of a surrogate endpoint evaluation, the verification of efficacy would also be covered in the survey. Furthermore, since information obtained during the drug development phase is from a very limited group

of patients where the drug is used under restricted conditions, the information from medical centres, where the drug is administered to patients with various background factors, becomes extremely important.

Complete count survey

Obligation to collect all information on patients using the drug product over a certain period of time after approval, or until a certain number of the cases has been collected after approval

- Detection of rare ADRs
- Detection of ADR occurrence frequency
- Collection of information on a group of specific patients
- Additional verification of efficacy
- Verification of efficacy on true endpoint
- Detection of problems in clinical use

Box 2

Post-marketing clinical studies

- Conducting those clinical studies after marketing, which were not performed adequately at the approval stage
- Conducting clinical studies, after marketing, to expand efficacy claims for a group of specified patients (e.g., paediatric group)
- Verification of the efficacy and safety of combination therapies
- Conducting clinical trials, after marketing, to revalidate the presence/absence of ethnic difference factors
- Conducting responder/non-responder analysis using pharmacogenomics

Post-marketing clinical studies

The second type of post-approval commitment Dr Doi discussed was the obligation to carry out post-marketing clinical studies (Box 2). It might be supposed, he said, that all necessary information should be obtained during the pre-application stage and form part of the data on which the authorisation decision is based, but this would be a very long process. The extent to which information should be obtained during the development phase or may be deferred to

the post-marketing stage varies for each product and needs to be decided on a case-by-case basis.

Dr Doi emphasised the importance of having the flexibility to make these decisions on a case-by-case basis in order to allow the pre-marketing stage to be shorter for some products. This must, however, be coupled with strict post-marketing safety controls.

Usage limitation

One type of conditional authorisation limits the marketing scope of the product to certain medical institutions or doctors only, for a specified period of time after the approval (Box 3).

The purpose is to limit the range of initial use of the medicine to medical practices with appropriate expertise in the particular field or readiness to deal with potential emergencies. Dr Doi pointed out that such limitations also help to slow the rapid expansion of use of the product before the company has obtained the necessary additional information from experience in specialised medical institutions.

Legal Background

The legal basis for requiring PACs and issuing conditional authorisations is contained in the Pharmaceutical Affairs Law (PAL) that was amended in April 2005. The PAL includes the following provisions:

- Conditions or expiry dates may be appended to the approval and may be subject to change;
- Conditions or expiry dates for the approval shall be confined to the minimum required to prevent the occurrence of hazards to the public health and hygiene;
- Conditions or expiry dates for the approval shall not impose improper obligations on the person intending to obtain the approval.

Before the amendments to the Act there were no provisions to deal with non-compliance with the conditions attached to an authorisation. Under the April 2005 amendments, however, the MHLW is empowered to order the revocation of an approval, or make partial changes to an approval, in cases where companies do not comply with the commitments and conditions attached to an authorisation.

Early Post-marketing Phase Vigilance (EPPV)

Japan was the first country to make special reporting requirements for new drug products a legal obligation. Dr Doi explained that Early Post-marketing Phase Vigilance (EPPV) was implemented in 2001 under a Ministry of Health, Labour and Welfare (MHLW) Ordinance. The objectives are to:

- Ensure that the necessary information on proper use of new drug products is provided to medical institutions two weeks prior to the delivery of the products to the institutions;
- Request that medical institutions expeditiously report on the occurrence of serious ADRs;
- Repeatedly request that medical institutions use new drug products properly and report on the occurrence of serious ADRs, during the 6 months after delivery of the products;

The ordinance underlines the fundamental duty of medical institutions to disseminate information on proper use of products within their organisation and to cooperate with pharmaceutical companies in collecting information on serious ADRs, under the Pharmaceutical Affairs Law.

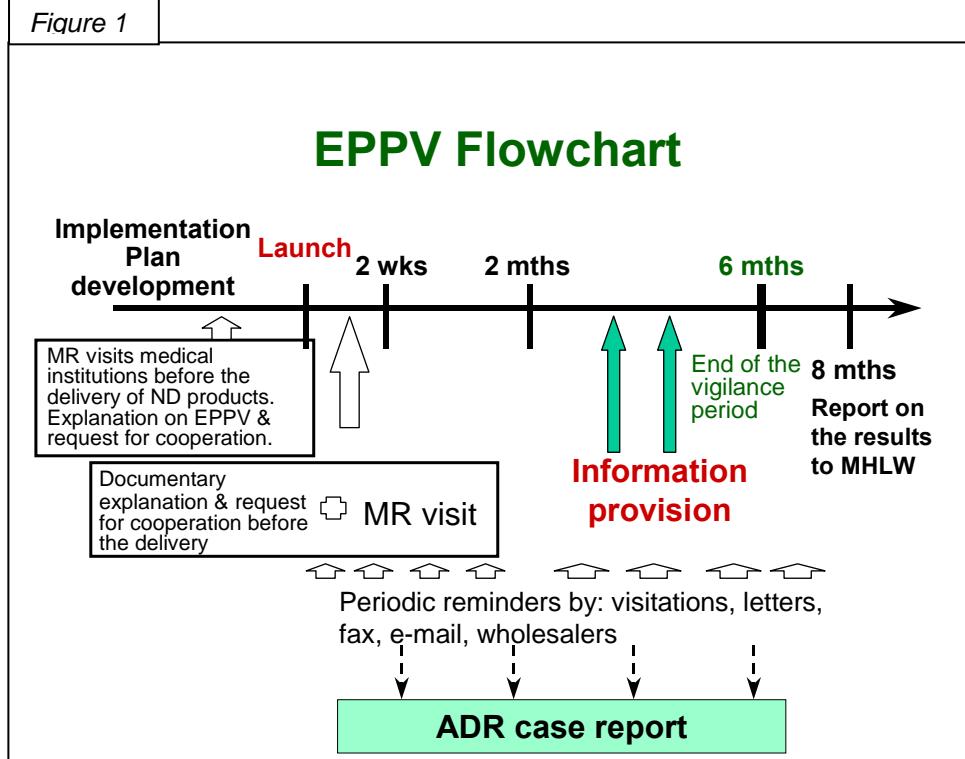
Box 3

Usage limitation

Limitation on use of the drug product to specified medical institutions or doctors only, for a specified period of time after approval. This may be necessary for the following reasons:

- The use requires high-expertise and urgent responsiveness
- To collect high quality patient information after marketing of the drug
- To prevent risks that may occur due to rapid expansion of drug use after approval
- To prevent the drug from being used inappropriately

Figure 1



EPPV is a post-approval commitment that is applied, not to the individual product, but uniformly to all new drugs.

The flowchart for the EPPV procedure is shown in *Figure 1*. Dr Doi explained that it is the companies' responsibility to ensure that, before new drug products are delivered to medical institutions, data obtained during the development phases is provided with information on the proper use of the new products. The company is also responsible for issuing repeated reminders on the need to report all serious ADRs expeditiously. The process, Dr Doi said, is intended to ensure that medical institutions do not start to administer new products without a full understanding of their use.

Impact of conditional authorisations

Dr Doi felt that some companies might have a somewhat negative impression of conditional authorisations but he believed they should, in fact be regarded positively. Investigations carried in a 'real-world' population in the post-authorisation phase can result in:

- A better understanding of safety:
 - Validation of safety in chronic administration and in specific patient groups;
 - Greater awareness of rare and unusual ADRs and better information on the incidence of known ADRs as a result of increased patient numbers;
 - Information on interactions with concomitant medication
- Enhancement of efficacy data:
 - Validation of true-endpoints based on chronic administration data, for products authorised on the basis of surrogate markers;
 - Confirmation of efficacy in specific patient populations, e.g., children, without delaying the application while paediatric data is collected;
 - Obtaining data to support extended efficacy claims and use in combination therapy, through careful study of results from the post-marketing phase.

Shorter development times

Another potential effect of the appropriate use of conditional authorisations was that it offered the potential of shortening development times for innovative and much-needed medicines. Some might argue that it is preferable to conduct all the necessary studies in the development phase but flexibility is needed. Well-founded decisions about the studies that must be carried out in the development phase and those that can be deferred until after marketing are of great value to both companies and regulatory authorities. Not only can access to new medicines be achieved more rapidly but such flexibility acts as an incentive to industry to innovate.

The Issues

Dr Doi discussed some of the issues that arise from the use of PACs and conditional authorisations to regulate and monitor the use of new medicines in the post-authorisation phase:

- The scale of the launch and market expansion for new drugs immediately after authorisation may be curtailed:
 - This may pose commercial problems for companies but provides safeguards for the authorities if early marketing has been allowed on the basis of limited pre-authorisation data;
- PACs can be costly for companies and time consuming for both industry and regulators, depending upon the contents of the post-marketing surveillance and tests to be conducted:
 - This emphasises the importance of considering all commitments on a case-by-case basis;
- The development of useful new drugs or the supply of those drugs to medical services may be inhibited if commitments are appended without careful consideration of the implications:
 - Safety must be given the highest priority
- Restricting the availability of new medicines to specified medical institutions means that there may be some patients unable to enjoy the benefits of the products;
- Requirements for clinical trial-level studies to be conducted before a full authorisation is granted may also cause delays in the development of other new medicines.

Status report

Dr Doi presented information on the current status of PACs and conditional approvals in Japan, as shown in Boxes 4 and 5.

He pointed out that there is also a system for dealing with orphan medicines where data from the clinical phase is limited. Approvals for orphan medicines are always issued as conditional authorisations with PACs. Follow-up is required for a specified period – or 10 years – on all patients to whom the medicine is administered.

As discussed, for other new drugs PACs are appended on a case-by-case basis. Although comparative quantitative data was not available, Dr Doi expressed the opinion that the number of PACs was increasing.

Box 4

PACs for ethical (prescription) drugs	
Approx. 12,000 products	
New drugs with post-approval commitments	
	144 products
• Antimalignant tumour drug	26
• Antibiotic drug	24
• AntiHIV drug/Antiviral drug	24
• Other	70
Type of commitment	
• Drug efficacy	114
• Drug safety	120

Box 5

Commitments for drug efficacy: 114 items

Confirmation of approved efficacy	53
Confirmation of efficacy other than the approved use (e.g., for paediatric patients)	12

Type of commitment

Post-marketing clinical tests	54
Post-marketing surveillance	78

Commitments for drug safety: 120 items

Surveillance/tests to confirm drug interaction and safety in paediatric/elderly patients	69
Provision of special information to medical institutions. Requirement to obtain informed consent from patients	34
Limitation on use of the drug product to specified medical institutions only	3

Type of commitment

Post-marketing clinical tests	11
Post-marketing surveillance	105

Dr Doi noted that when commitments are appended in Japan, it is obligatory to indicate them on the package insert.

Future expectations

In conclusion, Dr Doi turned to the future expectations and possibilities of conditional authorisations. He believed that, by improving the quality of post-marketing surveillance, it should be possible to curtail the increasing requirements for the number of patients in the clinical development stages and prevent development times from increasing. He also envisaged that conditional authorisations could facilitate the collection of data on efficacy in specific groups of patients, such as paediatrics, which is not easy in pre-authorisation development. This could pave the way for additional efficacy claims.

He suggested that the important and difficult issue of the impact of ethnic factors

could be addressed by collecting data from tests carried out in post-marketing clinical tests. It is essential, he said, to prevent the extension of development times and delays in submitting approval applications, that result in the so-called "drug lag", in Japan.

Dr Doi strongly advocated the exchange of information among Japan, the US, and the EU, not only on studies in the development phase, but also on post-marketing studies and test data. Such information sharing would allow the decision on whether or not to assign PACs to take account of whether the requested information has already been obtained elsewhere in the three regions.

The ultimate goal is to encourage the worldwide introduction of medical products with simultaneous R&D, global clinical trials, applications, review, approval and marketing in multiple areas. In order to achieve this vision of the future, Dr Doi looked forward to even closer cooperation with PMDA's counterparts in the EU and USA, not only at the pre-approval phase but also at the post-approval phase.

DISCUSSION

EPPV reporting: Dr Doi confirmed that the primary responsibility for reporting adverse reactions in the six months of the Early Post-marketing Phase Vigilance lay with the company. One of the objectives, however, was to ensure contact with physicians in order to educate them about correct prescribing of medicines. Many ADRs, he said, arise from inappropriate use and one of the main problems was side effects resulting from use of new medicines in combination with other products.

Future vision: Asked how progress could be made towards realising the vision of reduced development times through use of conditional authorisations, Dr Doi expressed the view that orphan medicine programmes and experience from HIV medicines were already showing the way. Such medicines had been approved in Japan with almost no experience in Japanese patients but with commitments to collect data after marketing. Extension to a wider range of medicines would depend on building up confidence in regulators that commitments would be honoured. The amended PAL had brought in penalties for non-compliance but greater trust between companies and agencies was the key.

CURRENT INDUSTRY PERSPECTIVE ON THE IMPACT OF CONDITIONS AND COMMITMENTS ATTACHED TO AUTHORISATIONS FINDINGS FROM A CMR SURVEY

Dr Mayu Hirako

Senior Analyst, CMR International Institute for Regulatory Science

Dr Mayu Hirako presented the results of a survey that had been carried out in preparation for the Workshop among the member companies of the CMR International Institute. The study investigated the perception that the number and complexity of post-approval commitments (PACs) attached to marketing authorisations was increasing and examined concerns about the time and costs involved.

Dr Hirako also referred to a recent US survey by the Tufts Center for Study of Drug Development CSDD that showed that the:

- Percentage of NME approvals with PACs increased from approx. 52% (1987-1993) to 73% (1998-2003)
- Number of patients in PAC studies has increased from a median of 123 (1980s) to 920 (1998-2003)
- Median cost of PAC studies rose from \$135,000 (70s and 80s) to \$3.7 million (1998-2003).

She noted that PACs have been brought into focus in two recent Institute Workshops and that the Institute's Advisory Board had recommended that the Institute should conduct a survey on the industry perspective.

Methodology

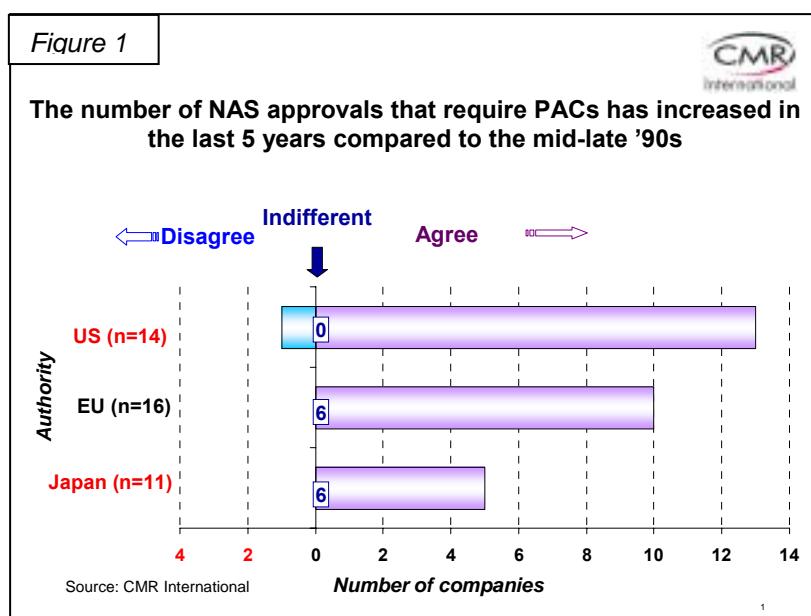
The inclusion criterion for the survey was new active substances (NASs) approved by FDA, EU or PMDA from 2000-2004. Responses to the survey were received from 17 of the Institute's member companies. The questionnaire sought companies' views on PACs as part of current regulatory procedures, the resource implications and their experience of PACs in the US, EU and Japan. Company strategies related to PACs were also covered in the study and participants were asked for their vision of an ideal future landscape.

A separate study had been carried out on information that is available in the public domain on the number of NASs authorised with PACs in the EU, US and Japan.

Changing requirements for PACs

Companies were asked to look at the statement: '*The number of NAS approvals that require PACs has increased in the last five years compared with the mid to late 1990s*' and say whether they agreed, disagreed or were 'indifferent' (neither agreed nor disagreed).

The results (Figure 1) indicated that almost all the companies perceived an increase in the number of PACs required in the US, and a smaller majority were of the view that there had been increases in the EU, but for Japan the results were equivocal.



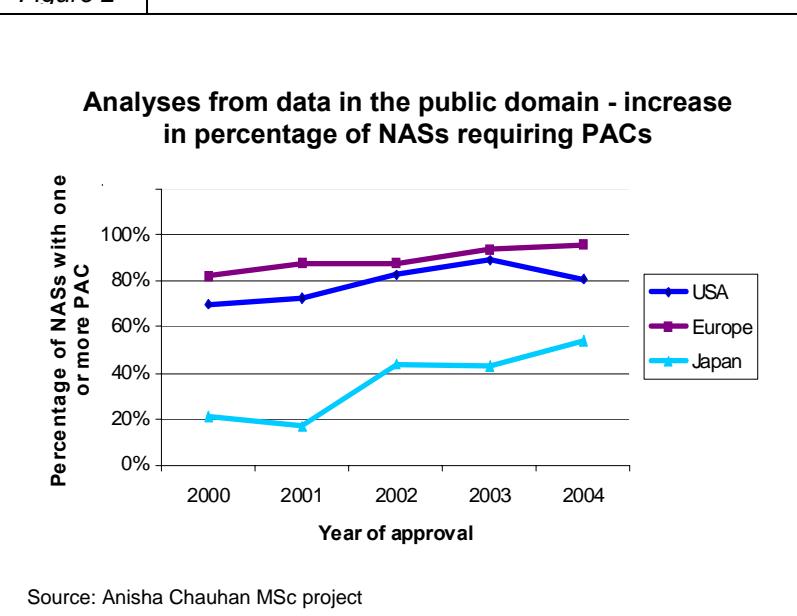
A related question asked about changes in the number and complexity of PACs requested in the last five years. For all three regions, the majority of companies reported an increase in both the number and complexity for PACs that related to clinical efficacy and to risk management (clinical safety). For PACs related to non-clinical testing the majority of companies either said there was no change or that they had no view or no experience, whilst for CMC data the majority said there had been an increase or no change.

Dr Hirako commented that the two clinical areas where there had been an increased assignment of PACs are the most resource-intensive and this was reflected in the responses to a later question on resources.

Study of published data

Data were presented from the study that had been carried out by collecting data from the websites of FDA, EMEA and PDMA and looking at the changes over time in the percentage of NASs approvals granted with one or more PACs (Figure 2). Dr Hirako noted that the percentages had increased for all three authorities but more markedly in Japan. The results indicated that PACs were more likely to be assigned in the US and EU than in Japan but Dr Hirako pointed out that this may be explained by the Early Post-marketing Phase Vigilance (EPPV) requirements that are applied routinely to NASs⁵. Studies that other authorities require as PACs may be covered by the EPPV process in Japan.

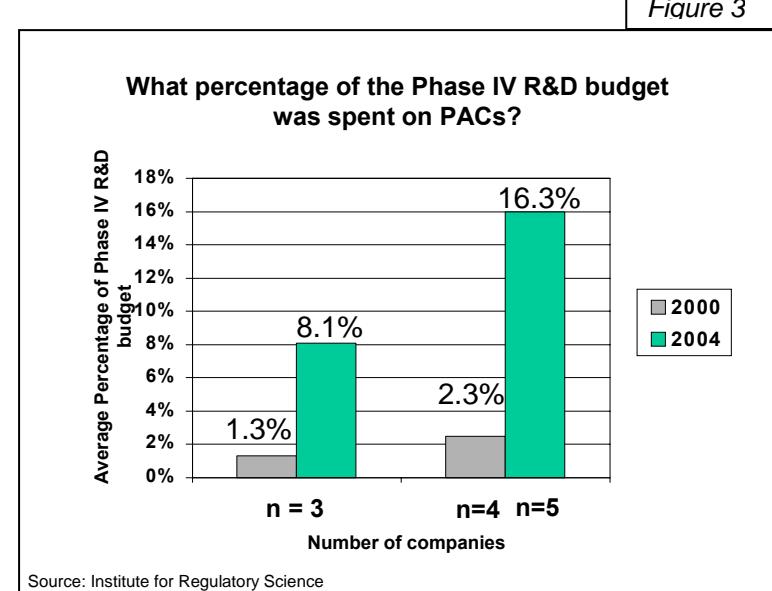
Figure 2



Resources

The survey included a question on the resources used for PACs, in terms of the percentage of the Phase IV budget. Referring to the chart in Figure 4, Dr Hirako explained that the bars on the left-hand side provide a direct comparison of the resources reported for 2000 and 2004 by the three companies that were able to provide data for both years. Other companies were only able to provide data for one of the years and the bars on the right hand side indicate an eight-fold increase when all responses are incorporated.

Figure 3



⁵ See presentation by Dr Doi, PMDA, Section 3, page 10 of this report.

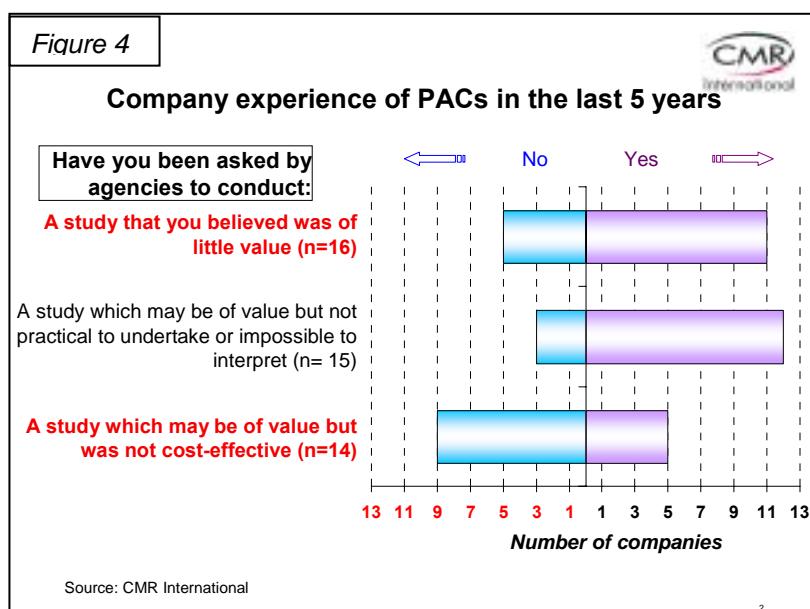
Company views about PACs

There were a series of questions intended to collect companies' perception of the value of PACs as a regulatory tool and the effectiveness of the current systems in the three regions. Once again, the methodology presented a series of statements and asked companies whether they agreed, disagreed or had no strong feelings on the subject ('indifferent'). The results are shown in Table 1.

Statement	US	EU	J
	Majority view		
PACs are a valued regulatory tool which enables faster access of medicines to patients in a 'real-world' setting.	✓	✓	≈
PACs are well thought out in relation to what they will deliver.	✓	✓	≈
One of the major reasons for PACs is a shift in authority requirement after dossier submission.	✗	?	✗
Agreeing to PACs at the last minute to gain approval is common occurrence within my company.	✓	✓	✓
Delivery of PACs should become legally binding on a company within an agreed time, with penalties if they are not met.	✗	✗	✗
PACs are required to fill gaps in the development programme.	?	?	?
PACs yield usable, useful data that advances scientific knowledge, enhances medical value.	?	?	?
PACs are reasonable from a scientific / regulatory perspective and contributes to safe, effective use of a new medicinal product.	≈	≈	?
Number of companies = 16	Key: ✓ = agree, ✗ = disagree, ≈ = indifferent ? = equivocal		

The responses to the first statement indicated that the majority of companies, at least in the EU and US, accept the value of PACs as a regulatory mechanism that can allow new products to be made available to patients more rapidly.

There was little surprise that all companies had experience of having to agree PACs at the last minute in order to gain approval and this was reported as a common occurrence in all regions. Similarly, it was not surprising that companies did *not* agree that PACs should be legally binding and attract penalties for non-compliance. The last three statements were intended to address the quality and usefulness of PACs at it appeared that companies were not convinced about the value of the studies that are currently being required.



The value of PAC studies

The value of the studies that had been carried out under PACs was explored further and companies were asked for feed-back from experience over the last five years. As the results in Figure 4 indicate, a clear majority of companies reported experience of PACs that were considered of little value or proved to be impractical to fulfil. There were fewer concerns about the cost-effectiveness of studies.

PAC Strategies

Companies were asked if they always present a risk management plan to agencies. Only 25% of the 16 responding companies reported that this was currently a routine part of the marketing application but over 80% predicted that they would be doing so by 2008.

Another question addressed companies' strategy for PACs (other than risk management plans) and asked whether this was:

- Most often to wait and see what additional PACs the agency requires at the time of approval? or
- Typically' to suggest, proactively, studies for areas in which there are gaps in the development programme?

The results from 14 companies showed that 57% currently adopt a 'wait and see' policy, 29% are proactive and the remaining 14% responded that their strategy differed according to the region. When asked to predict any change in strategy over the next three years (i.e., by 2008) 64% of the companies anticipated that they would become more proactive in proposing PACS.

Tracking and monitoring

When asked whether agencies actively follow-up the PACs that they have assigned, the majority of companies reported that PACs were monitored by FDA and under the EMEA centralised procedure but experience under the EU mutual recognition procedure (MRP) was more mixed. Six out of 7 companies reported that PACs were not monitored in Japan, with the remaining 8 companies having no relevant experience.

Companies were asked about the instances when it had not been possible to deliver a PAC within the agreed timeline and 12 out of 16 (75%) reported such cases. The reasons given included difficulty in recruiting patients and unrealistic timelines.

When asked about their internal procedures for monitoring PACs, eight out of 16 (50%) companies reported that they had carried out a review. Only one of the 16, however, had a system in place that was designed to evaluate the effectiveness and benefits of the studies they undertake as post-authorisation commitments.

The ideal future landscape

Dr Hirako concluded by summarising the results of questions in the survey designed to provide a vision of how PACs could be used most effectively. In general, the study participants recognised the importance of PACs and the increasing reliance that should be placed on their use in approval processes in the future.

Most of the recommendations for an 'ideal landscape' fell into three areas:

- Earlier dialogue with authorities, egg. PAC discussion as part of overall development plan at end of Phase II and pre-submission meetings;
- An alternative approach, such as earlier approval, with conditions attached, based on Phase II data or a small number of patient studies in Phase III;
- Global integration of requirements, i.e., better coordination and communication between the major regulatory bodies.

Companies were also asked to identify the main hurdles to be overcome to achieve these goals and the most frequently cited were:

- Political and public perception of changes to regulatory procedures;
- Risk aversion by agencies;
- Poor communication between industry and agencies.

The solutions that were proposed to address these issues included:

- Re-establishing the focus on benefit-risk and including the public in these discussion
- Ensuring open dialogue and collaboration between industry and agencies with an understanding by all parties that discussion of PACs does not impact the data required for approval;
- Developing clear criteria to determine when PACs are appropriate.

DISCUSSION

Data requirements: Clarification was sought on the suggestion that early discussion of PACs should not 'impact on the data required for approval' (see penultimate bullet, above). The concern was that such discussions of post-authorisation studies could be interpreted as meaning that the current data package was inadequate for submission, without such studies.

Extension of the Institute survey: The responses to the survey, especially in relation to PACs that were and were not considered valuable, had suggested that more detailed examples and case histories would be useful. Professor Walker, CMR International, reported that companies had expressed their willingness to provide more information and participants agreed that a further in-depth study should be considered.

Early approval: Mr Lönngren, EMEA, commented on the industry vision that better use of PACs could lead to more products being approved on the basis of Phase II or reduced Phase III data. He cautioned that the current and revised EU legislation would only permit this for products that met the strict criteria for authorisation under 'exceptional circumstances' and conditional authorisations⁶.

PACs that cannot be fulfilled: Referring to the problem of last-minute agreement to studies that turn out not to be feasible, participants reported experience from the US and the EU where requirements had been modified or the company had been released from a commitment' following discussion with the agency.

KEY ISSUES FOR COMPANIES IN MANAGING POST-APPROVAL COMMITMENTS

Dr Edmund P. Harrigan

Senior VP, Worldwide Regulatory Affairs and Quality Assurance, Pfizer Inc., USA

In his presentation, Dr Edmund Harrigan focused on the experience gained by Pfizer in managing post approval commitments in recent years.

Dr Harrigan presented data (Box 1) which indicated that roughly three-quarters of new molecular entities that were approved in the four years from 2001 to 2004 had post-approval commitments. He noted that there appeared to be very little trend in this particular data set and the rate of assigning PACs appeared fairly steady over that time.

Box 1

Recent US Industry Data for PACs	
Year	% of Approved NMEs with PACs
2004	74% (23/31)
2003	86% (18/21)
2002	82% (14/17)
2001	75% (18/24)

IIS Regulatory Reporter Feb 2005

⁶ See presentation by Dr Pignatti, Section 3, page 32 of this report

Pfizer experience

Box 2

Pfizer products 1997-2004

Axert	Relpax
Bextra	Somavert
Cardura XL	Spiriva
Detrol LA	Vfend
Diflucan	Xanax XR
Geodon	Xalatan
Inspra	Zithromax
Lyrica	Zoloft
Macugen	Zyvox
Neurontin	

Dr Harrigan discussed an illustrative list of 19 drugs (Box 2) from Pfizer that had been approved between 1997 and 2004. Not all were approved in all three ICH regions and some of the applications were for supplemental approvals.

Of these 19 products:

- 11 products had PACs as condition of approval, totalling 93 PACs:
 - 41 US
 - 48 EU
 - 4 Japan
- 8 were approved without PACs

The types of commitment are shown in *Figure 1*. Dr Harrigan pointed out that, in the US, the majority of PACs (albeit a slim majority) were clinical whereas in the EU there was a higher percentage of Chemical Manufacturing and Control (CMC) requirements. As far as resource implications are concerned, the clinical commitments are by far the most onerous.

Dr Harrigan gave an example of the type of commitment that would be classified as 'risk management'. This was a requirement to provide educational material for distribution to potential patients for a first-in-class therapeutic agent that required a surveillance plan to monitor hepatic safety.

<p>He confirmed comments by earlier speakers that resource data for PACs was very difficult to obtain. A simple drug-drug interaction study might involve one clinician for less than a year – less than 1 FTE. On the other hand, a long-term observational study may involve three clinicians for five years (15 FTEs) and neither estimate, he added, includes the resources required to manage and analyse the data and produce the necessary reports. As an illustration of this Dr Harrigan referred to a 3-4 year mortality/morbidity trial that had recently been required as a PAC. The total FTEs for the study was 81 of which seven were clinical.</p>	Clinical	51% (21/41)	33% (16/48)	50% (2/4)	42% (39/93)
	CMC	12% (5/41)	50% (24/48)	0%	31% (29/93)
	Risk-management	2% (1/41)	4% (2/48)	0%	3% (3/93)
	Total PACs	44% (41/93)	52% (48/93)	4% (4/93)	

Figure 1

Post Approval Commitments *Pfizer's Experience*

<u>Type of Commitment</u>	<u>Number of PACs</u>			
	<u>US</u>	<u>EU</u>	<u>Japan</u>	<u>TOTAL</u>
Non-clinical	34% (14/41)	13% (6/48)	50% (2/4)	24% (22/93)
Clinical	51% (21/41)	33% (16/48)	50% (2/4)	42% (39/93)
CMC	12% (5/41)	50% (24/48)	0%	31% (29/93)
Risk-management	2% (1/41)	4% (2/48)	0%	3% (3/93)
Total PACs	44% (41/93)	52% (48/93)	4% (4/93)	

Timing of PAC requests

Referring, again, to the eleven compounds with PACs, Dr Harrigan provided an analysis of the time at which the company heard about a 'significant' post-approval commitment and the extent to which at least one such commitment only came up in the last three weeks of the review. The timing and frequency were as follows:

- Prior to NDA/MAA submission 18% (2/11)
- During NDA/MAA review 18% (2/11)
- Less than 3 weeks before approval 64% (7/11)

Case Studies

Dr Harrigan provided three case studies, based on Pfizer's experience.

Product A

This was an anti-infective agent where there had been significant sponsor-FDA interactions throughout drug development. Sixteen PACs emerged during the review, of which eight were clinical. These were predominantly designed to collect data that could only be obtained in a 'real world' setting such as a surveillance plan to monitor the development of resistance or was efficacy data in new populations of patients with drug-resistant pathogens – e.g., methocillin-, penicillin-, vancomycin-resistant infections. These were specific patient populations that would not have been covered in Phase III unless the product indication was specifically for such patients. In addition the commitments included the development of a paediatric programme.

Dr Harrigan commented that this was the first drug of its type to be approved for over two decades and many of the PACs emerged during the FDA advisory committee discussions and so came about during a considered and thoughtful review. Whilst some of the issues came up late in the process, the company felt this was, in part, due to the 'enthusiasm' of the advisory committee and accepted that this was part of the development process.

Product B

The case study for Product B presented a contrasting picture. The product was approved for the treatment of a CNS disorder based on two trials in patients experiencing acute exacerbation of their illness. The trials were for short-term monotherapy, in accordance with the requested indications, and were carried out against placebo.

There were a number of meetings with the agency both before the development plan began and during the course of development. At the end of the FDA review, however, within the last few days of the action date, the company was informed that, in order to obtain approval, they would need to agree to perform long-term studies to demonstrate efficacy and safety in maintenance treatment. In addition the efficacy of the drug as adjunctive treatment with another therapeutic agent would need to be demonstrated. Neither of these had been raised as requirements in the earlier discussions of the development programme and the resource commitment was about 25 million dollars.

Dr Harrigan stressed that earlier discussion could have allowed consideration of alternative development options, in terms of managing portfolios and looking at other programmes competing for the same funds. If the 25 million dollar commitment had been known earlier it might have had an impact on the decision to go forward with that particular drug for that indication versus another that might have been a potential novel therapeutic agent for an untreated indication. This, he pointed out, is one implication of failure to identify post approval commitments at an earlier stage in the drug development process.

Product C

Finally, Dr Harrigan discussed product C, which is a broad spectrum anti-infective agent approved in the EU. Twenty-eight post-approval commitments were assigned during the review of the marketing application, with only one notified at the 'eleventh hour'. Twenty of the 28 were CMC-related commitments and the last-minute request was for a surveillance plan to monitor organ system safety. The CMC requirements were routine and included final inspection and approval of the sterile manufacturing facility. There was also a request to develop a paediatric formulation.

Dr Harrigan provided this as an example of a more manageable package that had emerged from a structured MAA review with interactions at day 150 and day 180 that help the development of these issues. Although there was one late request this was not a particularly difficult programme to manage and he suggested that it is, perhaps, unrealistic to expect agencies to eliminate such last-minute actions.

Summary and Conclusions

PACs that are received late during the review phase do not allow:

- Efficient use of sponsor resources especially if a more efficient study could have been designed.
- Time for adequate consideration of alternative development options to satisfy PAC
- Opportunity for sponsor to design robust study that may be suitable for use in multiple ICH regions e.g. efficacy study in new population

Dr Harrigan referred again to the case study on product B, where different development options would have been considered had there been advance notice of the investment required to achieve authorisation. He also emphasised that it is not possible to negotiate a mutually acceptable set of well thought-out PACs if, at a late hour, the authorisation is dependent upon agreement with the authority's conditions.

Regulatory strategies

Within the regulatory discipline companies try to avoid 'surprises', Dr Harrigan said, and obviously try to predict the PACs that might be requested. In order to achieve this, companies must rely significantly on:

- Input received at Health Agency meetings;
- Published up-to-date guidelines and points to consider;
- Consistent and well communicated regulatory requirements.

Recommendations to Industry

Dr Harrigan's advice to colleagues in industry was:

- To be aware of precedent and see what other sponsors have encountered: In many cases PACs can be anticipated based on prior industry experience;
- Make full use of Health agency 'milestone' meetings to minimise surprises during the review: Decide whether or not to be proactive in proposing PACs, and contingency-plan for all appropriate PAC options.
- Develop risk management programmes to anticipate and plan for the unexpected: Such programmes will clearly be an increasingly important part of the registration package.

Recommendations to health authorities.

In making recommendations to the authorities, Dr Harrigan suggested that they should:

- Ensure published guidelines reflect the current position regarding development and approval;
- Strive for a frank and collaborative environment with sponsors with an open discussion of the issues, in particular, through productive milestone meetings
- Provide feedback on the development program, particularly in relation to the desired labeling (Target Product Profile - TPP)

Finally, Dr Harrigan expressed the hope that that agencies would be proactive in avoiding '11th hour' PACs and take positive steps to reduce their occurrence to a minimum.

DISCUSSION

Quantifying resources for PACs: Asked what percentage of development costs could be assigned to PACs, Dr Harrigan replied that these data were not currently available as the costs of studies were not currently 'tagged' according to whether they relate to PACs or pre-authorisation development. Another participant noted that resources can depend on the type of portfolio: for companies developing oncology products in the EU, as much as 20% of

clinical studies can be carried out in the post-approval stage because of the need for long-term outcome studies.

Avoiding 'nice-to-know' PACs: Dr Harrigan was asked how he felt that agencies could ensure that PACs met the 'need to know' criterion and were not being asked out of general interest. He suggested that the key issues were: allowing enough time for a meaningful discussion of PACs with the company; assessing products on the basis of the target product profile rather than hypothetical extensions to 'off-label' use; ensuring that there was an internal system of 'peer review' among reviewers; and making better use of scientific advice, at an early stage. He felt that, in the case of FDA, greater interaction during the review process itself would be an additional advantage.

Scientific Advice meetings: During the discussion it was commented that companies rarely raise safety issues when seeking early advice on development programmes. Greater openness and frankness at that stage could avoid problems later. It was also noted that, in the EMEA system, the reviewers will not be familiar with the drug and its development and hence some issues might not arise until the second round of the review process (i.e., after receiving responses to the list of questions at day 120).

ARE CURRENT PROCEDURES ROBUST ENOUGH TO PROVIDE ADEQUATE SAFEGUARDS FOR DETECTING UNFORESEEN SAFETY ISSUES?

Dr Hugh Tilson

*Clinical Professor of Epidemiology and Health Policy, School of Public Health,
University of North Carolina, USA*

Dr Hugh Tilson opened his presentation by suggesting that the simple answer to the question that he had been posed in the title was 'No'. Current procedures are not ideal for detecting unforeseen safety issues but, in his opinion, the answer does not lie in more or different regulations but rather in developing information resources and building the scholarship to handle and interpret the data that is available. Equally important is the need to learn how to communicate about uncertainty – 'what we know and what we do not'.

Dr Tilson discussed the 'Centers for Education and Research on Therapeutics' (CERTs) initiative in the US as a potential model for moving forward. The message that he wished to convey was that academia and practice represent essential partners to regulators and industry in assuring 'adequate safeguards'. A new mechanism is being developed to address the issues of post-marketing monitoring and evaluation of medicines and that this mechanism is already starting to work, in the US.

CERTs

The CERTs were established under the Food and Drug Modernization Act (FDAMA) that, among many other provisions, mandated risk management initiatives. Dr Tilson pointed out that the Act makes it clear that it is a public health obligation of government not just to regulate and control but also to help the sector develop and thrive.

To this end, cooperative agreements have been established between government (FDA and the Agency for Healthcare Research and Quality - AHRQ) and academia to help academic centres of excellence to grow and carry out essential clinical and laboratory research, particularly to advance the translation of research findings into effective and safe medical practice. The remit of the CERTs covers drugs, biologics and medical devices.

FDAMA also establishes a principle that allows public-private partnerships where industry participates in the conduct of its academic research and there is sharing of resources. The CERTs were set up under cooperative agreements (initially for three years) that received some 17\$ million funding from AHRQ to start the initiative.

Structure

Dr Tilson presented the structure of the CERTs initiative, as shown in *Figure 1*. There are currently seven participating academic centres (CERTs), funded by AHRQ, with four more scheduled to be funded in 2005. The Coordinating Center for the project is located within Duke University, North Carolina, and there is a Steering Committee that oversees the CERTs activities.

The CERTs Risk Series

Topics related to the 'adequate safeguards' question at hand - benefit-risk evaluation of medicines and risk management -have been addressed through many individual research and education activities of the CERTs. In addition, working collaboratively, the CERTs programme held an unprecedented series of five focused workshops or 'think tanks', that were jointly sponsored as shown in *Box 1*. Dr Tilson explained that the methodology and organisation of these workshops needs to be follow strict 'rules' in order to achieve the objective of 'minimal exposition, maximal involvement':

- The selected participants may attend 'by invitation only';
- Constituency representation focused on regulators, sponsors, and scholars, but with practitioners and consumers always at the table

Dr Tilson also described the so-called 'ticket to dinner' strategy under which participants were each expected to:

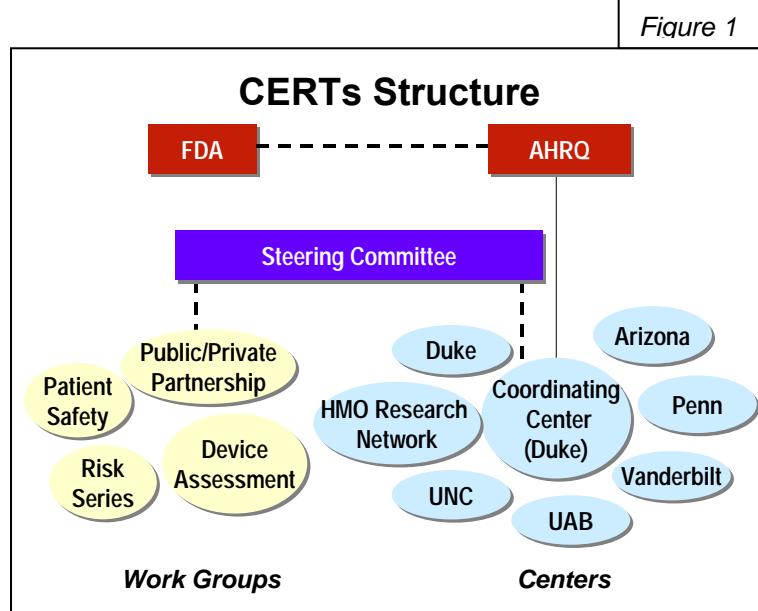
- Name at least one major gap in current knowledge ('toolkit') which, if addressed, would move the field forward;
- Name at least one research project/approach to address this gap;
- Name at least one major gap in our current policies (optional).

The task force then considers the recommendations using a modified 'Nominal Group' process with visible consensus voting and the outcome is submitted to the CERTs Steering Committee, which prioritises the proposals.

Workshops

Dr Tilson provided an overview of the five CERTs Workshops/Think Tanks held in 2001-2003 at the University of North Carolina, Chapel Hill, NC (see *Box 2*)

Figure 1



Box 1

Sponsors of the Think Tanks

- US Department of Health & Human Services
- Agency for Healthcare Research and Quality
- Center for Drug Evaluation and Research, FDA
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- Centers for Education and Research on Therapeutics (CERTs)

* Dr Hugh Tilson is the current Chair of the CERTs Steering Committee
Section 3 Page 24

Risk Assessment

The first *Risk Assessment* Think Tank started with consensus on the view that the current systems of safety surveillance in place globally 'are not working'. That is, systems that rely on spontaneous reporting by health professionals are plagued by under-reporting and it is not clear how the information should be handled, in relation to understanding the balance of benefit against risk. Dr Tilson also reported that there were serious concerns about the cost of such systems, in relation to their value. The need to look for better ways to allocate resources was among the key research questions addressed by the Workshop (see *Box 3*).

The 'bottom line' conclusions from the Workshop, Dr Tilson reported, was that the system of risk assessment requires a major overhaul and that this should be 'evidence based'. One overlooked aspect of the system received particular attention, namely, the workforce that is responsible for actually performing the risk assessments. An aggressive agenda to understand and improve the workforce was suggested to address the questions:

- What are the 'core competencies' needed by a pharmacovigilance professional?
- What are the dimensions and needs of the pharmacovigilance workforce?
- What will it take to improve the quality and adequately staff the effort?

Benefit Assessment

When looking at the question of defining therapeutic benefit, the Think Tank made a distinction between therapeutic benefit and the confirmation of 'efficacy' that results from routine clinical trials and are the basis for current regulatory approvals. Dr Tilson referred to the six main issues that were addressed by the meeting (*Box 3*) and commented on the need to define thresholds when making the rules for attaching PACs to drugs that are urgently needed and also when deciding on the need for further information from sub-populations.

The 'bottom line' from this Think Tank, Dr Tilson reported, was that one can *not*:

- Consider risk management outside of the context of understanding benefit
- Understand benefit outside of the context of understanding efficacy and effectiveness
- Understand benefit without understanding associated risk and finding a way to compare it in similar metrics ... the elusive benefit to risk ratio

Risk Communication

The two Workshops on communicating risk had participants from government, academia and industry. A few representatives of the media were invited to the first Workshop and made up some 50% of the participants at the second.

At the first meeting there was consensus that, when it came to effective communication of risk, one should not look to the printed product information/package insert that is required by regulation. It was equally clear, however, that the media do not know how to communicate risk and a main theme for the second meeting was to explore the

Box 2

The CERTs Risk Series of Workshops

2001-2003, Chapel Hill, NC, USA

- **Risk Assessment**, May, 2002
 - Theme: 'Post-marketing Assessments of Pharmaceutical Risk'
- **Benefit Assessment**, September, 2002
 - Theme: 'Overcoming Difficult Issues in Characterizing Therapeutic Benefit'
- **Risk Communication**, March, 2001
 - Theme: 'Improving Communication of Drug Risks to Prevent Patient Injury'
- **Risk Communication and the Media**, January, 2003
 - Theme: 'The Importance of the Media in Pharmaceutical Risk Communications'
- **Risk Management**, January, 2003
 - Theme: 'Managing the Risks of Therapeutic Products'

possibilities for 'partnership' with the media to communicate about medicines in a constructive way that does not put patients at risk or create unnecessary alarm.

There is no easy solution and Dr Tilson described the 'bottom line' as the urgent need to develop knowledge and practices that will 'attract and inform audiences, one news bite at a time'.

Box 3

Selected Key Research Questions from the CERTs Think Tanks	
<p>Risk Assessment, May 2002</p> <ul style="list-style-type: none"> • What system is needed to assure that we: <ul style="list-style-type: none"> – Routinely address long term adverse effects – Routinely address adverse events throughout drug development – Address the biological bases for adverse drug reactions, including adverse drug reactions in subpopulations such as pregnant women? • How useful are spontaneous reports from the following groups in determining new information about benefits and risks: manufacturers? consumers? practitioners? • Is the current U.S. approach of voluntary spontaneous reporting cost-effective? • What strategies increase voluntary adverse event reporting in clinical trials? • What are the best practices for finding a new drug risk from the FDA Adverse Event Reporting System (AERS) system? How do companies deal with "outlier" data? • What types of methodology are used to "mine" clinical data to study benefits and risks of medicines? What types of data are used? How effective are these approaches in identifying benefits and risks? • What do conflicts between results from analysis of structured studies, spontaneous reports and large, structured databases mean? • What level of risk associated with a drug is acceptable to the public? What level of risk is acceptable to a prescriber? What factors influence risk acceptability? 	<p>Benefit Assessment, September 2002</p> <ul style="list-style-type: none"> • What are the distinctions between symptomatic treatments and treatments to reduce the risk of significant morbidity or mortality in balance of benefits against risks? • What should be the standards for proof of principle vs. data applicable to specific patients or populations? • When is it appropriate/necessary to rely on Surrogates vs. "true" outcomes? Short term outcomes vs. long-term? • How do we translate group findings to individuals and subgroups • How do we get fair comparisons of therapies • How can we know about effectiveness of the baseline therapy when data come from add-on studies <p>Risk Communication, March 2001</p> <ul style="list-style-type: none"> • How can we "Personalise" Risk Communication? • What are the cost effective applications of Information Technology? • How can we assure Regulation for Outcomes? • How can we develop a comprehensive "Influence Model"? • What will be required to reform Education of Health Professionals? Curriculum, continuing education, creative techniques, competent educators?

FDA Follow-up

On the basis of extensive public hearings but also (FDA leaders report) substantially assisted by their participation in the CERTs Think Tanks, the FDA has developed three guidances that were published in March 2005:

- Risk assessment in clinical trials;
- Risk assessment (and epidemiology) post-approval; and
- Risk Minimization Action Plans (RiskMAPs)

Dr Tilson pointed out that each guidance is prefaced by a cautionary note: *'This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic ... does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements ...'*

Nonetheless, he suggested that this is a useful way to move forward in a quasi-regulatory mode without over-regulating in an area where there are so many unknowns.

On the subject of RiskMAPS, Dr Tilson referred to the advice that had been given by FDA, as shown in *Figure 2*.

Conclusions

Dr Tilson concluded by returning to the original question about the robustness of current procedures. Clearly, the answer is that more needs to be done to safeguard against unforeseen safety issues but, he suggested, it will need more than regulation to achieve the goals. He encapsulated what is needed as:

- A robust research community
- A solid well-supported set of data sources
- Clear rules of engagement for all partners and a level playing field
- A truly global perspective
- A spirit of inquiry and evaluation

In relation to the need for improved data sources, he stressed the important role of the large automated population-based multi-purpose databases that were being developed that integrate electronic medical records and hospitalisation data along with demographics and occupational data. Exploration of the full potential of such data sources is at the heart of the CERTs programme. HMO databases, of this type, in the US, including the HMO Research Network CERT at Harvard, are showing the way but it will take a significant investment of skills and resources by all stakeholders.

The way forward, Dr Tilson emphasised, is through thinking globally, not wasting resources on 'silo efforts' but sharing the workload and information to 'provide adequate safeguards' among all relevant global partners.

Figure 2

Key Points about RiskMAPs

- Start with good risk and benefit assessments
- Seek stakeholder input, transparency
- Set clear goals for health outcomes
- Define intermediate objectives
- Pick tools from 3 categories
 - Targeted education and outreach
 - Reminder systems
 - Performance-Linked Access Systems
- Evaluate and communicate with FDA about progress, possible changes



FDA

DISCUSSION

European Perspective: The meeting was informed of related initiatives in Europe where the European Commission (DG Research) is funding research programmes and holding discussions on putting in place private-public platform partnerships to look at issues related to the development of medicinal products, in a non-competitive way. There are on-going discussions between the Commission and EFPIA and there is agreement that one aspect that industry and academia must study is risk management and PMS. Dr Tilson commented that there were discussions about putting together a 'constellation' of academic centres in Europe, similar to CERTs, and welcomed trans-Atlantic dialogue with the CERTs.

Managing Risk: Asked about the barriers to achieving the vision for post-authorisation risk-management, Dr Tilson suggested that the first priority must be a structured approach to tackling some of the major unanswered questions. The development of better policy, such as PACs, must be evidenced-based. Otherwise one resorts to political arguments. Research is needed into cost-effective methods of identifying risks, scientific means of interpreting signals and creative ways of communicating about risk-acceptance and uncertainty that does not 'offend' people.

Population-based data: Dr Tilson was reminded of the series of 'Think Tanks' that had been convened in the mid 1980s and beyond, to discuss many of the same issues that CERTs have now begun addressing in an organised national-level effort, in particular the vision of using major data-bases as a source of post-marketing safety data (the 'Minster-Lovell Accords'). Although progress has not been as rapid as had been envisioned, he noted that there were now two particularly notable systems in the US, based on electronic medical records and linked to other data systems in line with the Minster-Lovell vision. One of these has 11 million covered lives with fully automated electronic linked data sets that recently announced that it will be able to take every new drug on the market and monitor every use and outcome, in order to achieve 'proactive' population-based surveillance. Another is an HMO research network of a dozen or so (depending on the project) managed care organisations that can carry out very similar functions and replicate studies. The development needs to be approached incrementally but he foresaw that industry would, in future, propose such 'proactive' surveillance as a routine part of post-approval development.

Sharing data: There was general agreement that the idea of companies each developing in-house 'data warehouses' is passé but there were some concerns about the practicality of 'generic' databases that everybody uses but nobody seems to 'own'. Concerns had also been raised that misplaced anxiety about patient privacy may block progress towards harnessing vital population-based data. Dr Tilson pointed out that academic institutions and medical care organisations can be as proprietary as pharmaceutical companies when it comes to sharing data but the CERTs serve as a model that such consortiums can work to make these population-based resources available for public health research while protecting the privacy of the engaged stakeholders.

EARLY ACCESS MECHANISMS FOR NEW MEDICINES – ACCESS TO GILEV

Dr Debra Barker

Regional Medical Director, Novartis Pharmaceuticals Corporation, USA

Dr Debra Barker had been asked to look at the lessons that can be learnt from experience of compounds that have been made available through accelerated approval or compassion use programs. The anti-cancer agent Gilev had been the obvious example from Novartis. The product, for the treatment of chronic myeloid leukaemia (CML), was more-or-less simultaneously in the EU, US and Japan, that is, within six months of each other, and the product was authorised on the basis of Phase II data.

Need for special measures

Cancer is a complex disease where there are still many areas of high unmet medical need and Dr Barker referred to the anticipated increase in the incidence of age-related cancers in an aging population, not only in the West but also in the developing countries of the world.

When the potential promise of Gilev in the treatment of CML became public knowledge, there was a tremendous demand from patients and their relatives. The company wanted to make the product available to patients but was faced with the inevitable 'gap' between filing the registration dossier and obtaining approval. The dossier had been filed early on the basis of limited Phase II data and, although an accelerated review was

anticipated, there was, nevertheless, an expected gap of a year between submission and authorisation. The Phase II studies had been carried out in a few centres in Western Europe and the US where patients could continue to be treated but there were many CML victims in the rest of the world who did not have access to the new product.

Novartis therefore embarked on an Expanded Access Program (EAP) with the objective of making the product widely available, on a non-commercial basis, as early as possible.

Expanded Access Program (EAP)

Dr Barker discussed some of the challenges of making a medicine available at an earlier stage than anticipated:

- **Drug supply:** Having to ensure that sufficient tablets, manufactured to GMP standards, were available for distribution before a full manufacturing scale-up had been carried out from the pilot production level in place at the end of Phase II;
- **Safety monitoring:** Although some 100 patients had been treated in Phase II and the benefit risk was favourable, it was essential to ensure adequate safety monitoring of patients in the EAP in order to have a real understanding of the potential safety issues;

The company wanted to reach a global patient population, Dr Barker said, and several options were discussed including initiating large trials or following a 'compassionate use' programme. The decisions on the type of EAP were finalised in consultation with patient advocacy groups and leukaemia experts and in discussion with the regulatory agencies. The US National Cancer Institute was also consulted.

EAP Framework

The design principle for the EAP treatment protocol was based on a simplified version of the Phase II studies, using experience of those factors that had worked well. At the start, the focus was on centres that already had experience of the drug where the doctors were comfortable with managing patients on the therapy. Dr Barker explained that, as a result of supply limitations, it had initially been necessary to limit patient recruitment:

- Patients in Phase II studies who had done well were rolled over into the EAP;
- Patients with the highest unmet medical need (no treatment alternatives) with blast crisis CML or advanced CML were given immediate access;
- Patients in chronic-phase CML with potential treatment alternatives were given limited access (a maximum of 10 patients per centre).

Unexpected costs

The early stages went well and most of the issues had been anticipated, Dr Barker said, but one unforeseen complication that arose was the cost of the programme. Since this was a philanthropic programme with the product being supplied free-of-charge, the company had expected that doctors might be prepared to participate in the EAP at a minimal or reduced cost. In fact, they expected the same level of payment as for a Phase II study and argued that it was taking them the same time and effort to recruit patients and collect safety data. The company felt obliged to accept this additional cost.

Global expansion of the EAP

As more drug became available a step-wise geographic expansion took place and, by the time the drug was approaching approval in the main markets, the expanded access programs was running in 115 centres in 30 countries. Dr Barker remarked that, while the programme was generally very successful it was a very expensive and extremely resource-intensive undertaking at both global and local level. In selecting the EAP centres the company chose only those establishments where there were trained oncologists who could work as partners with the company and collect good quality scientific data on the patients

they treated. It was also essential that the healthcare system could support the logistics of drug delivery and the requirements for following-up patients.

Recalling some of the unexpected issues that arose, Dr Barker said that, in order to comply with GCP patient records needed to be archived for 15 years. Many hospitals only had facilities for 10-year archives and the company became involved in paying for off-site storage.

Data from the EAP

Dr Barker presented comparative statistics on the number of patients that had been included in the Phase II clinical trials and in the EAP, which showed that a greater number of patients had received the product under the EAP. This was important both in terms of providing access to the treatment but also in terms of collecting data. Dr Barker stressed that this had justified the stringent standards they had applied in the EAP, since the bulk of knowledge about the drug actually came from this source. In terms of the quality of the data from the EAP, she provided further data indicating that the results of treatment, both in terms of safety reporting and efficacy were almost identical when EAP outcomes are compared with Phase II data. She felt confident that the EAP was a good mechanism for providing early access to patients and providing additional confirmatory data on the benefit-risk profile of the product.

Paediatric use

Dr Barker noted that, as well as expanding geographically, access had been extended to children with CML through a compassionate use programme that was run in parallel with the pivotal studies (see Box 1). This, again, provided useful preliminary safety and efficacy data.

Box 1

Access of children with CML

- 2000: Paediatric phase I trial in Canada-US
 - 31 patients, 23 centres
- 2001: Global Paediatric Compassionate Program
 - 62 patients enrolled in 53 countries
 - 30 patients enrolled within the framework of the EAP
- 2002: Phase II in EU and North-America

Glivec™ International Patient Assistance Program (GIPAP)

Regulatory approval for Glivec was granted in May 2001 in the US and in November 2001 in Europe. The question then arose of what happens to patients on the EAP once access, in the normal way, has been granted. First, Dr Barker suggested, one must define 'access' since availability does not depend only on regulatory status but also on the ability of health care providers or individuals to pay for a relatively expensive, high-tech medicine.

Recognising that many of the World's healthcare systems would not be able to make the drug available, Novartis, nonetheless, made a commitment to make the drug accessible to all patients in need and set up the *Glivec™ International Patient Assistance Program* (GIPAP). Dr Barker explained that this is a patient-directed donation programme under which Novartis provides the product free-of-charge in countries where reimbursement or health insurance coverage is not universal. Believing that it would not be appropriate for a pharmaceutical company to determine the recipients of the product, Novartis identified an independent organisation, *the Max Foundation*, to administer the programme. The organisation had expertise in CML and experience of helping patients in South America.

The programme has been set up in accordance with WHO Guidelines on Drug Donations which include criteria that:

- The drug should be approved for use in the receiving country; and
- Donations need to comply with national drug policies and essential drug programs in order to maximise the benefit of the drug to patients.

Putting the GIPAP into operation was not simple and required considerable global coordination and resources, but it has been very successful.

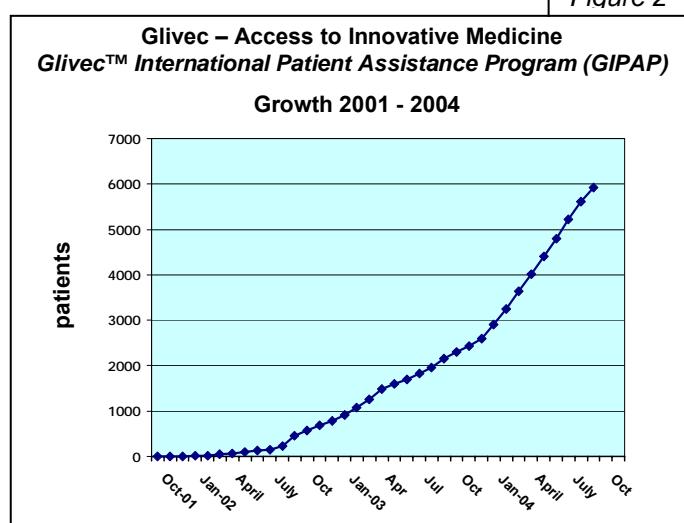
Figure 2

Dr Barker showed data (Figure 2) on the growth in the number of patients benefiting from the scheme between 2001 and 2004. The GIPAP today has a broader scope, covering both CML and gastrointestinal stromal tumours (GIST). There are now more than 7500 patients in 69 countries, involving some 600 physicians. Yearly audits are undertaken to identify issues and take action to improve the way the project functions.

Learning from experience.

Dr Barker referred to some of unexpected problems that had been encountered:

- Bringing free drugs into a country is not easy and requires administrative resources and local knowledge. Problems arise of classifying the product for tax purposes as it is not a clinical trial drug and, whilst being donated under a global patients' assistance programs, it is also commercially available.
- Cancer is not a therapeutic priority in some countries and anti-cancer drugs are not on the 'essential' medicines list with a result that these countries will allocate fewer resources to such programmes;
- Whenever 'means' tests are involved in selecting eligible patients there are many potential pitfalls, which can result in legal action.



In spite of the difficulties, however, Dr Barker affirmed that Novartis believes that the benefits of making a new medicine available globally outweighed both the risks and the financial penalties. The company is therefore considering projects for:

- An oral iron chelator being studied for transfusion-dependent anaemias (e.g., thalassemia and sickle cell disease)
- Other novel anticancer drugs that are in the pipeline

Conclusions

At the end of her presentation, Dr Barker re-emphasised the following points:

- Extended Access Programmes and global patients assistance programs such as GPAP are means of access to innovative drugs with unprecedented efficacy in patients with critical unmet medical need;

EAP and GPAP are feasible in oncology but there are critical conditions that apply:

- The pharmaceutical company:
 - Requires significant global capabilities and resource investments – not just local/regional strengths
- The participating countries/regions
 - Need to have an appropriate regulatory and legal environment as well as a sufficiently robust healthcare infrastructure;
 - Must have an oncology infrastructure with adequate expertise of the in-country medical community and sufficient oncology medical facilities.

DISCUSSION

Patient recruitment: Dr Barker was asked whether the EAP had interfered with the process of recruiting patients for controlled trials for regulatory purposes. She replied that this had not been a problem as the two activities focussed on different centres and had different objectives. She also commented that the specialist oncology centres rarely had problems recruiting patients for trials.

EAP vs. open-label clinical trials: Asked how she would distinguish between open-label clinical trials and the studies carried out under the EAP, Dr Barker agreed that there was less difference than had originally been expected. There were, however, fewer 'bureaucratic' issues to be addressed with the EAP studies – not least from the company's own regulatory department who would have insisted that the results of formal, open clinical trials be reported to FDA and other authorities.

Safety reporting: Feedback on adverse events from clinical use in developing countries is notoriously difficult to obtain, it was suggested. Dr Barker agreed that this would be the case for other types of medicines, for example antibiotics, where the patient might not return to the medical centre if the product was effective. Cancer patients, however, expect to visit the specialist repeatedly and obtaining feed-back was not such a problem. There was also the question of payment. Doctors had insisted on a fee for participating in the EAP but this would not be paid if the feed-back form was not completed and returned.

Scaling up production: Dr Barker was asked to comment further on the issue of scaling up production more rapidly than expected. She paid tribute to the experts who had worked 'round-the-clock' to overcome the main technical issues but noted that this reflected the motivation and 'excitement' engendered within the company by the project. It was also important that top management was willing to make the necessary resources available.

THE ROLE OF SPECIFIC OBLIGATIONS AND CONDITIONAL AUTHORISATIONS IN SUPPORTING INNOVATION - EU REGULATORY VIEW POINT

Dr Francesco Pignatti

Pre-Authorisation of Medicines for Human Use, European Medicines Agency (EMEA)

Dr Francesco Pignatti explained that his presentation was being made at a time when the implementation of new EU legislation was scheduled for November 2005 (see *footnote* on page 36). Some implementing regulations and guidelines relating to conditional authorisations and post authorisation commitments were still under discussion and therefore he could provide only preliminary thoughts about some of the expected changes. At this time, any comments he made on the role of these procedures in supporting innovation reflect past experience with the current procedures.

The relevant mechanisms, in EU terminology, are:

- Exceptional circumstances;
- Conditional marketing authorisations;
- Accelerated assessment;
- Risk management systems.

Exceptional circumstances

Dr Pignatti emphasised that the ability to grant authorisations under exceptional circumstances has been in the EU legislation all along but certain aspects are clarified in the new Regulation ((EC) No 726/2004). The criteria for invoking these provisions are

unchanged and, as the name implies, are intended to deal with situations that are outside the normal and where, because of the rarity of the disease, for ethical reasons or the state of scientific knowledge, a comprehensive drug development programme is impossible.

All such authorisations are granted with PACs – designated ‘specific obligations’ – but, in contrast to Conditional Authorisations, these are not necessarily expected to complete the data package and lead to a full authorisation. The objective is to collect data on the use of the product and continue to build up supplementary supporting data with a particular emphasis on safety⁷.

Conditional Marketing Authorisations

One of the new features of the new legislation is an explicit reference to ‘conditional’ marketing authorisations (see Box 1). The nearest equivalent, Dr Pignatti suggested, is the *accelerated approval* in the US.

Regulation (EC) 726/2004 sets the framework but calls for implementing regulations that will define the situations in which conditional authorisations may be possible. The draft implementing regulation had been published but not yet finalised⁸. It refers to the link between conditional authorisations and post-approval commitments and also includes requirements on transparency in relation to products released on conditional approval. Dr Pignatti highlighted the following aspects of the draft implementing regulation:

- **Purpose:** To make medicines available as early as possible to patients in medical need
- **Scope:** Orphan drugs, emergency threats, serious, chronic, life-threatening conditions
- **Criteria:**
 - A public health interest – fulfilment of an unmet medical need
 - Demonstration of a positive benefit/risk balance of the product, based on scientific evidence, pending completion of further studies

He emphasised that the purpose of a conditional MA was very different from an authorisation granted under exceptional circumstances in that it relates to a medicine where complete development is possible and, indeed, desirable. The challenge is to find the earliest moment when one can say that there is a presumed positive benefit risk and the drug can be released onto the market.

Role of specific obligations (PACs)

In the case of conditional MAs the role of the specific obligations is to confirm the positive benefit risk balance, said Dr Pignatti. The objective is also to ensure that sufficient data are obtained, as quickly as possible, in order to convert to a full authorisation and the draft regulation also states, explicitly, that the obligations placed on companies shall not exceed requirements for a full MA.

Referring to comments earlier in the Workshop about the need for PACs to be discussed between the company and regulatory authority, in a timely manner, Dr Pignatti reported that the draft regulation make provision for interaction between the sponsor and the EMEA’s Scientific Advisory Groups.

Box 1

Conditional Marketing Authorisation

Article 14(7) of Regulation (EC) 726/2004

“Following consultation with the applicant an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency.

The list of these obligations shall be made publicly accessible. By way of derogation from paragraph 1, such authorisation shall be valid for one year [instead of 5], on a renewable basis.”

⁷ “specific procedures, in particular concerning the safety of the medicinal product, ...” Article 14.8 of Regulation (EC) 726/2004 ...

⁸ Draft Commission Regulation on the conditional marketing authorisation for medicinal products falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004. Released for consultation 09/11/04. <http://pharmacos.eudra.org/F2/pharmacos/new.htm>

Dr Pignatti illustrated the differences between MAs granted under exceptional circumstances and conditional MAs, under the new legislation, as shown in *Figure 1*

He also provided an illustration of the types of product that had been authorised under the current procedures for 'exceptional circumstance' that might, in future, be eligible for a Conditional MA with specific obligations (*Box 2*).

Figure 1

Exceptional v. Conditional

Exceptional circumstances

- Comprehensive data cannot be provided (specific situations foreseen in the legislation)
- Reviewed annually to reassess the risk-benefit balance
- Will not (normally) lead to completion of the dossier and become a "normal" market authorisation

Conditional MA

- "Demonstrate" positive benefit-risk balance, based on scientific data, pending confirmation
- Authorisation valid for one year, on a renewable basis
- Should aim to become a "normal" marketing authorisation as early as possible

Box 2: Authorisations granted under exceptional circumstances

Out of 44 'Exceptional Circumstances' MAs the following 16 (37%) reverted to normal MAs after the Specific Obligations were fulfilled

• Epivir (HIV)	• Viracept (HIV)	• Taxotere (breast cancer)
• Norvir (HIV)	• Crixivan (HIV)	• Remicade (Crohn's disease)
• Kaletra (HIV)	• Zeffix (hepatitis B)	• Ferriprox (iron chelator)
• Invirase (HIV)	• Betaferon (multiple sclerosis)	• Tracleer (pulmonary hypertension)
• Agenerase (HIV)	• Rebif (multiple sclerosis)	• Ammonaps (urea cycle disorders)
• Viramune (HIV)		

Accelerated assessment

Another new element of the legislation that Dr Pignatti discussed is *accelerated assessment* and noted that this is a procedure where PACs fulfil entirely different role. The objective is to facilitate a very fast review and the legislation formalises a process that was available in the past but was applied *post hoc* and was driven by the quality of the dossier.

Based on previous EMEA experience, products eligible for accelerated review had to address serious diseases for which there was no alternative therapy, and had to have an exceptionally high benefit. Such assessments may result in a conditional authorisation with an extensive list of follow-up commitments. The objective of these will be to postpone, to the post-authorisation stage, any issue that is not crucial to the decision to approve the medicine.

An important difference between the EU accelerated assessment and, for example, the US priority review is that there is no provision to prioritise the review of one product in a way that might 'penalise' the review of other products.

Box 3

Accelerated assessment

Article 14.9 of Regulation (EC) 726/2004 "... [for] medicinal product[s] for human use which are of major interest from the point of view of public health and in particular from the point of view of therapeutic innovation, ..., the time limit [of 210 days] ... shall be reduced to 150 days."

Pharmacovigilance and Risk Management System

Dr Pignatti concluded his review of the new legislation by referring to new requirements to include in marketing applications a plan for post-authorisation pharmacovigilance and a risk management strategy (*Box 4*).

The guidance to support the regulation is currently being developed and there is also an ICH guideline that gives an international dimension:

- ICH E2E: Pharmacovigilance planning (<http://www.ich.org>)

Box 4

Pharmacovigilance and Risk Management

Article 8 (3) of directive 2001/83 "The application shall be accompanied by ... (ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce."

The EMEA experience of post-authorisation commitments

Dr Pignatti distinguished between the terminology used for PACs in the EU context:

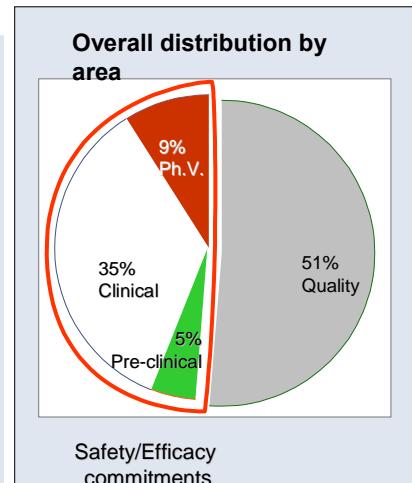
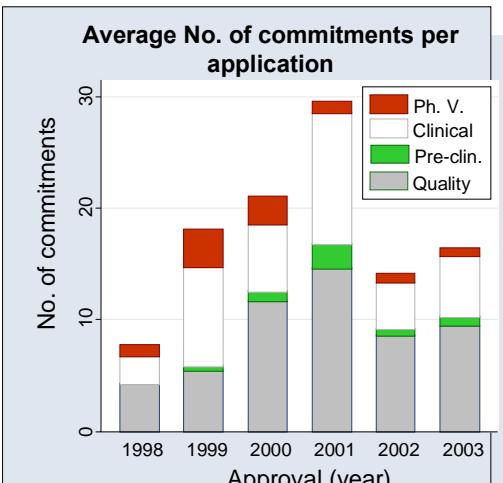
Follow-up measures: These can refer to any type of MA and less than 5% of products have no follow-up measures during the product lifecycle. They can relate to any aspect of the application and are intended to improve and 'perfect' the data set as well as confirming plausible assumptions.

Specific obligations: This term is currently only used for authorisations granted under 'exceptional circumstances' and will in future apply to conditional authorisations. The requirements relate to further assessment of benefit/risk and the confirmation of assumptions that have been made e.g., on surrogacy.

Dr Pignatti presented results from work in progress on the numbers of commitments attached to applications from 1998 to 2003 and the distribution between different aspects of the application (Figure 2). Clearly, the majority of commitments refer to quality and clinical issues. Over the years, he noted, there has been a variation in the average number of PACs per submission but there is not a clear, simple upward trend in requirements.

Figure 2

Follow-up Measures and Specific Obligations the EMEA Experience (1998-2003)



A further analysis had been carried out to identify the factors that most frequently 'trigger' requirements for safety and efficacy post-authorisation commitments. Anticancer drugs and products for HIV infections, applications with shorter review time, applications with major objections on non-clinical or clinical safety aspects, and applications with approval under

exceptional circumstances were all associated with a higher number of Safety/Efficacy PACs (multivariate analysis).

Conclusion

In conclusion, Dr Pignatti affirmed that, in EMEA's experience, the appropriate use of PACs has a pivotal role in allowing accelerated assessment of key products and allowing early approval of products fulfilling a major unmet medical need.

Although some legislation and guidelines are not yet finalised the new procedures are aimed at encouraging the rapid availability of innovative new medicines. As an illustration, Dr Pignatti quoted the 33 recital in the preamble to Regulation (EC) No 726/2004:

'In order to meet, in particular, the legitimate expectations of patients and to take into account of the increasingly rapid progress of science and therapies accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions'.

Footnote

New EU Legislation

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

This replaces Regulation (EEC) No. 2309/93/EC (of the same name) and some provisions came into force in 2004. Title II on the authorisation and supervision of medicinal products for human use will be implemented on 20 November 2005.

Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

This has to be implemented by Member States no later than 30 October 2005.

Other directives and regulations adopted under the review of EU pharmaceutical legislation are listed on the Pharmacos website: <http://pharmacos.eudra.org/F2/review/index.htm>

DISCUSSION

Accelerated assessment: Dr Pignatti was asked when the decision would be made that an application should be subject to an accelerated assessment. Noting that the details had yet to be confirmed, he gave his view that the matter would be discussed at the pre-review meeting but that the decision would be for the CHMP. In order to achieve a review in 150 days the decision most likely must be taken before the evaluation starts.

International cooperation: Asked about the possibility of trans-Atlantic cooperation between regulatory agencies over accelerated reviews, Dr Pignatti pointed out that the legislation did not envisage that priority review by FDA would automatically trigger similar action in the EU.

Dr Patrick Le Courtois, EMEA, confirmed that the plans for greater collaboration between EMEA and FDA over the scientific advice given on new products would also make it easier to coordinate action on urgently needed new medicines.

Advisory groups: A participant expressed concern that using the Scientific Advice procedure was somewhat bureaucratic and time-consuming but Dr Pignatti pointed out that the draft legislation on conditional authorisations primarily refers to Scientific Advisory Groups that can be convened rapidly during the evaluation, unlike the more complex procedures that accompany official consultations for Scientific Advice before Marketing Authorisation.

Data requirements: In response to a question about the difference in data requirements for a normal application and an accelerated review, Dr Pignatti indicated that there was not expected to be a difference. The conditional MA review provides a facility to postpone issues that are not critical to the decision to release products that are expected to have an exceptionally high benefit.

WHAT ROLE SHOULD POST-APPROVAL COMMITMENTS AND CONDITIONAL AUTHORISATIONS PLAY IN A REGULATORY ENVIRONMENT THAT SUPPORTS INNOVATION? AN INDUSTRY VIEWPOINT

Dr Don Stribling

Vice President and Head of Global Regulatory, AstraZeneca Pharmaceuticals, UK

In his presentation, Dr Don Stribling explored further the vision that conditional authorisations could be used as a way of allowing new medicines to be released earlier and evaluated in a 'real world' patient population. Against a background of increasingly onerous pre-submission requirements and the cost and time of drug development increasing, he suggested that a new way of thinking is needed to ensure that pharmaceutical innovation remains viable.

A Changing World

Medicines are currently being developed in a world that is changing rapidly, Dr Stribling said. On the one hand, there are enhanced patient services with the increasing use of telemedicine, digital data collection the prospect of collecting information from electronic medical records. On the other hand there is a toughening healthcare environment.

In the world of drug development, new disease targets present new opportunities for the use of biomarkers and demonstration of effects on surrogate endpoints but the validation of these could take many years. Similarly, studies to prove disease modification or the relative risk of medicines can be very sizeable and lengthy. Incremental benefits between one drug and another can represent very important steps forward in medical care but proving those benefits adds to the time and cost of drug development.

At the same time, companies are facing curtailment of the life-cycle of products, with sales being eroded through the early appearance of generics in some parts of the world, which, with the growth of Internet prescribing, will soon become a global issue.

Drivers for change

The vision that the viable life-cycle of medicines could be extended by allowing their early effective launch is an attractive one. Dr Stribling, however, highlighted some of the caveats to be borne in mind:

- The product would be prescribed by community physicians who are less expert, or specialised than those conducting the clinical trials, who would be relying solely on the product prescribing information as their primary source of information;
- Obtaining follow-up patient information in the post-approval phase is notoriously difficult as it requires the prescriber and, in some cases the patient, to invest additional time and effort;
- Agreement to release medicines early may be increasingly difficult in the 'risk averse' regulatory and political environment. Companies must also contend with an 'aggressive' media and the threat of opportunistic litigation that can have crippling results;
- Even with an expedited approval, companies are still faced with the 'fourth hurdle' of having the product accepted for reimbursement or supply by the healthcare providers and their advisers such as the UK National Institute for Clinical Excellence (NICE), who often require the full outcome data to be available before agreeing to list the product.

The potential role of conditional approvals

Dr Stribling discussed the key questions that need to be addressed in seeking to turn the 'risk' of conditional approvals into an opportunity:

- Can conditional approvals be used to reduce development times?
- Is it time to extend accelerated approvals and conditional authorisations to a greater proportion of medicines in development?
- What safeguards are required to protect patients?

Can conditional approval reduce development times?

Dr Stribling suggested that there were further questions to be asked in order to address this issue:

- *Do we need two adequate and well-controlled pivotal Phase III studies?* By definition an 'adequate and well-controlled' pivotal study should not need a second, he argued, and suggested that it seemed to be a 'tradition' rather than any mathematical logic that required the second study;
- *Could the period between the end of Phase III and approval be used more effectively to generate useful clinical experience to be included in labeling?* Dr Stribling referred, in particular, to the situation in Japan where it becomes almost impossible to run meaningful studies in the window following submission of the dossier and marketing.
- *Could some issues on long-term safety of efficacy be better answered during the post marketing period?*
- *Are 'Real-World' studies more relevant in some diseases?*

Clinical trials in centres of excellence do not necessarily produce the best answers in some conditions. Dr Stribling referred to the way in which diabetes patients on placebo show significant improvement merely because they are being seen regularly by a doctor. Studies in the real world would be much more relevant to define the benefits of the product that would be achieved in actual clinical use.

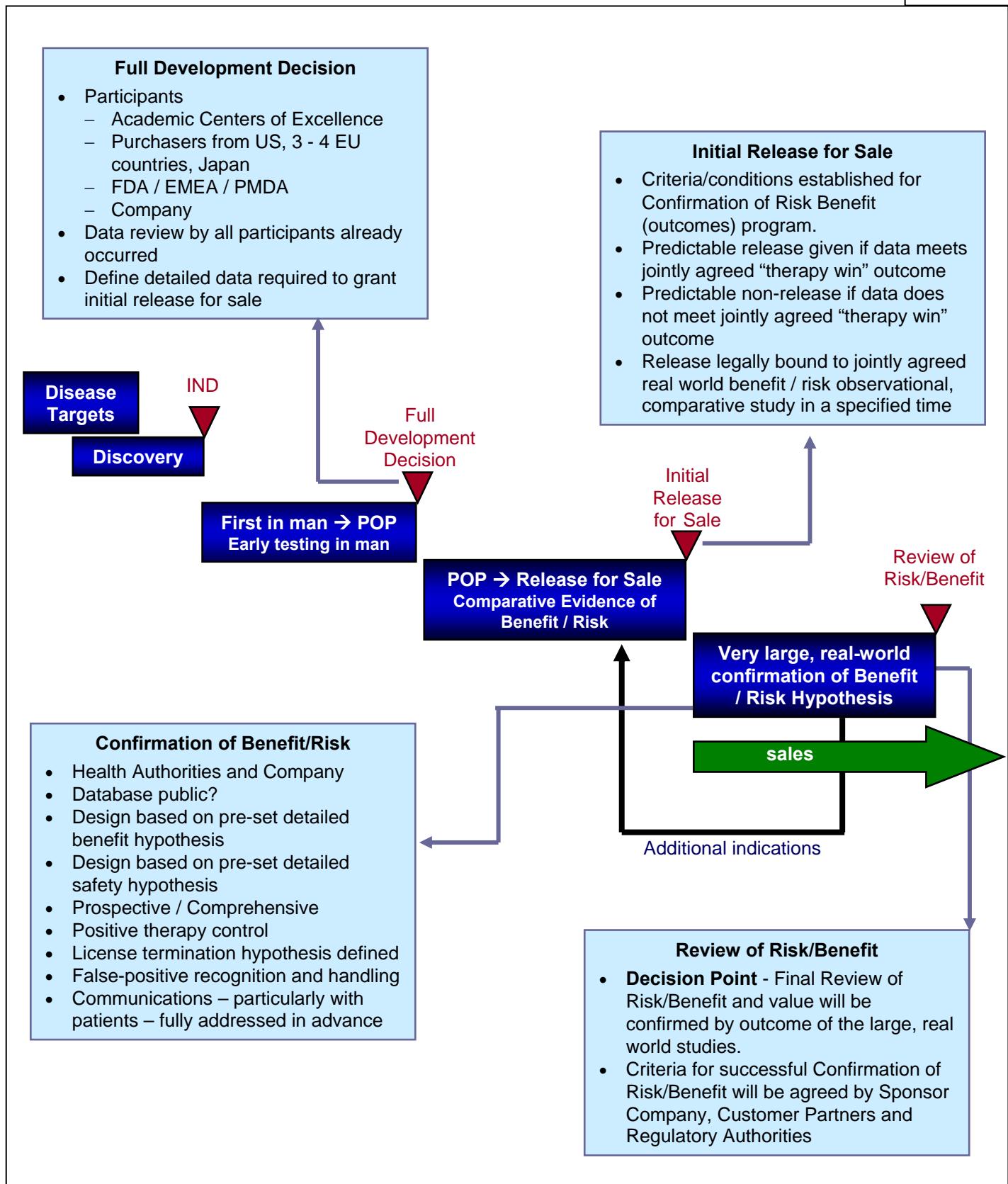
Testing in the real world

Dr Stribling re-visited the ideas that had been put forward previously by George Butler⁹ and are illustrated in Figure 1. This is the proposal that some products could be released for sale, on a conditional authorisation (CA), once proof of principle has been achieved, thus allowing large real-world studies to be carried out in parallel with initial sales. He stressed the point that, in developing a product under a CA rather than through a normal Phase III programme there would need to be partnership between the product sponsor, the regulatory agency and the healthcare providers as all three would be involved.

This is an attractive vision that George Butler had suggested and could, potentially, reduce the time lag before a new medicine was available to patients by some two years (Figure 2). Dr Stribling voiced some cautions, however. If the data from the studies carried out under the CA do not return the results that were expected the company and authorities would be faced with the problem of whether the product can be withdrawn. Once a medicine has become established in the 'pharmacopoeia' there will always be some patients who are benefiting and will suffer if the product is discontinued.

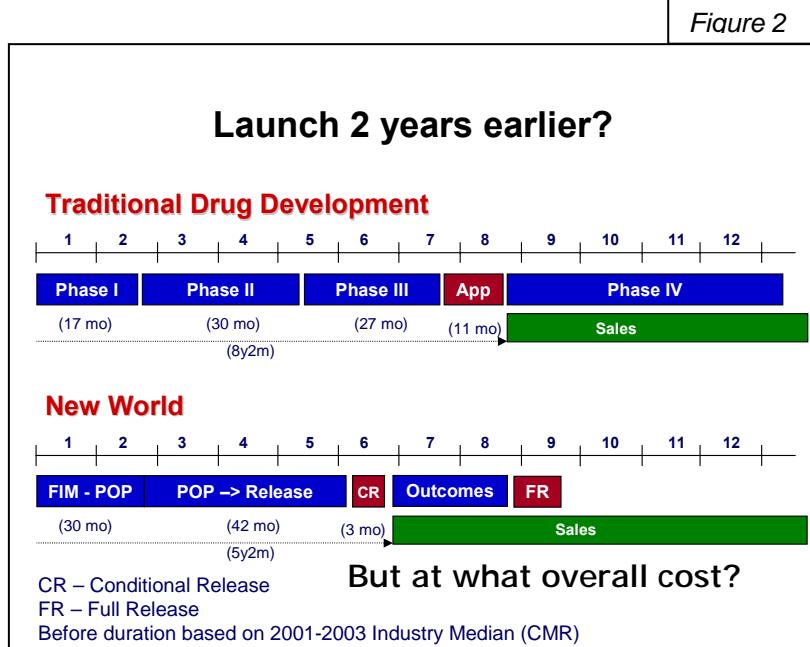
⁹ Dr George Butler, AstraZeneca, CMR International Institute Workshop on 'Global Drug Development', Tokyo, Japan, May 2004

Figure 1



POP = Proof of Principle i.e. Compound does what it was designed to do at a safe and well tolerated dose

Figure 2



Extension of Conditional Approvals to a greater proportion of medicines

The shortcomings of existing medicines, for many patients, are well recognised but the development of novel medicines e.g. targeted at disease modification, may depend on new surrogates and biomarkers that can take a great deal of time to gain acceptance. Validation procedures for regulatory acceptance are not well defined.

The benefits of early access to innovative new medicines should not, Dr Stribling suggested, be restricted to life-threatening conditions. Patients with chronic and debilitating diseases should also be considered for priority access to medicines that might improve their quality of life. For such patients the overall benefit-risk might only be apparent in long-term treatment but there are real opportunities to reduce the costs of healthcare in a 'win-win' situation where patients are kept mobile rather than hospitalised.

The 'building blocks' for progress

Dr Stribling suggested that certain 'building blocks' would have to be put in place in order to move towards a more widespread use of conditional authorisations and earlier marketing:

- The focus of the development work prior to launch would need to be on safety at the efficacious dose rather than on relative efficacy;
- It must be accepted that long-term efficacy and usage data would be generated under the studies agreed as post-approval commitments;
 - Such studies must be realistic and deliverable whether they involve collecting real-world data or carrying out further controlled clinical trials;
- Early and close collaboration must be established between companies, healthcare providers and regulators in order to agree early release at national level. Even more challenging is the need for understandings between the major regulatory bodies (FDA/EMEA/PMDA) in order to ensure that the data generated under a CA are recognised as valid.

Some practical issues

Dr Stribling also struck a cautionary note in respect of the practical aspects of undertaking 'usage' studies after the early launch of a product:

- Such studies are only really feasible in large markets with compatible health care delivery, in terms of the standard of treatment and accessibility of medical records;

- As the studies may fall outside the terms of conventional clinical trials there are questions of the legal liability and where it rests;
- There is also the question of whether informed consent/IRB clearance is required or whether the studies are considered as uncontrolled observational data;
- In clinical studies there are extensive checks to ensure that specific measures are standardised, in order to make valid comparisons. In usage trials the lack of these controls mean that the studies must be enlarged to compensate;
- Although there is much mention of electronic records and IS/IT links, in practice many hospitals and general practitioners are not well connected for on-line information exchange;

Even if these are solved, a fundamental issue, said Dr Stribling, is the question of the costs of the post-launch studies and the impact that a restricted launch may have on the return on investment.

What safeguards are required to protect the patient?

One safeguard that could be applied is to slow the launch of a product under a CA, by restricting its availability to specialist doctors and treatment centres that can provide the relevant clinical data on safety and efficacy. However, Dr Stribling noted, this would also slow down the collection of data and would delay access to patients, thus defeating the objectives that are being pursued.

He believed that it would be better to implement 'reinforced' prescription event monitoring to provide rapid feedback during the post-launch period. This could best be achieved through monitoring electronic health records. Although this may still lie in the future, Dr Stribling believed that a system that could take data from medical records would provide a robust way to accumulate knowledge quickly and effectively and 'stop disasters before they had become established'.

Whatever other measures are adopted, however, the fundamental requirement is for a product-specific Risk Management plan and post marketing surveillance strategy that needs to be discussed and agreed as part of the conditional authorisation and post-authorisation commitments. Furthermore, such plans need to take account of global experience with the product and not be built up on a national basis, until the whole scheme becomes impossible to navigate.

Benefits from an integrated approach

Summarising, Dr Stribling looked at the benefits to be derived from an integrated approach to the expedited introduction of innovative medicines under conditional approvals. These included:

- Access to real-world data to validate unproven surrogate markers;
- Better control of unpredicted events in the post-launch period;
- Faster clarification of benefit/risk in a broader patient population;
- Arrival at better labelling sooner rather than later;
- Establishing a better and more credible dialogue with patients and prescribers.

He warned, however, that if we go down this route it must not become a fourth or even a fifth hurdle. That is, in a worst-case scenario:

- The existing Phase I-III studies under existing time lines to which are added:
 - Post Marketing Commitments;
 - A slow, controlled launch that reduces revenue; and
 - The possibility of withdrawal from sale at the time of review for a full release for marketing.

The result would be longer development times with no return on investment and 'no one would be in there innovating'.

Defining the objectives

In order to avoid this negative outcome, Dr Stribling stressed the importance of defining clear objectives. He was concerned that the concept of accelerated review in exchange for post-approval commitments was becoming caught up in a wish for enhanced post-marketing safety surveillance and moving away from the genuine conditional approval designed to allow early patient access whilst long term efficacy data are generated.

It is important to be 'honest' on a drug-by-drug basis of whether the objective is:

- To slow down or control the release of a new medicine in order to control the risks; or
- To accelerate approval of new medicines whilst being able to obtain valid outcomes data to improve health care

DISCUSSION

Failures in Phase III: In view of the substantial number of drugs that fail in Phase III, it was suggested that there is a danger in moves towards early release and, in effect, carrying out Phase III after launch. Dr Stribling agreed but suggested that the fault lay in the Phase II studies that are often not sufficiently well designed for defining risk and dosage regimes or identifying interactions. He welcomed proposals for improved access to early scientific advice, in the EU and believed that it was most important for the EMEA and FDA to work together on discussions of the design of Phase II studies.

Large, automated population-based databases: There was a comment that, although the establishment of electronic health record databases in Europe had been somewhat slowed by data privacy constraints, progress was being made and such data sources were already available in the US. It was suggested that the best way to demonstrate that it is possible to carry out valid safety and efficacy studies in the post-launch period would be to carry out a pilot study in a population where appropriate databases exist.

Control groups for observational studies: The question of the basis for evaluating results from studies in 'real usage' in patients as opposed to controlled trials. Dr Stribling agreed that a control group is needed and that the results could not be evaluated against the 'basket of other studies' as this could introduce bias and not be comparing like with like. He suggested that the studies could use a 'nested case control' design where baseline characteristics of patients commencing therapy are recorded and then are assigned at the physician's discretion to the test agent or other available treatments. The outcome is tracked for all patients and comparisons made between matched subsets or by correcting for baseline factors on the whole population.

Pharmacogenetics: Asked about investigation of pharmacogenomics/pharmacogenetics aspects, Dr Stribling replied that this is one of the factors that can be evaluated in broad population studies. In fact, it is only when one moves to large populations that meaningful observations can be made. It is quite legitimate, he suggested, to carry out retrospective pharmacogenetic correlations based on blood samples from post-approval patients (with the appropriate consent). Such investigations could lead to improved labelling at a much earlier stage.
