

# **New Approaches to Product Approval:** *Balancing early release with improved safety monitoring*

## **WORKSHOP REPORT**

**14-15 June 2007  
Washington, D.C., USA**



October 2007



**Institute for Regulatory Science**

### **CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE**

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### **Workshop on New Approaches to Product Approval Balancing early release with improved safety monitoring**

14-15 June 2007

Sofitel Hotel

Washington, DC USA

#### **Workshop Organisation**

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## WORKSHOP ON NEW APPROACHES TO PRODUCT APPROVAL: Balancing early release with improved safety monitoring

### Section 1: Overview

#### Background to the Workshop

Different approaches have been adopted throughout the world for making new medicines available to patients more rapidly. Orphan drug programs, conditional approvals, and accelerated approval procedures are some of the approaches used by countries to provide more rapid access to important new products. Early availability, however, must be balanced by appropriate safety monitoring in the post-approval phase.

This workshop consolidated previous Institute discussions on changing development and review paradigms. In particular it looked at faster access to new medicines through early release and follow up in the 'real world' patient population and through the appropriate use of large-scale databases of electronic medical records (EMRs)

It also explored the question of whether early availability models should be extended to less urgently needed medicines.

#### Conclusions

##### *Review models*

Having considered the current models for standard and accelerated review and possibilities for early release based with post marketing commitments it was recommended that the focus should be on **improving the current models** rather than looking for radical new models which, for example, would extend the range of medicines eligible for early release.

This recognised that industry and regulators are working in a risk-averse environment with ever-increasing concerns about balancing the benefit and risks of new medicines.

##### *Safety issues*

It was agreed that the safeguards provided by the current safety criteria are adequate for standard approvals but it was recommended that **new measures for post-approval monitoring** for safety need to be adopted if early release is to become a realistic alternative.

##### *Population-based EMR Databases*

One of these measures is the improved and better coordinated use of large-scale databases of health information and it was recommended that a **forum** should be established to discuss database **standards**, develop **guidelines**, gain agreement between industry and regulators about database capabilities, and encourage **training** and education regarding database technology.

##### *Communication*

There was consensus that **better communication** is the key to ensuring that any changes are brought about in a way that is understood and accepted by **all stakeholders**.

It was recommended that a multidisciplinary group should focus on the way in which the **benefits and risks** of new medicines are currently communicated and the need for information on any proposals to change or develop review procedures and post-marketing surveillance methods.

##### *Specific recommendations*

The following are some of the specific recommendations relating to these conclusions:

■ **Unmet medical need** should remain the threshold condition for models such as *Conditional Approvals* that provide early access to new medicines but International agreement on a definition would be an advantage.

■ The on-going **incorporation of science** into regulatory processes is essential to achieving improvements in review and approval models.

■ Safety is closely linked to ensuring that products are used only in the **intended target patient population** and measures are needed to discourage **off-label use** which may impact the benefit-risk balance.

■ The safety risks of new medicines include 'theoretical' risks that can best be assessed from experience of similar therapeutic classes but this would require a **willingness to share information** among regulatory agencies and companies

■ The utility of EMR databases for **signal identification** needs further study, especially in relation to verifying signals across databases and evaluating and interpreting results.

■ A single, global **centralised EMR database** is unlikely to be feasible. Consideration should be given to a **distributed model** to bring together data sets as needed.

■ **Discussions on better communication** must take account of Pharmacists, Physicians, Patients/ General public, those concerned with Insurance plans and Policy makers as recipients of information.

■ Of particular importance is **transparent disclosure**, at the time of authorisation, of information on what is known and what is not known of the safety risk of new medicines.

Safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit and the alternatives available.

Task Force on Risk Management, US DHSS, FDA, May 1999

## Workshop highlights

The first session addressed **Issues of Concern** in current approaches and was chaired by **Dr. Steve Ryder**, *Senior Vice President and Therapeutic Area Development Group Head, Pfizer Inc., USA*, who was also the first speaker.

He focused on challenges and opportunities in the development of innovative new medicines and emphasised the complexities of the current drug development process. Dr Ryder covered the need for improved clinical assessments to predict impact on individual clinical conditions and the importance of a better understanding of variables associated with disease in relation to assessing benefit and risk during drug development.

**Dr. Marlene Haffner**, *Executive Director, Regulatory Affairs, Amgen, Inc., USA*, then spoke about the US Orphan Drug Act, approval processes for orphan medicines, and specifics regarding the orphan product development staff. **Dr. Hans-Georg Eichler**, *Senior Medical Officer, EMEA*, concluded the session with a discussion of early access models and introduced the conditional approval model as used in Europe.

### Drivers for Recent Authority Initiatives

Session 2, also chaired by Dr Ryder, looked at the development, risks, and rewards of approval systems in Europe, the United States, Australia, and New Zealand.

**Dr. Bruno Flamion**, *Chairman, EMEA Scientific Advice Working Party*, further elaborated on the European conditional approvals system and provided first-hand experience from the early cases reviewed by the EMEA/CHMP (Committee for Medicinal Products for Human Use) under the revised legislation, of November 2005.

**Dr. Martha Brumfield**, *Senior Vice President, Worldwide Regulatory Affairs and Quality Assurance Pfizer, Inc., USA*, gave an industry perspective on use of the revised provisions for EU conditional approvals. She reviewed her company's European submission strategy and success factors for the conditional and subsequent full approval of a novel compound.

**Dr. John Jenkins**, *Director, Office of New Drugs, CDER, Food and Drug Administration, USA*, presented the history, specifics, and key learnings regarding the FDA Pilot study for Continuous Marketing Applications (CMA). Although FDA and industry agreed that the CMA Pilots would not continue he concluded that the pilots had provided valuable lessons that can be applied to future interactions on Fast Track products

**Dr. Leonie Hunt**, *Director, Drug Safety and Evaluation Branch, TGA, Australia*, spoke next about the merger of the regulatory agencies of Australia and New Zealand in the Trans Tasman Therapeutic Products Agency and the challenges of establishing a system for sharing the work of reviewing new medicines.

**Dr. Supriya Sharma**, *Acting Director General, Therapeutic Products Directorate, Health Canada*, looked at joint activities between agencies from the perspective of the joint-review initiatives in which Health Canada has been involved. A key to success lies in confidence-building between agencies

### Building Systems to Balance Access with Safety for Patients

Session 3 was chaired by **Dr. John Lim**, *Chief Executive Officer, Health Sciences Authority, Singapore*, and focused on considerations when balancing faster access to medicine with patient safety.

**Dr. Robert Temple**, *Associate Director for Medical Policy, Food and Drug Administration, USA*, presented key components of safety and efficacy from the regulatory perspective. He concluded that this is 'certainly not the year to be advocating less safety data as a matter of routine' but FDA acknowledges there are cases that create 'a sense of urgency' and, initially, accepts less information at the time of review.

**Dr. Alexander Walker**, *Senior Vice President, Epidemiology, i3 Drug Safety, USA*, reviewed large-scale population-based databases, discussed the utility of these for safety surveillance, and outlined the need for enhanced information on medical records, laboratory data, hospital information, comprehensive processing, and rapid cycle analysis.

**Dr. Kathleen Stratton**, *Scholar, Institute of Medicine (IOM), The National Academies, USA*, spoke next about the IOM Committee on Drug Safety report on 'Managing safety for the life cycle of a product'. This includes a suite of 25 recommendations that aim to provide a cohesive, integrated approach to transforming drug safety.

**Dr. Dorian Lo**, *Chief Medical Officer, Health Plans, Medco Health Solutions, Inc, USA*, concluded Session 3 by addressing the decision factors that face the 'payer' when considering products released for early access to treat life-threatening diseases. He concluded with factors related to the novelty of the product, affordability and cost effectiveness and measures to ensure clinically appropriate use.



## WORKSHOP QUALITY DECISION-MAKING: Procedures and practices in drug development and the regulatory review

### Section 2: Outcome

#### Syndicate Discussions

Session 4 of the Workshop, during which the Syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Professor of Paediatrics, University of British Columbia, Canada*.

The Workshop participants formed three Syndicate groups to address:

- **Approval Models** – current models and models for the future
- **Managing Safety** – realities pre- and post-authorisation
- **Databases** – critical success factors for use of large-scale population databases

The Chairpersons and Rapporteurs for the three groups were:

<b>Syndicate 1</b>	<i>Chair:</i>	<b>Dr. Christopher Milne</b> , <i>Assistant Director, Tufts Center for the Study of Drug Development, Tufts University, USA</i>
	<i>Rapporteur:</i>	<b>Dr. Supriya Sharma</b> , <i>Acting Director General, Therapeutic Goods Directorate, Health Canada</i>
<b>Syndicate 2</b>	<i>Chair:</i>	<b>Dr. Sandra Kweder</b> , <i>Deputy Director, Office of New Drugs, CDER, Food and Drug Administration, USA</i>
	<i>Rapporteur:</i>	<b>Dr. George Butler</b> , <i>President, SingEval Inc, USA</i>
<b>Syndicate 3</b>	<i>Chair:</i>	<b>Robert Reynolds</b> , <i>Executive Director/Global Head, Epidemiology, Pfizer, Inc., USA</i>
	<i>Rapporteur:</i>	<b>Dr. Graham Burton</b> , <i>Senior Vice President, Regulatory Affairs, Pharmacovigilance and Project Management, Celgene Corporation, USA</i>

### 1. BACKGROUND AND RECOMMENDATIONS

#### 1.1 Previous discussions

This Workshop followed-up discussions at previous Institute Workshops on ways to speed the review and approval process in order to make innovative new medicines available more rapidly to patients. At a Workshop on *Global Drug Development*, in May 2004, the Institute was urged to take a lead in encouraging international debate on a 'new paradigm' for drug development and regulatory review. Accordingly a Workshop on *A New Paradigm for Clinical Research* was convened in October 2005 at which the models that were discussed included the simplified two-stage 'Learn and Confirm' research paradigm: *Learn* from discovery to 'proof of concept' and *confirm* from PoC to marketing submission.

**Education and awareness:** Any moves to change the current paradigm will require a major campaign to reassure the public and political bodies and, in particular, healthcare providers, that safety standards will not be compromised.

*Report of the Institute workshop on 'A New Paradigm for clinical Research'*

Among the visions for the future were proposals for extending the scope of 'conditional' approvals such that a wider range of products should be reviewed and made available to patients at an early stage after PoC. In other words, much of the Phase III (or 'Confirm') studies would take place in 'real world' patient populations with intensive safety monitoring and feedback.

This built on recommendations from a Workshop in May 2005 that had previously looked at the value and scope of conditional authorisations as a way of achieving faster access to new medicines. Recommendations from both Workshops had urged the Institute to look further into the potential role of large-scale population-based databases of medical information as a source of post-marketing information on medicines



## 1.2 Recommendations

### 1.2.1 Approval models

In an environment of ever-increasing concerns about balancing benefit and risk, **it was recommended that** the focus should be on improving the current models for the development and review of new medicines rather than looking for radical new models.

- Any **novel approaches** to allow early access to new medicines by changing the regulatory process must be balanced by equally novel approaches to:
  - Education of the professions and public
  - Exerting an influence on drug utilisation
  - Ensuring adequate post-marketing surveillance
- The threshold conditions for using models such as *Conditional Approvals* to provide early access should remain as **unmet medical need** (i.e., the first in class for an untreated disease or presenting a significant incremental benefit-risk balance). International agreement on a definition would, however, be an advantage.
- Improvements in approval models will best be brought about by accelerating the **incorporation of science** into regulatory processes and adopting the attitude that better benefit-risk will result from scientific advance and not by 'quick fixes' that respond to a perceived crisis.

### 1.2.2 Current Safety Criteria

The safeguards provided by the current safety criteria are regarded as adequate for standard approvals by those involved in medicines development and regulation but **it was recommended that** the safety measures for post-approval monitoring need to be addressed if early release is to become a reality for a wider range of products.

- Models for accelerated access through early approval may require specific safety measures to limit utilisation to the **intended target patient population** and **avoid off-label use**. Such measures might include limiting products to specified medical centres, or dispensing outlets.
- There is a need for a **standardised 'tool kit'** of such safeguards to enable the earlier release of new medicines and manage their proper use. A cross-functional group of experts should be convened to produce proposals that would apply on a non-company specific basis.
- The safety risks of new medicines include 'theoretical' risks that can best be assessed from experience of similar therapeutic classes but this would require a **willingness to share information** from regulatory files or from industry on failed products.

### 1.2.3 Databases of Electronic Medical Records

Improved and better coordinated use of large-scale databases of health information is an important goal for the future to improve post-marketing surveillance and facilitate earlier release of new medicines. **It was recommended that** a forum should be established to discuss database standards, develop guidelines, gain agreement between industry and regulators about database capabilities, and encourage training and education regarding database technology.

- The group could also address the utility of databases for **signal identification** and propose rules for verifying signals across databases and for evaluating and interpreting results.
- Interpretation is vital. Combining data in a single, global, centralised model would be very valuable, but this is unlikely to be feasible. The feasibility should be considered of developing a **distributed model** to bring together data sets as needed.

### 1.2.4 Communication

Better communication is the key to ensuring that changes are brought about in a way that is understood and accepted by all stakeholders. **It was recommended that** a multidisciplinary group should focus on the way in which the benefits and risks of new medicines are currently communicated and the impact of any proposals to change or develop review procedures and post-marketing surveillance methods.

- The **recipients of information** whose interests must be met include: Pharmacists, Physicians, Patients/ General public, Insurance plans and Policy makers
- Of particular importance is **transparent disclosure**, at the time of authorisation, of the information on what is known and what is not known of the safety risk and lessons may be learnt from the way in which this is achieved in the EU documentation.

## 2. DETAILS FROM THE SYNDICATE DISCUSSIONS:

### 2.1 Review models

*In an environment of ever-increasing concerns about balancing benefit and risk, it was recommended that the focus should be on **improving the current models** for the development and review of new medicines rather than looking for radical new models.*

Given the current environment, the regulatory and medical community does not want to give the impression of “lowering the bar” for safety data. Approvals must ensure appropriate safeguards for the patient, according to the nature of the disease and differences in procedures and data requirements for reaching those approvals already exist:

#### **Procedural**

- **Standard Reviews** where no special procedures are applied and normal review targets and assessment processes are followed;
- **Priority/ Accelerated reviews** which are normally applied to products addressing unmet medical need and review times are shortened.

#### **Data requirements**

- **More limited data set** accepted for products for unmet medical needs where patient population is small (e.g., **orphan** medicines and EU approvals under **exceptional circumstances**) or the product is authorised on the basis surrogate end-points or biomarkers that are not yet fully validated. In the latter case approval is normally agreed with **post-approval commitments** for confirmatory studies to be carried out (e.g., **conditional approvals** in the EU and *accelerated approval rule* (**Subpart H**) in the US).
- **More extensive data set**: This applies when there are known reasons to require additional studies that may slow development and delay the stage at which application is made, although the review time is not affected. Examples include QT prolongation studies and cardiovascular testing for non-steroidal anti-inflammatory drugs (NSAIDs).

It was agreed that these procedural and data categories do not need to change but that the focus should be on ensuring that products are **triaged more efficiently** into the right category.

#### **Science and Regulation**

There was discussion of the need for science to be at the centre of regulation and to be the focus of interaction on the practice of medicine as it impacts drug use. Concern was expressed about the need to **keep critical path initiatives focused** on the scientific issues and on preventing them from being sidetracked by reactions to the current *crise du jour*.

Scientific developments that were cited for improving drug development included:

- **Targeted patient selection**, pharmacogenetics and genomics, Voluntary Genomic Data submission (VGDS);
- **Better efficacy and/or safety endpoints** through biomarkers (agency approved biomarkers and industry validated ones)
- **Study Design:**
  - Exploratory INDs (to decrease failure rate and take better, fewer candidates forward)
  - Responder Studies (also known as subtraction trials)
  - Adaptive Clinical Trial designs

## 2.2 Current Safety Criteria

*The safeguards provided by the current safety criteria are regarded as adequate for standard approvals but it was recommended that the safety measures for post-approval monitoring need to be addressed.*

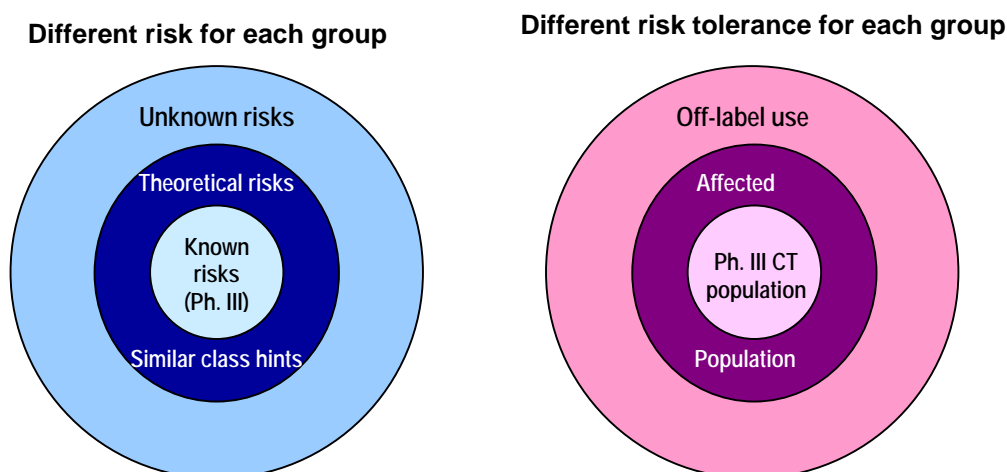
A release paradigm was constructed to look at normal approval stages and then assess the comfort level with safety data requirements and practices pre- and post-approval.

It was agreed that the safety criteria applied by companies and required by regulators for standard review and normal release are working by the two parties provided that **'approval' is seen as a continuum** and not an end to the safety review. An essential point is that "input by the right people with the right input" is critical and extends beyond regulators and industry. Politicians, the public, and perhaps even physicians are not necessarily satisfied with current safety criteria requirements.

With respect to post-approval safety measures it was felt that there is a need for substantial **improvement in communication** with all parties and for new study designs. In particular, new tools need to be developed if progress is to be made in the concept of early approval with post-approval data collected from real-world studies.

### Types of risk

The different types of risk that exist when a product is approved and the different risk tolerances were set out diagrammatically:



The different risk types are those that are **known** from Phase III clinical trials, the **theoretical** risks identified by comparison to products of a similar therapeutic class, and **unknown** risks. These risks can be extrapolated to groups in the post-launch population: those that match the Phase III criteria, the wider population of patients within the labelled indications and 'off label' use in patients that do not fall within the conditions of the authorisation.



### ***Managing 'unknown risk' for early release products***

It was suggested that the risk of 'unknown' safety issues might be related to **off-label use** and that such use could become a particular issue for conditional approvals and early-release products where there are strict limitations on use. Points to consider in managing such risks include:

- **The voice** of the prescriber and the patient in relation to risk acceptance and restrictions on use of the product;
- **The nature of the disease** and different considerations that apply to serious and life-threatening conditions and to short-term symptomatic treatment and chronic use;
- The availability of **alternative treatments**.

### ***Addressing off-label use***

Pre-approval studies show the benefit-risk in specific populations specified in the conditions of approval but, notwithstanding these, the product will subsequently be prescribed off-label for a broader population, which might **shift the benefit-risk balance**.

Measures were discussed for limiting the use of early release products including restricting products and/or prescribing to **certain centres**, to **named physicians**, and even **named patients**, so that a regulated, safe access system controls the product.

There was discussion of defining the scope of competency for physicians to be able to use new 'early release' products in the form of a **positive 'accreditation'**. The emphasis should be on 'allowing' rather than 'restricting' use. An example was cited where availability is controlled by allowing the product to be dispensed only through specified pharmacies with appropriate training.

### ***Managing 'theoretical' risk for early release products***

The discussions echoed previous recommendations from CMR International Institute Workshops for a mechanism to be sought whereby **unpublished results** could be made available from studies on products with a similar mode of action, pharmacological group or therapeutic use<sup>1</sup>. The possibility of FDA collating anonymised data from its files was noted but this would be a long-term project. Companies would also need to agree to greater transparency in **sharing outcome data** that reveal potential safety hazards in order to alert others to theoretical risks.

## **2.3 Databases of Electronic Medical Records (EMRs)**

The role of large-scale population-based databases in the pre- and post-approval stages was discussed:

- EMRs were not, currently, felt to have a **pre-approval role** in standard approvals or in enabling early release
- They are potentially useful for **conditional approvals** of products and their use could be specified as part of the **post-approval commitments**. Examples of this exist in the devices sector and it was suggested that EMR databases could be used where large-scale controlled clinical trials are not feasible or are unethical (e.g., when a placebo is not ethical and there is no appropriate reference product).
- EMR databases are used in numerous ways in the post-approval environment. They incorporate demographic information and may prove useful in **post-approval screening**, in the **detection of new signals**, **data-mining**, and in **assessing outcomes** relative to pricing.

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<sup>1</sup> Report of the CMR International Institute Workshop on *Rethinking early clinical testing: the translation from laboratory to clinic*, 16-17 April 2007, Cobham, Surrey, UK. Report available to member companies and regulatory agencies from [institute@cmr.org](mailto:institute@cmr.org)

## Risk management

EMR databases are already being utilised in risk management and safety assessment in the post-marketing environment. They can **allay suspicion** about product safety and perform **hypothesis-testing** for not-very-important signals. There is a risk-management component to examine whether a population is given doses according to the label or whether variations exist. This can trigger the need for education campaigns directed at the populations prescribing, dispensing, or receiving the new medicines.

## Need for standardisation

There were concerns about the increasing use of EMR databases without an apparent **standardisation of approach** or criteria that prompted the recommendation for a forum to discuss guidance on the appropriate use of EMR data for activities related to the regulation of medicines.

There is a need for more formality regarding studies conducted in different databases. For example, some protocols change as a study is conducted. It was suggested that **publication** and **registration** of these database investigations, e.g., on *clinicaltrials.gov* would also prove useful. Guidance on data content that is applicable across **industry**, **academia**, and **HMOs** is also needed.

Because of heterogeneity of terms, guidance is also needed on **types of events** that might be detected in EMR databases. Moreover, **training and educational initiatives** are critical as study interpretation should only be conducted by those familiar with these systems, and the population parameters, etc.

## 2.4 Communication

*Better communication is the key to bringing about change in a way that is understood and accepted by all stakeholders.*

**Health systems infrastructure** and health system limitations can impede the ability to communicate effectively. Communication issues affect product utilisation in targeted populations and, ultimately, off-label use. There exists a need to better communicate the balance of benefits and risks of drugs.

There was discussion of the need to increase communication so that it is effective, accurate, and **tailored to recipient**. Misconceptions exist regarding ‘collusion’ between industry and agencies in assessing the risks and safety of medicines. It is critical that patients, consumers, advocacy groups, and other stakeholders are engaged via **communication tools** with industry and regulatory bodies regarding risks and benefits associated with products and improvements needed for current medications.

“We should move away from describing medicines in terms of ‘safety’ and ‘efficacy’. Benefit-Risk assessment is the preferred terminology”.  
Syndicate report

The discussion of communication tools ranged from using popular television productions as a medium to the use of simple printed information sheets for patients. The value of online sources was recognised as a way to empower people to make better health care decisions. Ultimately, the use of **objective, trusted sources** to disseminate risk and benefit information is imperative and it was felt that communication through physicians remains the key.

## Communication at the time of authorisation

The need for clear and transparent information, particularly on safety, at the time of approval was emphasised. This is especially important for products released with **conditional post marketing commitments**. Data and questions that arise in the post-approval stage have also to be translated and communicated to ensure that patients and physicians understand the issues.

It was suggested that lessons could be learnt from the use and content of the Summary of Product Characteristics (**SPC**) in the EU.

**Annex 1**

**WORKSHOP PROGRAM**

<b>SESSION 1: ISSUES OF CONCERN IN CURRENT APPROACHES</b>	
<b>Introduction</b>	<b>Professor Stuart Walker</b> , <i>Vice President and Founder, CMR International Institute for Regulatory Science</i>
<b>Chairman</b> for Session 1 and 2 and opening presentation	<b>Dr. Steven Ryder</b> , <i>Senior Vice President and Therapeutic Area Development Group Head, Pfizer, Inc. USA</i>
<b>Challenges and Opportunities in the Development of Innovative New Medicines</b>	
<b>Approval Processes for life-saving and orphan medicines</b>	<b>Dr. Marlene Heffner</b> , <i>Executive Director, Global Regulatory Intelligence and Policy, Amgen, Inc., USA</i>
<b>Early Access Models</b>	<b>Professor Hans-Georg Eichler</b> , <i>Senior Medical Officer, EMEA</i>
<b>SESSION 2: DRIVERS FOR RECENT AUTHORITY INITIATIVES</b>	
<b>The European Conditional Approvals (CA) System: Regulatory aspects</b>	<b>Professor Bruno Flamion</b> , <i>Chairman, EMEA Scientific Advice Working Party</i>
<b>An Industry Case Study</b>	<b>Dr. Martha Brumfield</b> , <i>Senior Vice President, Worldwide Regulatory Affairs and Quality Assurance, Pfizer, Inc., USA</i>
<b>FDA Pilot Study: continuous marketing applications (CMAs)</b>	<b>Dr. John Jenkins</b> , <i>Director, Office of New Drugs, CDER, Food and Drug Administration, USA</i>
<b>New approaches to approvals: Joint-agency and joint-review Initiatives</b>	<b>Dr. Leonie Hunt</b> , <i>Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia</i>
	<b>Dr. Supriya Sharma</b> , <i>Acting Director General, Therapeutic Products Directorate, Health Canada</i>
<b>SESSION 3: BUILDING SYSTEMS TO BALANCE ACCESS WITH SAFETY FOR PATIENTS</b>	
<b>Chairman's Introduction</b>	<b>Dr. John Lim</b> , <i>Chief Executive Officer, Health Science Authority, Singapore</i>
<b>Learnings before an agency will consider early release</b>	<b>Dr. Robert Temple</b> , <i>Associate Director for Medical Policy, Food and Drug Administration, USA</i>
<b>Population-Based Databases for post-marketing surveillance</b>	<b>Dr. Alexander Walker</b> , <i>Senior Vice President, Epidemiology, i3 Drug Safety, USA</i>
<b>Managing safety for the life cycle of a product: a report from the IOM</b>	<b>Dr. Kathleen Stratton</b> , <i>Scholar, Institute of Medicine, the National Academies, USA</i>
<b>A Payers' View of early access</b>	<b>Dr. Dorian Lo</b> , <i>Chief Medical Officer, Health Plans, Medco Health Solutions, Inc., USA</i>
<b>SESSION 4: SYNDICATE DISCUSSIONS</b>	
<b>Chairman</b>	<b>Professor Robert Peterson</b> , <i>Professor of Paediatrics, University of British Columbia, Canada</i>

## WORKSHOP ON NEW APPROACHES

## TO PRODUCT APPROVAL:

### Balancing early release with improved safety monitoring

### Section 3: Summary of Presentations

*Note:* These brief summaries are intended to be used in an electronic, web-based version of the report that will give access to all the slides presented at the Workshop

## SESSION 1: ISSUES OF CONCERN IN CURRENT APPROACHES

### Challenges and Opportunities in the Development of Innovative New Medicines

*Do the current systems for approval provide incentives  
or encourage companies to develop innovative medicines?*

**Dr. Steven Ryder**

*Senior Vice President and Therapeutic Area Development Group Head, Pfizer, Inc. USA*

Drug development is the process of translating drug discoveries into new medical treatments. It is a continuous process that runs throughout the life of a product. Two models to describe the process are the traditional development paradigm (discovery followed by Phases I to IV) and the decision-based development paradigm. Contemporary development of new medicines involves aspects of both.

The number of approvals of new medicines in recent years has remained relatively constant. Spending for pharmaceutical research and development, however, has increased dramatically.

Challenges for the future include improving ways to assess efficacy, identifying novel clinical and laboratory tools that can help define the safety and efficacy profile of a product, individual patient assessment, incremental innovation, and “real-world” assessment of benefits and risks.

Incremental pharmaceutical innovation can occur via coincident development (several companies pursuing the same target) or deliberate incremental improvement (working to reduce the side effects and improve the efficacy of drugs).

Real-world assessment needs to focus on gathering information from more free-ranging experiences and on data management systems and standards as key enablers.

- Challenges include detection of rare adverse events and assessing long-term safety.
- Opportunities include shifting from segmented to continuous development and refocusing on the individual patient.

### Discussion

- Physicians can be educated on the risks and benefits of new drugs using tools like those used by other industries to train physicians, such as with credit courses and self-assessments.
- Appropriate use of drugs can be promoted by defining competent prescribers, limiting the number of prescribers, and tracking prescribers' use of drugs.
- Randomised withdrawal studies can be used to assess long-term safety and the development of drug tolerance.



**Approval processes for life-saving and orphan medicines:**  
*Why are they not suitable for a wider class of new drugs?*

**Dr Marlene Haffner**

*Executive Director , Global Regulatory Intelligence and Policy, Amgen Inc, USA*

The Orphan Drug Act in the US was enacted in 1982/1983. It provided monetary incentives for development of drugs with otherwise limited economic potential: 7 years of exclusive marketing for the approved indication, waiver of the PDUFA application filing fee, tax credits for clinical trials, the Orphan Products Grants Program for small and medium-sized firms, and the assistance of the Office of Orphan Products Development Staff. Orphan drug programs have since been implemented in Japan, Australia, and Europe.

Orphan diseases are serious or life-threatening and affect small to very small patient populations. Half of the orphan diseases are paediatric disorders. Many are genetic diseases.

### **In summary**

- There are no special administrative mechanisms for orphan product development and approval
- Development and review are virtually identical to non-orphan products
- Incentives of Orphan Drug Act save development dollars, not necessarily time
- Faster approval times are related to serious and life-threatening illness (not to orphan status)
- Usually orphan drugs are the only drug available to treat the disease in question

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AMGEN

There are no short-cuts for orphan products: They must be safe and effective for the intended use. Approval usually requires two clinical trials, usually controlled and double-blind. Many trials involve very small populations. To reach statistical power in trials, orphan drugs must be more effective than non-orphan drugs. Safety is generally defined only after long-term use.

The FDA has a separate staff for development of orphan drugs. The staff is small and deals with pharmaceutical firms on a very close, individualised basis. The agency expends resources for orphan drugs that are not available for all drug development.



### Early access models:

*How can regulators ensure that specific obligations are fulfilled?*

**Professor Hans-Georg Eichler**

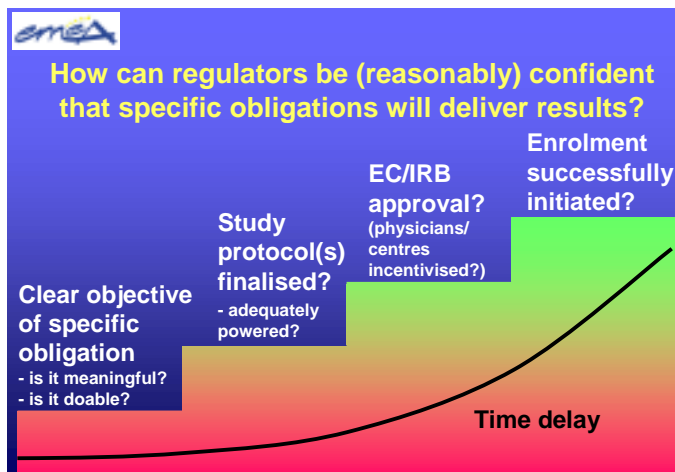
*Senior Medical Officer, EMEA*

The European approach to enabling early access to certain medicinal products is primarily through the conditional marketing approval process. This process balances an acceptable level of uncertainty against the severity of disease conditions and unmet medical needs to derive a perceived net benefit.

Granting early access through conditional approval depends on the nature of the knowledge deficit regarding the product. Efficacy may be granted on the basis of the use of a surrogate endpoint or circumstantial evidence from a less-than-stringent confirmatory trial.

Conditional approval may have unintended consequences: It challenges the concept of equipoise. It may raise ethical implications, reduce the availability of patients for randomised clinical trials, and close the window of opportunity for certain randomised clinical trials.

**Discussion:** The process and scope of conditional marketing approval may change, but it will be a while before this happens.



## SESSION 2: DRIVERS FOR RECENT AUTHORITY INITIATIVES

### New approaches to approval: The European conditional approvals (CA) system Professor Bruno Flamion

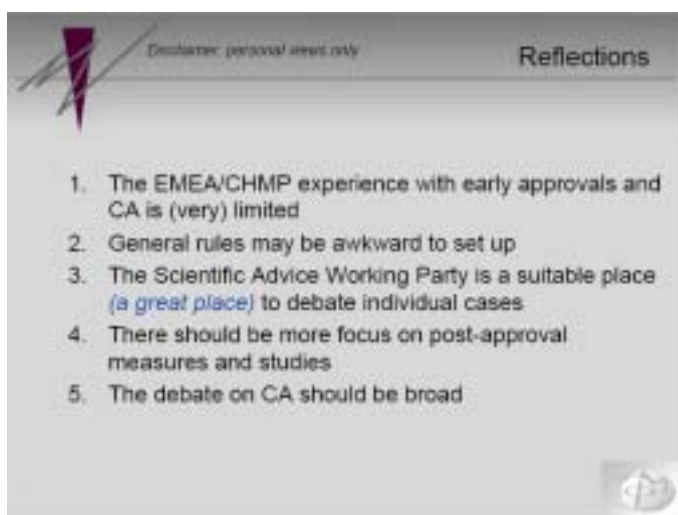
*Chairman, EMEA Scientific Advice Working Party*

Two products were evaluated under the CA system in 2006: Sutent® and Diacomit®. The history of these drugs provides useful case studies in the CA process.

Requirements in the EMEA guidelines on CA include seriously debilitating or life-threatening diseases, a positive benefit-risk balance, the likelihood of providing comprehensive data through specific obligations, and a demonstration that the benefits of immediate availability should outweigh the risks.

Negatives of CA evaluations have included inadequate endpoints, disagreement on or the lack of an active comparator, and the lack of an unmet medical need.

Positive aspects of CA include the use of faster access tools, which will be refined as experience with CA increases.



### New approaches to approval: The European conditional approvals system.

**Dr Martha Brumfield**

*Senior Vice President, Worldwide Regulatory Affairs and Quality Assurance, Pfizer Inc, USA*

The example of Pfizer's antitumor drug, Sutent® (sunitinib malate), provides a case study for a successful strategy in gaining CA and then converting that CA to full marketing approval, which Pfizer achieved in a little more than 1 year.

Factors contributing to Pfizer's success included the following:

- Ongoing dialogue with pre- and post-authorisation EMEA project managers
- Ongoing dialogue with rapporteurs
- Significant amount of safety data from a second indication
- The company's global plan to address needs on each side of the Atlantic
- Proactivity on the part of EMEA, rapporteurs, and the company.



Reimbursement for *Sutent* varies from one country to another within the European Union.

**New approaches to approval:  
FDA pilot study for continuous marketing applications (CMA)**

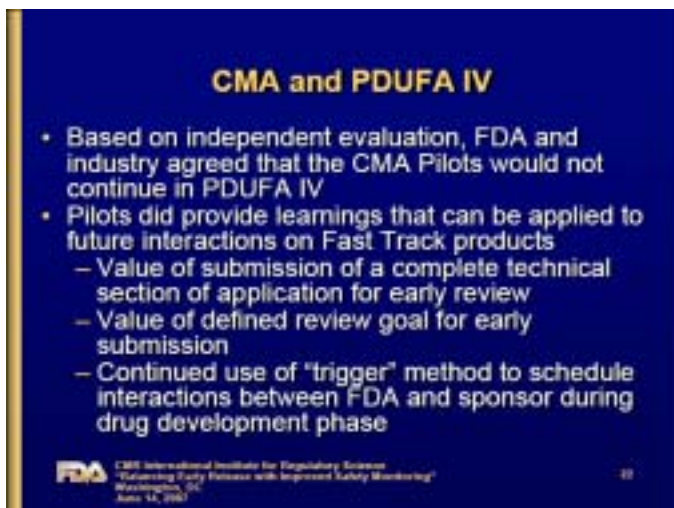
**Dr John Jenkins**

*Director, Office of New Drugs, CDER, Food and Drug Administration, USA*

Rolling review of Fast Track applications was made possible under the FDA Modernization Act of 1997. An industry proposal for CMA was made during PDUFA III discussions. The proposal called for the FDA to conduct reviews and provide “binding” feedback to sponsors in “real time” throughout drug development.

The FDA concerns included resource implications, potential for actual delays because of full FDA review, the difficulty of providing binding advice on early studies, and the possibility that final action on marketing approval might not be well predicted by cumulative IND advice.

The FDA has therefore conducted pilot programs to evaluate CMA. In Pilot 1, which examined Reviewable Units (RUs), the agency reviewed 34 RUs for 17 applications from 2004 through 2007 to date.



The first-cycle approval rate was not significantly different from a comparator cohort of priority reviews conducted in 2002 to 2004. There was no evidence of an impact of the pilot on application quality or communications between the FDA and the sponsor.

An independent evaluation concluded that there was no evidence of a benefit of the program to increase first-cycle approval, and that the conclusions were limited by small sample size and the “usual” high level of FDA attention to standard priority reviews.

The Pilot 2 program included nine products and assessed agency-sponsor interactions during drug development. The program employed two approaches to developing a meeting schedule: a fixed-schedule method and a trigger method that was more flexible. The results were inconclusive because of limited sample size and the inability to follow applications through the entire process to submission of a marketing application.

CMA Pilots will not continue under PDUFA IV. However, the pilots already conducted have provided learnings that can be applied to future interactions on Fast Track products.

## New approaches to approval: Joint-agency and joint-review initiatives.

**Dr Leonie Hunt**

*Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia*

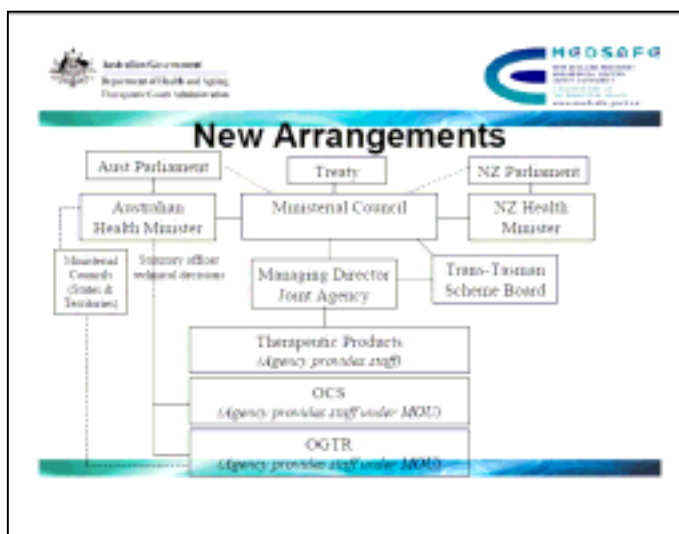
The Therapeutic Goods Administration (TGA) in Australia is responsible for the regulation of therapeutic products, including medicines and medical devices. Its operations are 100% cost-recovered through fees. The TGA has a system of expedited medicine reviews.

Currently, the TGA is implementing the Trans Tasman initiative with New Zealand. This initiative, based on treaty, legislation, and regulatory processes, will establish the Australia and New Zealand Therapeutic Regulatory Agency, to become operational in 2008.

A major challenge facing the new agency is to be a single agency operating in two countries, with different laws and legislative bodies.

Benefits so far have included the following:

- Exchange of information on processes
- Exchange of information on other specific issues
- Each country is allowed to consider steps to improve processes
- Reviewer exchange builds on experience of staff and potentially can lead to earlier resolution of issues.



## New approaches to approval: Joint Review: Current and Future Considerations

**Dr Supriya Sharma**

*Acting Director General, Therapeutic Products Directorate, Health Canada*

Health Canada has engaged in international cooperation, particularly for early access and appropriate safety monitoring.

Pilot projects have looked at common public health interests. An area of focus has been comparative demographics in population or disease entities. Health Canada is interested not just in sharing information, but in working actively with other regulatory bodies.

Important considerations include equitable sharing of the workload (especially important when regulatory agencies are of different sizes) and comparable resource capacities. National sovereignty is an important complication.

Models for cooperation include shared oversight, equivalent processes and procedures, agreed review timetables, and mechanisms for reaching consensus.

Working with other regulatory agencies requires confidence building.

### SESSION 3: BUILDING SYSTEMS TO BALANCE ACCESS WITH SAFETY FOR PATIENTS

#### What needs to be learned about a new medicine before an agency would be willing to consider early release?

##### Dr Robert Temple

*Associate Director for Medical Policy, Food and Drug Administration, USA*

The “regular” expectations for the normal drug approval process include demonstration of efficacy (usually with two adequate, well-controlled clinical studies) and safety (using “all tests reasonably applicable”). Existing rules have allowed approval based on less than the usual volume of data for new therapies for life-threatening and severely debilitating illnesses, especially where no satisfactory alternative exists.

Subpart H (21 CFR 314.500) provides for accelerated approval, based on a surrogate or short-term endpoint, and reflects a specific permission to approve a drug *before* all the desired data are available, for a good reason. After such approval, however, further studies are required to “verify and describe” the actual clinical benefit of a drug.

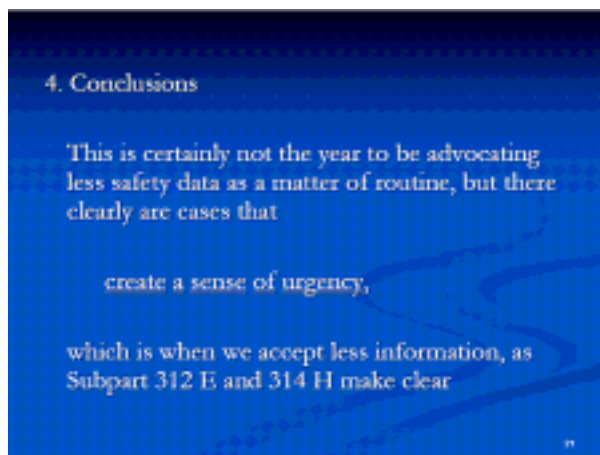
The FDA recognises that some drugs must be used for long periods, even a lifetime, which could require extensive long-term animal and clinical tests.

“The therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread use pending completion of such long-term studies.”

Early approval may rely on a single study.

Additional factors considered in granting early approval include public policy, the risk of major safety events, the existence of a familiar class of related drugs, and orphan drug status. Steps that pharmaceutical companies can take to increase the urgency of an application include the following:

- Show effect in non-responders to, or intolerants of, available prescription medicines (randomise failures to new and previous treatments)
- In symptomatic conditions, show effect on the most disabled patients
- Show an effect when the new drug is added to all available therapy.





## Population-based databases for post-marketing surveillance:

*Are the available systems good enough?*

**Dr Alexander Walker**

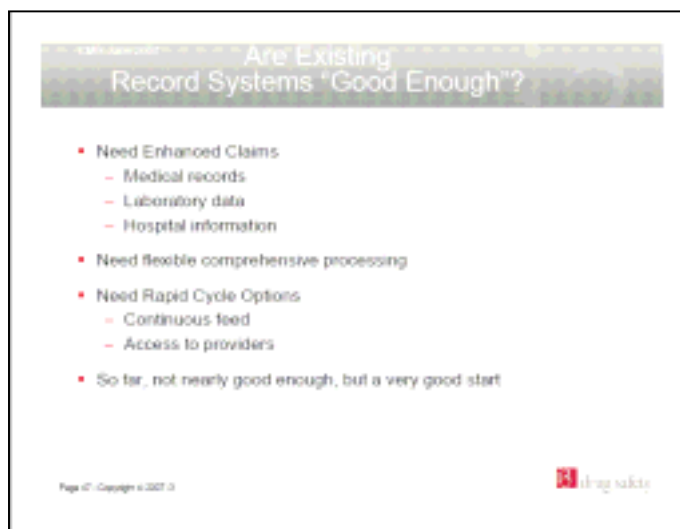
*Senior Vice President, Epidemiology, i3 Drug Safety, USA*

Elements of safety surveillance include a large number of users, real-world use, rapid feedback, comprehensive outcome monitoring, and the ability to “dive deeper” into the data. Insurance claims databases provide easy access to large numbers and detailed drug-exposure information, and they have no reporting bias. However, they have shortcomings that make them insufficient for documenting safety.

Enhanced claims databases have the advantages of the claims databases, plus verification of the disease and the availability of timings from the medical record. A negative is a significant time lag. These databases are OK for research.

Automated surveillance provides access to large numbers, simple exposure metrics, absence of reporting bias, and very many outcomes. Negatives include lack of disease confirmation, adequacy of timing for acute conditions, claims and database lags, and the large number of outcomes (which requires special medical and statistical expertise). This type of surveillance should be used with caution.

Rapid-cycle surveillance provides speed near that of active surveillance, easy access to large numbers, and an absence of reporting bias; it fits well into a public health surveillance paradigm and gets to the patient and physician when an event is fresh. Negatives include that it is best suited to “risk transients,” there is little control for covariates, the physician is not the reporter, and the method requires continuous staffing. However, rapid-cycle surveillance is a first-line defence.



## Managing safety for the life cycle of a product:

*A report from the Institute of Medicine (IOM).*

**Dr Kathleen Stratton**

*Scholar, Institute of Medicine, The National Academies, USA*

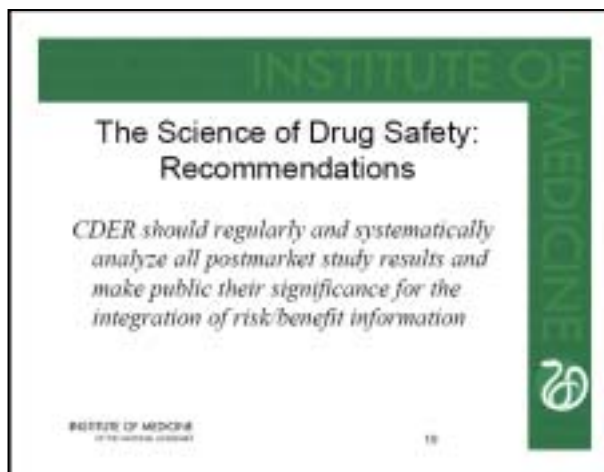
The IOM's Committee on the Assessment of the US Drug Safety System was charged with making recommendations in the areas of organisation, legislation, regulation, and resources to improve risk assessment, surveillance, and the safe use of drugs.

The committee identified vulnerabilities, including chronic underfunding, organisational problems, unclear regulatory authority and insufficiently flexible regulatory tools, inadequate quantity and quality of post-approval data, and inadequate capability to systematically monitor drugs' risks and benefits post-market.

The committee produced a suite of 25 recommendations that aim to provide a cohesive, integrated approach to transforming drug safety (8 directed to Congress, 3 directed to the Secretary of Health and Human Services, and 14 directed to the FDA/CDER).

Among the most important recommendations:

- Formal integration of post-marketing safety staff into the drug review process and sharing of post-approval authority with the drug review staff
- Congressional authorisation of a flexible and enforceable “tool kit” of regulatory *options* that *may* be applied at *or after* approval
- The FDA should become *the* nation’s trusted intermediary between the pharmaceutical industry and the end users (physicians, pharmacists, and the patient); to do so, the FDA must be in command of all the data, and those data and CDER decisions must be credible.



### Early Access for medicines treating life threatening and other conditions:

*Payers view*

**Dr Dorian Lo**

*Chief Medical Officer, Health Plans, Medco Health Solutions Inc, USA*

Payers’ decision factors for life-threatening conditions include financial costs, quality and safety, and access.

The trend to specialty pharmacy is seen as a proxy for novel treatments. Payers are trying to discourage drug treatments as an income source for physicians. An estimated 35% to 40% of drugs in the development pipeline through 2009 are specialty products, and nearly one third of those are for cancer.

Additional factors in decisions regarding early access include distinguishing “true” patient demand versus demand created by direct-to-consumer advertising, determination of reimbursement rates on an annual basis (a possible financial disincentive), and the role of employers and self-funded groups. The affordability of consumer-driven health benefits requires more consideration.

Current efforts include working to derive integrated pharmacy data in real time. Pharmacy benefit managers (PBMs) need to talk knowledgeably with physicians and be able to question prescribing practices.