



# NEW DEVELOPMENT PARADIGMS:

BUILDING REGULATORY CONFIDENCE  
FOR THE EARLY RELEASE OF MEDICINES

WORKSHOP  
11- 12 OCTOBER 2010  
SURREY, UK

## WORKSHOP REPORT



International

INSTITUTE FOR REGULATORY SCIENCE

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# NEW DEVELOPMENT PARADIGMS:

## Building regulatory confidence for the early release of medicines

### Section 1: Executive Summary

#### Background

Over the last 5 years Institute Workshops have suggested a number of approaches to reducing time and cost of medicines development, including considering developing early-release strategies that can make medicines available while establishing their full therapeutic profile and cost benefit. Mechanisms are in place for the early release of certain types of medicines, such as cancer therapies, to gain real-world experience under controlled conditions to expedite patient access to these therapies, while more fully assessing the product's benefit-risk profile. Therefore, in part because of legal constraints, regulatory agencies have focused on improving the current models and pathways of review leading to early release in lieu of undertaking radical new approval models. In particular, new measures for post-approval monitoring for safety and effectiveness need to be adopted if early release can be applied to a broad spectrum of new medicines. This has in part stimulated the evolution of risk management plans and Risk Evaluation and Mitigation Strategies (REMS). Now the question is what would be needed, pre- and post-release to provide confidence to the regulators and payers to apply early-release models to a wider set of medicines?

#### Objectives

- Identify current companies' and agencies' perspectives on the need for a development and review process which has the flexibility to enable early, controlled, real-world access to medicines
- Discuss different strategies for different medicines and their potential consequences for both regulators and Industry
- Recommend possible new development and review approaches and pre- and post-release requirements to enable regulators to have the confidence in new models being developed with a focus on early-release mechanisms

#### Forum introduction

**Day 1 Chairman, Prof Trevor Jones**, Director, Allergan Inc, USA outlined several important

issues to be considered at the Workshop: Does the technical evaluation of therapeutic value at the same time as quality, safety, and efficacy represent a "fourth hurdle" for medicine development? Can new paradigms accommodate these aligned requirements and expedite the release of new medicines? How do patent protection and market exclusivity provisions affect decisions to go to market with an early-release plan?

#### Presentations

According to **Thomas Lönngren**, Executive Director, European Medicines Agency, whilst unmet medical need may justify the increased risk attendant on the early release of medicine, this early release can best be accomplished using existing channels of approval. Furthermore, for most new medicines, designing strategies to close the efficacy/effectiveness gap and improving safety profiles through targeted, personalised medicine could likely contribute significantly to building confidence for a medicine's early-release strategy.

However, **Dr Thomas Unger**, Executive Director, Worldwide Regulatory Strategy, Pfizer Inc, USA explained that the urgency of patient needs requires us to take bold steps towards accelerating medicines development, and the progressive authorisation of medicines allows us to work with a flexible and dynamic mechanism to collect downstream information about a medicine's safety and effectiveness in real world practice.

Explaining that system transformation requires concerted participation of a broad consortium of stakeholders, **Dr John Lim**, Chief Executive Officer, Health Science Authority, Singapore detailed the collaboration of the Singapore Health Science Authority with the NEW Drug development paradigm – (NEWDIGS) group. Originating within the MIT Center for Biomedical Innovation, the NEWDIGS group aims to transform the drug development paradigm by facilitating collaborative research, developing demonstration pilot programmes and sharing learning among stakeholders.

When the expectations (efficacy) for a new drug don't match reality (real-world effectiveness) **Hans-Georg Eichler**, Senior Medical Officer, EMA advised a two-prong approach be considered

to reduce uncertainty about the new therapy: regulators could request that the sponsor conduct studies with high external validity (real-world, “pragmatic effectiveness” trials) to better define the product’s profile, and clinicians should be encouraged to optimise treatment in everyday practice by ensuring the selection of the most appropriate patients for therapy and educating them to maximise the benefits of treatment.

**Moira Daniels**, *Global Head Regulatory Policy Intelligence and Labelling, AstraZeneca, UK* advocated for the broader use of conditional approvals based on appropriate safety, albeit when there is limited efficacy experience. This model requires shared risk taking by both regulators and industry and should include the implementation of an appropriate patient access model.

Database studies may be used to supplement and complement data from randomised clinical trials to facilitate the early release of medicines, but **Dr Michael Devoy**, *Head of Global Medical Affairs and Pharmacovigilance, BayerSchering Pharma AG, Germany* explained that this requires both the identification of a suitable post-release database and the use of an appropriate collection and analysis methodology. Electronic medical records databases and claims databases will play a role in building the experiential knowledge base around an early-release product, thereby helping to define on an ongoing basis its benefit and risk profile.

The traditional research approach is often inapplicable to the development of new therapies for rare diseases (such as Duchenne Muscular Dystrophy). **Dr Tony Hoos**, *Senior Vice President, European Medical Affairs, GlaxoSmithKline, UK* described how the use of surrogate markers, novel validated endpoints and safety databases can be integrated into an innovative research programme to mitigate risks associated with accelerated development and make critical treatments available to patients more rapidly yet under controlled conditions.

Although CHMP experience with conditional market approval has been variable, **Dr Eric Abadie**, *Chairman, CHMP/EMA, France* proposed that a “cumulative approval process,” different from the conditional marketing authorisation process now in place, may be possible, guided by a collaboration between industry, regulators and payers throughout the product life cycle. Furthermore, he noted that as early-release paradigms advance, so too will post-marketing activities evolve from focused “risk management” to a more inclusive approach to “benefit-risk

management” to mitigate uncertainties and build regulatory confidence.

Providing the perspective of patients on the early release of medicines, **Dr Mary Baker** *President, European Federation of Neurological Associations* suggested that excessive emphasis on risks can stifle innovation, in particular for those diseases where patients may be more risk-tolerant than sponsors or regulators. She proposed that industry take better advantage of the potential contribution of patients living with a target disease, suggesting that patient-reported outcomes could play a valuable role in providing real-life evidence of therapeutic activity, ideally contributing to the expedited availability of critical therapies.

**Meindert Boysen**, *Programme Director Technology Appraisals, NICE*, explained that earlier access/ approval models will inevitably be associated with increased levels of uncertainty. He concluded the Workshop presentations by asking several questions relevant to that uncertainty: can we agree on what aspects of the uncertainty can be resolved through the use of earlier access (i.e., coverage with evidence development) models; can we determine whether investing in post-release evidence collection and analysis is an efficient use of resources to inform the early-release decision; and what will we be able to learn from these approaches to inform future early-release decisions?

These presentations made clear the need to further define the issues and boundaries surrounding the early release of medicine and to better coordinate the input of many stakeholders into the multiple initiatives currently underway in this regard. Early access schemes, such as those proposed by organisations such as the Athenaeum Group and NEWDIGS in which there is collaboration between industry, regulators, payers coupled with appropriate incentive structures represent important new opportunities to facilitate the confident early release of medicines.

### Syndicate discussions

Three syndicate discussion groups were asked to discuss two topics relevant to the early release of medicines and develop recommendations for action centred on those topics. Two groups discussed the scientific and regulatory components that need to be in place, pre- and post-release for an early-release paradigm to become a reality beyond oncology/niche medicines, and the third syndicate debated the implications, both positive and negative, for the various stakeholders in an early-release model.

**General Recommendations Across Syndicates**

1. Establish a common definition of early release
2. Conduct a survey of the many ongoing initiatives that are investigating new drug development paradigms – C-Path, IMI, NEWDIGS, Athenaem group etc, to avoid duplications and look for synergies
3. Study how other industries manage risk while expediting product development, and draw on applicable learnings
4. Optimise use of currently available tools such as:
  - Frameworks for consistent benefit-risk assessment
  - Registries to monitor patient exposure
  - Post-approval monitoring programmes (RMPs/REMS)
  - Companion diagnostics to identify best responders and to mitigate safety issues
  - Adaptive trial designs to build confidence around early-release models
5. Implement a more proactive approach to “bespoke development” within current regulatory frameworks, to determine the quantity and type of data that are appropriate pre- and post-approval to address benefit-risk issues of products targeted to particular diseases and patient types
6. Promote discussion between companies and regulators earlier in the application process regarding the development of post-approval market monitoring plans
  - Define those post-market studies most likely to identify unknown risks and improve quantification of known risks
  - Include studies of patient-reported benefits and effectiveness as part of the overall development strategy
  - Develop methodologies to assess whether post-approval activities, such as REMs, are adding value to the medicine’s profile– what is the return on investment for each stakeholder on these activities?
7. Establish a clear profile of the patients’ needs by involving patients early in the development process
  - Develop a systematic method of assessing patient acceptance of risk for a particular disease and determine how this influences the development strategy and regulatory decisions
  - Promote use of patient-reported outcomes
  - Develop strong communication tools and plans to more fully explain benefits and risks of early-release
  - Educate different stakeholders in the healthcare system – companies, regulators, practitioners and patients – on the responsibility for proper use of drugs, and establish the level of risk the stakeholders are willing to undertake
8. Identify a candidate product, company and agency for a comprehensive assessment of a pilot early-release model

## Workshop Programme

DAY 1: Monday 11 October 2010	
<b>Chairman's welcome and introduction</b>	<b>Prof Trevor Jones</b> , <i>Director, Allergan Inc, USA</i>
<b>Is there a need for a more flexible approach to both drug development and review strategies for the medicines of the future?</b>	
<b>Regulatory Viewpoint</b>	<b>Thomas Lönngren</b> , <i>Executive Director, European Medicines Agency</i>
<b>Industry Viewpoint</b>	<b>Dr Thomas Unger</b> , <i>Executive Director, Worldwide Regulatory Strategy, Pfizer Inc, USA</i>
<b>NEWDIGS Initiative – A Regulator's Perspective on New Drug Development Paradigm</b>	<b>Dr John Lim</b> , <i>Chief Executive Officer, Health Science Authority, Singapore</i>
<b>Post-marketing strategies for identifying benefit and risk – Risk Management Plans: Are these providing the reassurance agencies require and how should benefit be measured?</b>	
<b>Regulatory Viewpoint</b>	<b>Prof Hans-Georg Eichler</b> , <i>Senior Medical Officer, EMA</i>
<b>Industry Viewpoint</b>	<b>Moira Daniels</b> , <i>Global Head Regulatory Policy Intelligence and Labelling, AstraZeneca, UK</i>
<b>Creating an evolving evidence base to enable early release models</b>	
<b>Healthcare databases – Are these ready to be harnessed for assessing post-marketing benefit and risks?</b>	<b>Dr Michael Devoy</b> , <i>Head of Global Medical Affairs and Pharmacovigilance, BayerSchering Pharma AG, Germany</i>
<b>An alternative model to enable early patient access: Proposal for an orphan drug and implications for real world data</b>	<b>Dr Tony Hoos</b> , <i>Senior Vice President, European Medical Affairs, GlaxoSmithKline, UK</i>
<b>Syndicate sessions on</b>	
<b>TOPIC A: Early-release paradigm – What are the scientific and regulatory components that need to be in place post-release for this to become a reality beyond oncology/ niche medicines?</b>	<b>Chairperson: Dr Supriya Sharma</b> , <i>Director General, Therapeutic Products Directorate, Health Canada</i> <b>Rapporteur: Dr Kian Ming Lam</b> , <i>Director, Corporate Development and Operations Division, Health Sciences Authority, Singapore</i>
<b>TOPIC B: What are the implications, both positive and negative, for the various stakeholders (companies, regulators, patients, healthcare providers, payers) in an early-release paradigm?</b>	<b>Chairman: Prof Hubert Leufkens</b> , <i>Chairman, Medicines Evaluation Board, The Netherlands</i> <b>Rapporteur: Mark Hope</b> , <i>Head of EU/ROW Program Management and EU/ROW Head of Oncology, F. Hoffmann-La Roche Ltd, Switzerland</i>
<b>TOPIC C: Early-release paradigm – What are the scientific and regulatory components that need to be in place pre-release for this to become a reality beyond oncology/ niche medicines?</b>	<b>Chairman: Dr David Jefferys</b> , <i>Senior Vice President, Global Regulatory and Government Relations, Eisai Europe Ltd, UK</i> <b>Rapporteur: Dr Steve Caffé</b> , <i>Senior Vice President, Global Regulatory Affairs and Pharmacovigilance, Baxter Healthcare Corporation, USA</i>

<b>DAY 2: Tuesday 12 October 2010</b>	
<b>Chairman's introduction</b>	<b>Prof Robert Peterson</b> , <i>Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research</i>
<b>Feedback of day one syndicate discussion</b>	
<p><b>Panel Discussion: Early-release models – Reflection on the syndicate recommendations</b></p> <p>As companies and agencies work through how to regulate new therapies and new development pathways, dialogue between companies and agencies and between agencies will be essential for acceptance of any changes to the traditional view of development. However there other stakeholders in the today and tomorrow's development including patients, health technology assessment, payers etc. What is the right level of co-operation and how can these parties play their part in ensuring any early-release model meets their needs?</p>	<p><b>Margaret Jackman</b>, <i>Group Manager, MHRA</i></p> <p><b>Prof Hans-Georg Eichler</b>, <i>Senior Medical Officer, EMA</i></p> <p><b>Dr Mary Baker, President</b>, <i>European Federation of Neurological Associations</i></p> <p><b>Dr Richard Barker</b>, <i>Director General, ABPI</i></p>
<b>Lessons learnt from "live license" or life cycle regulatory management for oncology /niche medicines – How could these be translated to a wider set of medicines?</b>	<b>Dr Eric Abadie</b> , <i>Chairman, CHMP/EMA, France</i>
<b>Early-access scenarios – The patient perspective on the concept</b>	<b>Dr Mary Baker President</b> , <i>European Federation of Neurological Associations</i>
<b>Early-access models: What is the perception of those organisations responsible for health technology assessment?</b>	<b>Meindert Boysen</b> , <i>Programme Director Technology Appraisals, NICE</i>
<b>Summary of key outcomes and possible next steps</b>	

## Section 2: Syndicate Discussions

Three syndicate discussion groups were asked to discuss two topics relevant to the early release of medicines and develop recommendations for action centred on those topics.

- Syndicates 1 and 3: What are the scientific and regulatory components that need to be in place, pre- and post-release for an early-release paradigm to become a reality beyond oncology/niche medicines?
- Syndicate 2: What are the implications, both positive and negative, for the various stakeholders (companies, regulators, patients, healthcare providers, payers) in an early-release paradigm?

The Chairpersons and Rapporteurs for the groups follow:

<b>Syndicate 1</b>	Chair:	<b>Dr Supriya Sharma</b> , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
	Rapporteur:	<b>Dr Kian Ming Lam</b> , <i>Director, Corporate Development and Operations Division, Health Sciences Authority, Singapore</i>
<b>Syndicate 2</b>	Chair:	<b>Prof Hubert Leufkens</b> , <i>Chairman, Medicines Evaluation Board, The Netherlands</i>
	Rapporteur:	<b>Mark Hope</b> , <i>Head of EU/ROW Program Management and EU/ROW Head of Oncology, F. Hoffmann-La Roche Ltd, Switzerland</i>
<b>Syndicate 3</b>	Chair:	<b>Dr David Jefferys</b> , <i>Senior Vice President, Global Regulatory and Government Relations, Eisai Europe Ltd, UK</i>
	Rapporteur:	<b>Dr Steve Caffè</b> , <i>Senior Vice President, Global Regulatory Affairs and Pharmacovigilance, Baxter Healthcare Corporation, USA</i>

### Syndicate 1

What are the scientific and regulatory components that need to be in place post-release for an early-release paradigm to become a reality beyond oncology/niche medicines?

#### OUTCOME OF DISCUSSION

##### Critical issues

##### *Defining "early release"*

The early-release of a new therapeutic is best accomplished by setting realistic expectations regarding premarket regulatory requirements, thereby supporting innovation in specific disease areas. Early release must be complemented by good post-market strategies and tools to better manage uncertainties. These post-market approaches include risk management plans, adjusted to requirements that are specific to disease areas and patient risk tolerances. Early release should not involve taking on risks above those typically assessed for standard review medicines. Pre-approval strategies should

drive towards improving productivity of the process and encourage innovative new drug development.

Terminology is important: Health Canada uses the term *progressive* instead of *early*, to reflect a modern approach in a non-static evaluation process. If *release* is taken to mean market authorisation, it should be understood that no current European legislation allows early release, and it may take years to make a legislative change that would permit this type of authorisation. If, however, *release* is defined as the point at which patients have market access to medicines, HTA and payer considerations must be brought to the fore to ensure payment for these new therapies.

##### *Post-authorisation activities*

Medicines that meet unmet medical need may be eligible for an accelerated review/approval pathway in some countries. However, the post-approval regulatory requirements for these treatments will necessarily continue to be distinct from those applied to the post-approval

assessment of medicines used to treat large populations with common chronic diseases. While post-approval monitoring has historically been focused on safety, a new paradigm of early release will need to address both the concepts of harm (risk) and effectiveness (benefit).

Discussion between industry and regulators of post-approval assessment plans should be initiated as early as possible during development, ideally before phase 3 studies begin. Where possible within the legal regulatory framework, submission guidelines could be adapted to address specific types of post-approval monitoring requirements. Most currently used post-authorisation tools, although based in good science, are not yielding their maximum benefits. Therefore new approaches such as the use of adaptive, pragmatic study designs should be employed and methodologies developed to assess the product's clinical success during the post-approval period.

#### **HTA interface and requirements**

There is general confidence among sponsors and regulators that the current, mature regulatory frameworks and supportive tools have benefitted from decades of development and practical experience, and that most barriers can be overcome through the joint efforts of regulators and companies; by comparison, it is less clear by what mechanisms the concerns of the new challenging hurdles that the health technology assessment (HTA) front can be addressed. Better alignment on the requirements between regulators and recommenders/payers is required; parallel scientific advice given by regulators and HTA early in development is one approach, but still finds only limited use. Such joint discussions can, for example, determine if concerns about the incorrect use of a therapy is the main barrier to regulatory approval and reimbursement, in which case greater education of practitioners and patients and incentives for proper use can be designed into the post-approval period strategy. As key stakeholders, patients need to play a more active role in ensuring their compliance and proper use of medicines.

#### **Systems, stakeholders and other opportunities to enhance a new development paradigm**

The importance of rational use of medicines needs to be instilled in all stakeholders within the healthcare system through communication with and education of practitioners and patients. The dissemination of up-to-date clinical practice guidelines can serve to encourage if not ensure adherence to prescribing guidelines, thereby enhancing the probability of a given therapeutic outcome while minimising associated risks. We must consider how effectively off-label use can be managed in real-life situations, perhaps examining the impact of divergent uses in clinical studies. Tools to assess patients' benefit-risk tolerance and acceptance of a new therapy must be developed because their perceptions are often quite different than those of sponsors or regulators. Finally, we can learn from other regulated, yet rapidly evolving technology-based industries, such as aircraft manufacture, where regulators and companies work closely to manage risk during product development and throughout a product's lifecycle.

#### **Strategies**

- Examine new development paradigms at higher perspective – through overall healthcare management lens
- Coordinate between the many current new medicine development initiatives
- Define specific issues, identify who is best suited to address these, and establish clear boundaries of engagement
- Integrate HTA considerations into the solutions
- Engage patients, whose views and education are playing increasingly important roles in issues and solutions
- Explore opportunities to adopt best practices of other industries

### Syndicate 1 recommendations

1. Promote the discussions between companies and regulators around the development of post-approval plans earlier in the application process
2. Consider how adaptive clinical study designs can serve as the basis for both market authorisation and ongoing post-approval data collection
3. Design post-approval studies that will build confidence in detecting unknown risks. Better quantify known risks with risk management plans
4. Develop a framework to examine benefits as well as risks during the post-approval phase
5. Develop methodologies to assess whether post-approval monitoring activities are adding value to the product, and are bringing good return on investment on these activities; conduct a survey to determine effectiveness of post-approval monitoring plans.
6. Conduct a survey of how other technology-intensive, regulated industries manage risk, both during development and after product launch, and apply learnings to the new drug development paradigm
7. Conduct a survey of the many ongoing new drug development paradigm initiatives – C-Path, IMI, NEWDIGS etc, to avoid duplications and look for synergies
  - If a new early-release approach can be developed, then the various initiatives should be aligned to contribute their specific expertise to a different aspect of the approach

### Syndicate 3

*What are the scientific and regulatory components that need to be in place, pre-release for the early-release paradigm to become a reality beyond oncology/niche medicines?*

### OUTCOME OF DISCUSSION

#### Critical issues

Sponsor and regulators must collaborate to decide just how early a release is intended, and for which type of products. Candidate products for the treatment of an unmet medical need or life-threatening conditions among clearly defined patients would be primary candidates; some mechanisms for the early release of these types of therapies are in place but are not implemented consistently across jurisdictions. Can we extend those mechanisms to other therapeutic areas, especially to the management of chronic illnesses such as diabetes, chronic obstructive pulmonary disease or Alzheimer's disease?

### Strategies

- Decision sharing: sponsors and regulators need to seek mechanisms to address the voice of the patient during development and at the time of the initial approval
- Risk management plans must include strong compliance components
- Communication strategies are needed to engage stakeholders in the process, including developing partnership with patients in supporting the development of a new release model
- Different incentive strategies for all stakeholders must be considered
- Exclusivity, pricing/reimbursement issues need to be addressed by the HTA early during the development process

**Syndicate 3 recommendations**

1. Build a “coalition of the willing” to support the broader use of new accelerated release paradigms and to enhance the legitimacy of the release decision
  - The time is right to take a “big tent” approach, given the changing mindset of large pharmaceutical companies and the increased role and importance of small companies in the discovery process
  - Other constituencies in the decision-sharing process would include HTAs, payers, commercial partners, patient groups, elected decision makers and regulators
2. Maximise use of currently available tools and encourage the use of innovative approaches
  - Benefit-risk assessment frameworks, registries, risk monitoring plans, companion diagnostics, adaptive trial design, predictive toxicology, new methods to accurately identify target populations, tax incentives for special medicines
3. Clearly define the target patient populations (use biomarkers and other novel technologies to identify those who will be the most likely responders and at lowest risk for harm)
  - Extrapolation to a broad population is unlikely to be allowed following initial release of a new medicine under an early release paradigm; rather, the definition of the target population will be tighter and strictly based on the characteristics of who was studied up to decision date
4. Characterise regional levels of risk tolerance and determine how this will influence the application. Since regional differences in risk tolerance are real factors but may be amenable to local harmonisation sponsors may consider regional approaches to drug development as part of an early-release paradigm
5. Engage HTAs and payers at a very early stage of study design. This is essential to contribute to the definition of the type of data needed for early/progressive release, and this advice can be carried into the post-initial approval studies
6. Explore language for the initial phase authorisation that will differentiate from the full marketing authorisation milestone, thereby avoiding triggering the start of exclusivity period

**Syndicate 2**

*What are the implications, both positive and negative, for the various stakeholders (companies, regulators, patients, healthcare providers, payers) in an early-release paradigm?*

**OUTCOME OF DISCUSSION**

**Critical issues**

**Stakeholder perspective**

The definition of “early release” is not entirely clear or consistent. Furthermore, the perspective on the adequacy a dataset for early approval frequently differs between regulator and sponsor.

Incentives are critical to all stakeholders to foster innovation. For industry the incentive is intellectual property protection; for regulators it is consideration of protection versus promotion

of health; to payers it is providing a rationale for reimbursement under conditions of reduced certainty and for patients, early release fosters access to innovative medicines for which they as stakeholders agree to share some risk. Overall, the focus of a new drug development paradigm should be on improving the efficiency of the development and regulatory review processes which expedite not only regulatory review but as important, patient access to medicines. This requires a balance between accelerating a submission with the seemingly increasing regulatory requirements that are designed to mitigate uncertainty around a new product.

A plan for post-approval studies and monitoring for medicines granted early release is critical. A subsequent withdrawal of such a medicine because of the results of this research should be regarded as an indication of the success of planned risk management.

### HTAs and reimbursement

Within the EU alone, there are 27 countries, in some cases with more than one HTA per country, each using different assessment methodologies, making it difficult to apply a single common approach to a globally acceptable early-release model. Pricing remains a major challenge in this setting as the potential increase in uncertainty associated with early release confounds the HTA's ability to predict the ultimate value of the new therapy in the target population; therefore, the alignment of basic HTA requirements is essential to ensure speedy patient access commensurate with an accelerated regulatory review process.

### Strategies

- Patient involvement and perspective will become a key components of new medicine development paradigms
- Expand framework for new drug development beyond the immediate need of rapid regulatory review to consider ways to monitor the product's profile and adjust the information regarding its most effective use with the emerging data
- Ensure identified risks are acceptable and manageable and can be converted into opportunities for benefit

### Syndicate 2 recommendations

1. Establish a clear understanding of patient or public needs to identify those products that are suitable candidates for an early-release process, providing many benefits to the patient, society and national healthcare
2. Develop a common definition of early release
  - Understanding/definitions and expectations may vary across stakeholders and therapeutic areas
3. Within current regulatory frameworks, implement a more proactive approach to "bespoke development"
  - Stakeholders (regulators, companies, HTAs and patients) should determine the quantity and type of data that are appropriate pre- and post-approval to identify and monitor benefit-risk issues associated with a new product
4. Develop strong communication tools and plans that clearly describe the medical need for and correct use of the product; patients need to fully understand the drug development process and the inherent uncertainties surrounding these. New development paradigms should be designed to mitigate and inform stakeholders about risks associated with the product at any point in its lifecycle
5. Optimise use of patient-reported outcomes from early to confirmatory approval (get patients on board as part of the development process!)
6. Using clear communication tools, including novel graphic approaches, change society's interpretation and understanding of risk, moving away from the perception of the absolute safety of a product, to a continuum of risk that is shared by all stakeholders
7. Identify a candidate for a pilot programme for early release
  - Pilot scenarios: Break-through medicine or significant incremental improvement of a chronic disease (based for example on metrics such as QoL), reasonable strong understanding of or likely ability to characterise the product's ongoing safety profile risk management will be key; medicine must be highly innovative with convincing benefits; consortium of companies may be ideal. Other groups (eg, MIT NEWDIGS) are working towards identifying a candidate product so collaboration is encouraged amongst groups

## Panel discussion

### Early-release models: Reflection on the syndicate recommendations

As companies and agencies work through how to regulate new therapies and new development pathways, dialogue will be essential for acceptance of any changes to the traditional view of development. There are other stakeholders in this development, however, including patients, health technology assessors and payers. What is the right level of co-operation among the groups and how can these parties play their part in ensuring any early-release model meets their needs? Professor Robert Peterson introduced a panel of four participants to discuss the Syndicate recommendations.

**Margaret Jackman**, *Group Manager, Medicines and Healthcare products Regulatory Agency (MHRA)* discussed plans in development at MHRA to provide earlier patient access for medicines showing significant promise in areas of unmet need. The MHRA would give an opinion on an unlicensed drug at the end of phase 3 clinical trials based on a scientific review of clinical, safety and quality data undertaken by the agency. Although this early-release plan does not involve changing the drug development pathway, it does act to fill that gap when patients are waiting for a new and significant treatment option to become commercially available, and it is expected that the sponsor would continue to finalise the regulatory dossier for this medicine and submit it for a license. Furthermore, the willingness for healthcare payers to fund unlicensed medicines is a significant challenge that must be faced.

In consulting individual patients and patient groups regarding this programme, the MHRA discovered that they are less risk averse than regulators and clinicians and they highly value the opportunity to participate in their own treatment decisions. Many healthcare practitioners, however, do not feel that patients are properly equipped for this participation and it is important to recognise that the earlier availability of medicines is based on sharing safety information with all stakeholders and having a robust safety surveillance system.

The work of the Athenaeum Group in the early release of medicines was detailed by **Dr Richard Barker**, *Director General, Association of the British Pharmaceutical Industry (ABPI)*. The Athenaeum Group, a forum for senior regulators and industry members, policy makers and patient

representatives to discuss pharmaceutical development has created “a new and flexible blueprint for development of regulatory affairs.”<sup>1</sup> Although the old developmental blueprint of phase I, II, III and IV is outmoded, it is clear to Dr Barker that no single model can take its place. Factors such as the type of medicine, patient population, existing treatment options and benefit-risk ratios will result in the need for highly variable development paradigms. There is a fundamental shift underway from the old model in which industry discovers and develops medicine, applies for regulatory approval in a somewhat confrontational system and then broadly markets the medicine to as many people as possible – to one where there is a cooperative process between industry and regulator, and then industry and the health system. In this model, all are seeking out the patients who will get the best value from that medicine; demonstrating the product’s value on outcomes, rather than clinical novelty; and then tracking and monitoring those outcomes. Whilst it is important to couple the regulatory perspective of benefit-risk assessment with the health technology assessment, the two processes will not likely be fused in the near future because of differing systems and criteria.

Dr Barker agrees with the Syndicates that it is likely that Europe rather than the United States will take the lead in these developments and suggested the necessity to run multiple pilot programmes that reflect the need for multiple models of change, each pilot with a clear patient, business and healthcare rationale based on patient needs. He concluded by suggesting that the pharmaceutical development crisis is in part a political rather than a scientific or business problem and will require a visionary political leader to affect change.

The patient perspective on the early release of medicines was provided by **Dr Mary Baker**, *President, European Federation of Neurological Associations*, who explained that following a diagnosis of long-term illness, patients experience a feeling of profound loss of control. This loss can be mitigated through the communication of information about disease, prognosis, and treatment. The doctor-patient relationship is key in this communication, but across Europe there is a great disparity in patients’ ability to access information about their disease. In fact, by and large there is a fundamental lack of knowledge, with many patients assuming the infallibility of clinical diagnosis and the absolute safety of all

industry-produced medication. Patients do not understand the length and complexity of the drug development process, in which it can take as much as 13 years for a medicine to be approved or the function or place of health technology assessment. Therefore, adding the patient's voice to a new drug development paradigm will be key.

Although patients are central to developmental change, their engagement remains a significant challenge.

Industry has funded educational efforts through programmes that provide patients with the background education and knowledge that would allow them to act as credible advocates, but the truth is that it is extremely difficult to ensure representation of all patients at all levels. Physicians are doing a better job of listening, but much work remains in educating patients to ask better questions and public perceptions that cooperation between industry and regulatory agencies amounts to conflict of interest must be changed.

**Professor Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency (EMA)* began by stating that it is important to recognise that the early release of medicine involves flexibility and a tolerance for increased risk of uncertainty.

Expediting the availability of medicine through improvements in efficiency is vastly different than changing the societal threshold for the acceptability of uncertainty.

He further stated that there is unanimous agreement that an early-release developmental model will not work without the involvement of patients and payers. Unlike the recent past, payers now are willing to engage with industry in early development programmes and offer scientific advice. It is therefore critical that they now be involved in discussions of new early-release programmes. Enlisting patients as educated political advocates as mentioned by Dr Baker is necessary, but not sufficient. We should also make them part of the drug development programme, developing questionnaires and other tools with their help that would allow us to access their preferences, into the drug development programme, determining for example, their willingness to trade potential benefits for the risks of a negative impact of a particular adverse event on their quality of life.

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## Section 3: Presentations

### Chairman's welcome, introduction and setting the scene

**Professor Trevor M Jones**

*Director, Allergan Inc, USA*

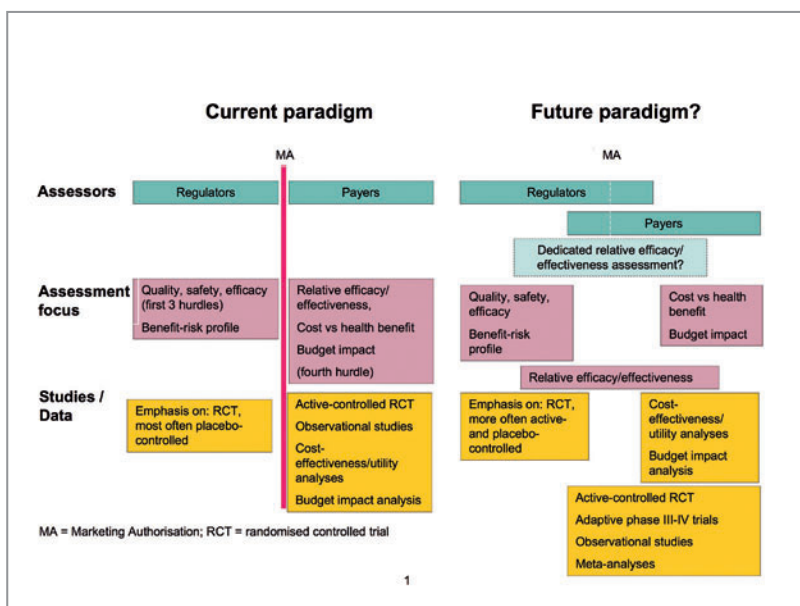
Over the last decade there has been an increasing demand to change the model of drug development to include nontraditional parameters into confirmatory trials in early drug development. Unfortunately, the many different healthcare stakeholders all have diverse ideas as to what those parameters should be, with those differences driven among other things by regional preferences, regulatory constraints, political expediency and financial concerns. Furthermore, the incorporation of some of those parameters results in a concern that price (rather than value) will quickly join quality, safety and efficacy as the fourth hurdle in drug development. The challenge to all stakeholders is to develop an evolutionary development paradigm that addresses each of these needs, builds confidence in the value of the medicines yet does not unduly limit patient access to potentially valuable new therapies. The undue emphasis on any one of these 'hurdles' too early in the development process may result in some clinically valuable products being rejected because of financial risks. Therefore, a balanced

approach to addressing these requirements while addressing patient access needs seem to support an expanded role for "early release" development and approval models.

The primary worry to many stakeholders surrounding early release, however, is that it equals limited release. Patent exclusivity starts with the first launch. By the time additional monitoring permits a wider release, a significant proportion of the patent term may have eroded and the innovator may not be able to recoup its investment costs. Changes to patent protection laws would be arduous and lengthy procedures. Therefore, some have countered this concern with the idea of setting higher prices post-launch once value has been established, although historically, prices for medicines have always dropped after first launch. Despite the numerous new initiatives that are underway to address ways to streamline the medicines development and approval processes, consensus has yet to be reached on the core elements of an optimal new paradigm. These new approaches continue to grapple with basic issues including:

- Is the combination of a technical evaluation of therapeutic value at the same time as quality, safety, and efficacy a fourth hurdle in price?
- Is going to market early with the potential the loss of opportunity to regain the cost of drug development a fatal paradigm flaw?

It is within the context of these difficult issues that this Workshop has been charged with discussing and identifying the basic elements that could underpin a simple, regionally acceptable early-release paradigm to expedite the development of new safe and cost-effective therapies.



## Drug development and review strategies: Is a more flexible approach possible?

**Thomas Lönngren**

*Executive Director, European Medicines Agency*

The prospect of every more stringent regulatory requirements not only increase the cost of drug development and time to market, but could also contribute to lack of drug development in important therapeutic areas, such as neurologic research and antibiotics, where there is now a 5-year gap in drug development. The current crisis in drug development, however, is not caused by regulatory requirements, but rather by the focus on developing products with limited efficacy and generally poor safety profiles. One could point therefore to suboptimal drug development management and poorly informed or risk-averse benefit-risk decision making as factors contributing to the current difficult development environment.

The universal goal of shortened developmental timelines is subject to the pressure of the disparate needs of healthcare stakeholders. Industry needs favourable conditions for innovation without unrealistically high regulatory impediments, regulators require sufficient evidence to make a confidently informed decision to protect their constituencies, patients want earlier access to medicines and payers are requiring increasing amounts of specific data to make cost-effectiveness value judgements.

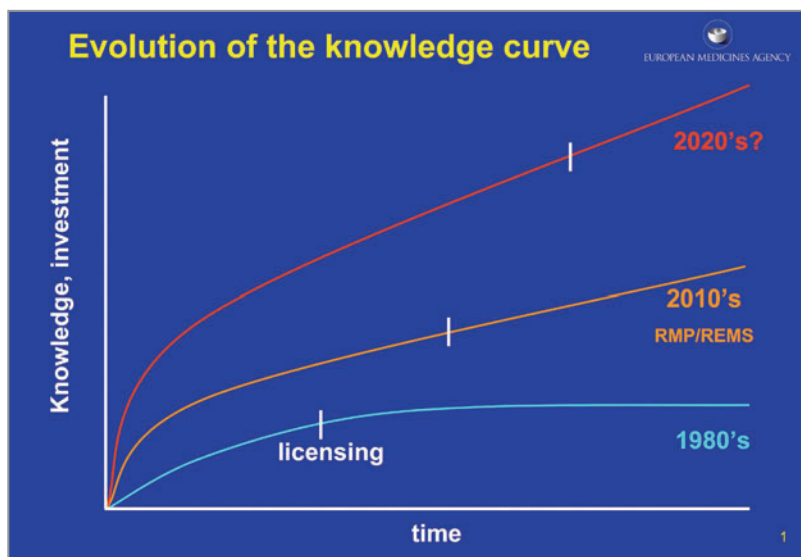
Unfortunately, the consequence of shorter development, approval and release timelines is a higher level of uncertainty about the product at the time of its release.

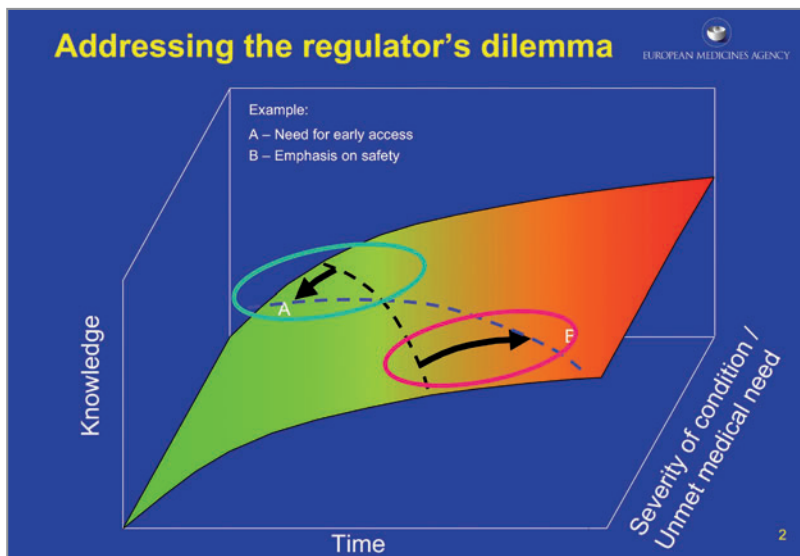
One of the most important things to be determined is what we want to achieve by early release and whether it is indeed the best way forward. Do we want to control the increasing cost of drug development, to reduce time to the market or to develop more effective and safer medicines through better informed decisions on benefit-risk?

In the current paradigm, regulatory pathways are aligned with the drug development process, a process that has been used for the past 50 years in many countries. Changing regulatory practice through legislation to reflect a radical change in the drug development paradigm will be extremely time-consuming, taking multiple years to effect. Data requirements, including those involving increased numbers of patients for clinical trials have steadily risen over the last thirty years, increasing time to drug approval and may soon be at unsustainable levels. One approach to mitigate these demands involves the European model to address exceptional unmet medical needs; many products have been approved with less clinical data when accompanied by valid risk management plans, but these approvals have been limited.

### Conditional approval and risk

Investigating whether these instances of conditional approval in Europe have led to more frequent or more rapid identification of serious safety issues, Arnardottir and colleagues in a submitted manuscript have retrospectively studied new drugs approved in Europe between 1999 and 2009, looking for the frequency and timing of a first Direct Healthcare Professional Communication (DHPC) for conditionally approved drugs compared with those approved under standard mechanisms (manuscript submitted). During this time period, 284 new drugs were approved, 46 (16%) conditionally. The probability of having a DHPC issued (used as an indicator of safety issues) for standard and conditionally approved drugs during a three-year follow-up was 10% and 7.2% and during an 11-year follow-up was 22% and 26%, respectively (Log-Rank  $p=0.756$ ). These data do not support the view that early drug approval increases the risk of serious safety issues emerging after Marketing Authorisation. It is not clear, however, if similar outcomes would be achieved in studying safety risks associated





with conditionally approving drugs that do not address an unmet medical need and for which there are alternative treatments. Data requirements may be increasing for approval of therapies for non-life-threatening diseases where alternate approved therapeutic options exists because of a sensitivity to the potential shift in benefit-risk ratio that can occur once a medicine is used outside a controlled clinical trial population in patients that may have comorbidities or other issues or if used off label or improperly. Because this approach creates a financially unsustainable and logistically impractical approach to medicines development, approvals of the future will need to rely on more robust risk minimisation plans that will manage products in clinical realities.

**The way forward**

Models for change currently under consideration include one that calls for an initial authorisation, controlled distribution with active surveillance,

and then consideration for full approval. This may not be a legally feasible approach because of the blurred distinction created between pre- and post-approval phases and because it would necessitate globally legislated changes in approval and release policies. One option is to optimise the identification of target populations through the use of such tools as validated biomarkers. Targeting specific patients allows for a decrease in the number of patients required for clinical trials with a concomitant decrease in development cost as well as a presumed increase in efficacy rates. Providing regulators with market authorisation dossiers demonstrating optimised efficacy and manageable safety profiles provides confidence for the early release of these products to targeted patients in the general population with the expectation of closing the efficacy-effectiveness gap.

**Conclusions**

In cases of high unmet medical need for which the severity of the disease justifies increased risk taking, conditional approval is justified. However, more broadly applicable methods for early access need to be created through the existing legacy legal-regulatory framework to expedite patient access to innovative therapies. We must find methods such as the use of biomarkers that will challenge the increasing data requirements yet produce the improved rates of efficacy and effectiveness demanded by regulators, patients and payers in the optimal target populations. Post-authorisation risk minimisation plans must be developed around the clinical realities of product use that will allow decision makers to be more willing to make an earlier decision in order to expedite market access.

## Industry viewpoint: Is there a need for a more flexible approach to both drug development and review strategies for the medicines of the future?

**Dr Thomas Unger**

*Executive Director, Worldwide Regulatory Strategy, Pfizer Inc, USA*

It is helpful to understand the driving forces behind the need for change. In the case of drug development, the place to begin is with a retrospective analysis of whether the drug development and approval processes have adequately protected and advanced public health and whether we have provided patients and physicians with appropriate science-based information to make informed therapeutic decisions. Using quantitative metrics in analysing the past decade, we can ask "Have we produced increasingly well tolerated and effective drugs? Have we improved the confidence in the processes and the systems?" Using this approach it is clear that although the industry has achieved great success there remain many aspects that can benefit from change.

If the current drug development model remains unaltered, as the costs of doing business and deploying new technologies increases, less

money will be available to invest in developing new drugs. Rising costs will also raise the bar of what is required for business success, continuing to foster a "blockbuster" model. Ultimately, fewer companies will be producing fewer and higher cost medicines, which is obviously not in the best interest of the innovators nor the patients. The current system, which introduced pharmacology, statistics and a whole set of supportive technical methodologies has served us well and produced many safe and effective medicines, but it remains essentially unaltered after 50 years. During this half century, as the complexities of drug discovery and investigation increase, productivity has decreased in large part because the industry has not effectively adapted to change. There remain a number of unmet medical needs that are unaddressed for commercial rather than scientific reasons. New technologies and modalities such as gene therapy, bi-functional monoclonal antibodies, stem cell therapies, personalised medicine and combination drug-device therapies will need to come market; these products will increase the pressure on the system and raise questions as to its ability to address the development and approval of these new therapies.

There are a number of ongoing initiatives to change the model. Progress is slow, however, and these initiatives must be coordinated to achieve success. Incremental improvement within the system is no longer sufficient, predominantly because patient and societal needs for new effective medicines are ever more difficult to address. Looking outside the pharmaceutical model, the semiconductor industry has delivered both technologic and societal change using a process of continuous improvement and rapid-cycle learning. Although costs in that industry are almost exponentially increasing, they are delivering such transformational products that it fosters a valuable construct. The key message here for the pharmaceutical industry is that the semiconductor industry has been transformed because it's been continually flexible and adaptive, feeding on rapid-cycle learning, a model that could be applicable to addressing the needs of the pharmaceutical industry.

Despite the promise of the past several decades for more effective, safer therapeutics with higher specificity for newly treatable diseases, all stakeholders are still looking for that transformation in healthcare. For example, patients are starting to speak with louder voices, forming advocacy groups who themselves are

**Many efforts attempting to alter the approach**

**Critical Path Initiative**  
Transforming the way FDA-regulated products are developed, evaluated, and manufactured

**EU Clinical Trials Directive**

**CTI CLINICAL TRIALS TRANSFORMATION INITIATIVE**

**IRI Focus Research Areas**  
SAFETY, EDUCATION & TRAINING, EFFICACY

- Uncoordinated
- Moving too slow – stretching collective and individual resources
- Not sufficiently "moving the needle"

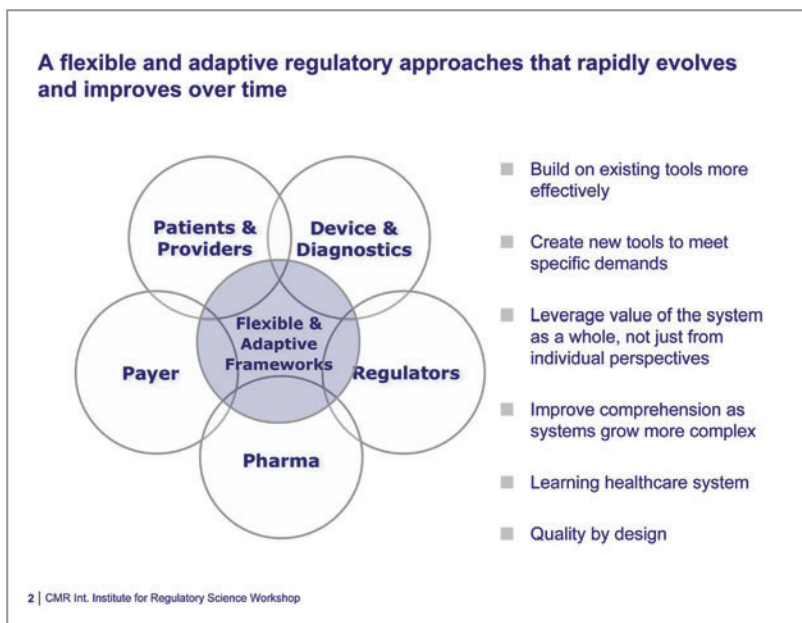
1 | CMR Int. Institute for Regulatory Science Workshop

beginning to fund R&D because they believe the system is not working effectively. In the United States, healthcare reform has in large part been stimulated because rising costs have not been offset by concomitant improvements in therapy or in the way that we are managing disease.

There are a number of opportunities for flexible adaptive change. International cooperation in recognising consistent standards, greater regional recognition of therapeutics or private certifications of approved products would help bring products to global markets more quickly. A robust educational programme around regulatory science is required, not just for regulators and industry strategists, but also payers and other key stakeholders who may be less familiar with the tools underlying development and approval approaches. Healthcare should be regarded as an ecosystem in which each stakeholder can communicate and contribute to actually solving some of the problems, ultimately resulting in a healthcare system that also benefits from rapid-cycle learning.

Progressive authorisation is one way to distribute across stakeholders in a more flexible, adaptable manner the burden of fully characterising a medicine from discovery throughout its life cycle. It allows us to provide a mechanism of downstream correction in real-time as we generate more information about how a medicine is really used. This is also a way to foster more innovation; having tools and frameworks that are dynamic and appropriate for the technology that is under investigation will be critical. Progressive authorisation may also allow us to think differently about innovation, how we can use real-world data to feed back into our understanding of the medicine's characteristics (as reflected in its label) and how we therefore, can better manage disease. This allows us to envision real-time data collection, integration of diverse pharmacoepidemiologic data sets, and maybe even the use of third-party data houses where we can post confidential data and allow regulators to begin to review these in a very different way.

Moving forward, the revised model has to embrace well-controlled real-world experimentation. Our regulatory standards for safety and efficacy need to remain unchanged but we need adaptable, flexible frameworks to integrate the input from diverse stakeholders to streamline the development and access process. To stimulate innovation, we need to work together in a very different way than we have historically, with cooperation and data sharing between partners feeding this information back into a healthcare environment that is constantly benefiting from this new information.



## NEWDIGS Initiative – A Regulator’s Perspective on a New Drug Development Paradigm

**Dr John Lim**

*Chief Executive Office, Health Sciences Authority, Singapore*

There is an increasing demand for industry to deliver more affordable drugs associated with good tolerability, effectiveness and value through the application of innovation, predictive information and a reduction in the complexity of moving a new medicine from the bench to bedside. Regulators meanwhile face challenges that include improving the use of increasingly limited resources to achieve internal efficiency and effectiveness and optimising the harmonisation of a highly globalised process. Asian pharmaceutical developers and regulators face different issue than the Eurocentric pharmaceutical system, which may be either a liability or an opportunity.

Flexibility, business process reengineering and thought leadership as well as international networking and collaboration are critical for regulators to improve their processes. In Singapore the legislative framework has been adapted to give regulators the flexibility to examine new approaches and systems to facilitate marketing authorisations. “Environmental scanning” to anticipate upcoming science and technology developments underpins the agency’s ability to flexibly adapt to new approaches such

as progressive market authorisation. For example, by assessing new development paradigms, it is clear that a new model of risk management will be needed because the standard approaches may be insufficient to support a new model of progressive authorisation.

A workshop held in Singapore in 2009 led to the collaboration with the NEW Drug development paradigmS (NEWDIGS) project. Originating within the MIT Center for Biomedical Innovation, the NEWDIGS group aims to transform the drug development paradigm by facilitating collaborative research, developing demonstration pilot programmes and sharing learning among stakeholders.

NEWDIGS is trying to improve therapeutic product innovation in healthcare by applying structured systems engineering and modelling methodologies for the goal of improving individual and interdependent systems. Although the project is very much focussed on progressive authorisation during drug development, it is also looking at the broader aspect of innovation and healthcare as a whole, reducing time to market, generating and validating new regulatory science tools and frameworks, and in building the foundations for healthcare learning environments. As has already been stated, many believe that this change cannot be incremental. It needs to be transformative and global. A very broad stakeholder consortium that looks across this whole issue is required and NEWDIGS involves participants from industry, regulatory agencies and academia. Openness and transparency among these groups are critical. Important questions to be addressed include how to leverage the participation of diverse participants, how to generate information that will contribute meaningfully to the greater body of knowledge about optimal approaches to drug development, to enhance healthcare systems as a whole and to determine how best to make these assessments and findings publicly available.

There are several opportunities for Singapore to collaborate with NEWDIGS because the drug approval system in Singapore reflects a tiered, flexible approach, from relying on reference agency decisions to undertaking full independent evaluations, depending on the nature of the product. As we are evaluating changing the drug development paradigm, this regulatory flexibility becomes even more critical, providing opportunities to develop new methodologies in a more coordinated effort. For example, Singapore is currently not much involved in aligning health technology assessment with a medicines review

**NEW Drug development paradigmS NEWDIGS** 

**NEWDIGS' mission – to improve therapeutic product innovation in healthcare**

- NEWDIGS applies structured systems engineering & modeling methodologies for the goal of improving individual & interdependent systems
  - Innovation in healthcare, not merely drug development
- Primary objectives:
  - Develop products that are more effective than existing therapeutic options
  - Reduce time-to-market, cost & late stage attrition/in-market withdrawals
  - Generate & validate new regulatory science tools & frameworks
  - Build the foundations of a healthcare learning environment
- Additional strategic objectives:
  - Catalyze change across the healthcare industry
  - Transformational impact, not incremental
  - Global scope & impact
  - Cross-stakeholder input & engagement, not just industry

Source: MIT-NEWDIGS

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To be the LEADING INNOVATIVE AUTHORITY protecting and advancing NATIONAL HEALTH and SAFETY

**NEWDIGS Aims to Transform Drug Development Paradigm**

By facilitating collaborative research, demonstration pilots & learning among stakeholders required

- **Safe & transparent environment led by MIT's Center for Biomedical Innovation**
  - Collaborative experimentation & learning among industry, academia, government, clinicians & patients
  - Opportunity to collaborate with strategic partners including FDA, NIH, HSA & others
- **Open collaboration**
  - Gaps & challenges addressed through collaborations with other Universities, consortia & agencies (Duke University, C-Path, CDISC, etc)
- **Leverage strengths of MIT & Harvard-MIT Division of Health Sciences & Technology (HST)**
  - Access proven structured methodologies successfully applied to transform other industries
  - Build on well documented, root-cause analysis to focus efforts on key levers
  - Catalyze cross-disciplinary research (science, systems engineering/engineering, policy, management & clinical medicine) focused on high impact solutions

Source: MIT-NEWDIGS

Center for Biomedical Innovation, HST Harvard-MIT Health Sciences and Technology, MIT, SUVA, Georgetown, AHRQ, FDA, CDC, HSA, NATIONAL INSTITUTE OF HEALTH, And global counterparts, Aetna, Bayer, Johnson & Johnson, Lilly, medco, Pfizer, QUINTILES, VERTEX, WELLPOINT, And others including: BROOKINGS, CDISC, Patient and advocacy groups, Providers

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process. However, there is clearly a possibility through the NEWDIGS initiative to align these requirements during drug development to address healthcare needs and access, cost-effectiveness assessments, and to apply the strength of regulatory science along the way.

As might be expected, NEWDIGS is faced with multiple challenges including global alignment with the many other groups investigating these issues to avoid duplication of effort. Additionally, appropriate methodologies such as global benefit-risk models must be adopted and the correct sponsor candidate to pilot an experimental new framework must be identified. Good communication methods including a common development language will be essential to bring a successful model to a wider community of regulators, researchers, payers, and patients.

There is strong government support for biomedical science development in Singapore. The government has committed to increasing the support for research to approximately 3.5 percent of the gross domestic product, with \$3.7 billion committed to biomedical science research for the next five years. As a compact island state with a good healthcare research infrastructure, a strong global network and a commitment to innovative regulation Singapore has the potential to pilot an innovative project. Although there may be risks in participation, success will result in significant benefit being realised by all stakeholders both locally and in the worldwide healthcare system.

WORKSHOP REPORT

## Post-marketing strategies for identifying benefits and risks

**Professor Hans-Georg Eichler**

*Senior Medical Officer, European Medicines Agency*

Post-marketing studies for an approved therapy are frequently conducted as part of risk management plans or are requested by marketing departments, but an important reason for a company to engage in this research may be to protect its assets. The ongoing improvement in safety data gathering tools for medicines has led to a growing sense of risk awareness; it may become increasingly difficult to keep new medicines on the market in light of recent experience in which industry and regulatory agencies are no longer in complete control of the public agenda for medicines. As Michele and colleagues stated in a recent publication "We've entered an era of increasingly frequent publications, some of which identify potential safety signals, and very often there is an urgent call to take immediate regulatory action."<sup>1</sup>

In some instances, the risk is not genuine. Some time ago, some medicines became associated in public perception with an increased risk of suicidality. This perception, however, has since dissipated with the availability of more robust real-world data. In another example of "phantom risk," although a new medicine for chronic obstructive pulmonary disease (COPD) was approved with a non-significant hazard ratio of 1.37 for cardiovascular events, a later meta-analysis published by Singh and associates<sup>2</sup>, reported a significant relative risk of 1.6. The company, however was in the process of conducting a major well-designed, well-executed randomised control post-marketing trial, and could show that contrary to the meta-analysis, the actual risk is below zero.

There are also, however, true risks. Rimonabant was approved in Europe for treatment of obesity in June 2006, but in January 2009, was withdrawn from the market in light of post-approval data that showed the benefits realised by patients in real-life were approximately half of those demonstrated in clinical trials, while the rate of adverse events was greater, creating a negative benefit-risk ratio for use of the drug.

This variance between clinical trial results and real-world post-marketing use, or the efficacy-effectiveness gap (See Thomas Lonngren's summary p 6) has two sources: biology and behaviour. Once approved, a medicine will be used by a more heterogeneous, more high-risk population than that tested in clinical trials, in which patients are selected who are most likely to benefit from treatment and less likely to experience adverse effects. In addition, physicians may sometimes misprescribe medication and real-life patients are often noncompliant with administration instructions. In fact, some would argue that the single greatest source of variability to drug response is poor patient adherence.

There are two ways in which to address the efficacy-effectiveness gap. In the first

method, regulators can follow the advice of the philosopher Seneca and lower their expectations to match reality by requesting that industry conduct studies with higher external validity, the so-called pragmatic or effectiveness trials. Although this would seem to result in more accurate benefit-risk profiles for drugs, in reality, many medicines would be lost to development because the resulting margin of benefit would be judged by developers to be too small. These drugs, which would have had some beneficial effect for some people under some circumstances, would not be pursued. The second approach to address the gap is not to lower expectations for reality, but to improve reality. That is, we should protect these pharmaceutical assets by ensuring optimised treatment in everyday clinical practice.

In future post-marketing environments, more studies that involve surrogate endpoints may be required. Tiotropium, for example, was authorised on the basis of showing sustained bronchodilation, a non-clinical surrogate end point. Post-approval studies, however, showed that the drug also reduced COPD exacerbations, which is very much a clinically relevant endpoint. Potential safety concerns must also be addressed using proactive modelling.

The optimal methodologies for observational trials have not yet been fully characterised, but it should be remembered that the current high standard of randomised clinical trials took over five decades to develop. We have to learn how to integrate information from registries and other studies into the characterisation of a new medicine; furthermore, patient preference studies for risk acceptance, values and utilities represent an undeveloped opportunity to more fully assess a medicine's real-world utility. Treatment, meanwhile, can be optimised through several methods including ensuring appropriate patient selection, prescribing and compliance. Current tools could be used to link electronic drug information to patients' healthcare records, electronic prescribing, and to patient reminders. Whether it is called "staggered approval", "progressive licensing" or "progressive authorisation", a managed gradual entry into a market starts narrowly and grows. Market size increases with knowledge, and this ultimately requires collaboration among stakeholders.

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2. Singh S, Loke YK, Furberg CD. *JAMA*. 2008;300:1227-1230.

EUROPEAN MEDICINES AGENCY

## Pre-approval: efficacy and adverse event data from clinical trials

A substantial increase in the weight on Unfavourable Effects would be required for the Placebo to be at most just slightly preferred.

The graph plots FEU/E Balance (0-90) against Total weight on Unfav Effects (0-100). Two lines represent Rimonabant (red) and Placebo (green). Rimonabant starts at (0,0) and ends at (100,90). Placebo starts at (0,0) and ends at (100,71). A vertical line at weight 67 intersects the Rimonabant line at a balance of approximately 55 and the Placebo line at a balance of approximately 45. A callout indicates 'Current weight on Unfavourable Effects, 67'.

1

EUROPEAN MEDICINES AGENCY

## Post approval: new evidence from real life scenarios

Double all proportions of unfavourable effects. Halve weight-reducing effect.

Now rimonabant looks only marginally better than the placebo.

The graph plots FEU/E Balance (0-100) against Total weight on Unfav Effects (0-100). Two lines represent Rimonabant (red) and Placebo (green). Rimonabant starts at (0,0) and ends at (100,72). Placebo starts at (0,0) and ends at (100,71). A vertical line at weight 67 intersects the Rimonabant line at a balance of approximately 48 and the Placebo line at a balance of approximately 47. A callout indicates 'Same weight on Unfavourable Effects, 67'.

2

## Risk Management Plans: Are these providing the reassurance agencies require and how should benefit be measured?

**Moira Daniels**

*Global Head, Regulatory Policy Intelligence and Labelling, AstraZeneca, UK*

### Safety evaluation tools

There are many safety evaluation tools available that have been developed by the US FDA, the EMA, Health Canada, the Therapeutic Goods Administration of Australia and others. These tools identify, collate and communicate new emergent safety signals, but also increase our expectation of certainty. Improvements have been made in the quantification of risk, but do those quantifications provide the right confidence in a regulated product within this regulatory framework, can the controls and restrictions be enforced, and are they practical? With increased transparency and public access to safety data, we must consider how we will manage the growing amount of "noise" within the surveillance system. Many other questions surround the practical use of these tools:

- Can they all work together as a harmonised approach?
- How can we derive the best value from these safety evaluations tools?

- Have we truly embraced the determination of benefit-risk, the use of decision trees, the more quantitative analysis of benefit-risk so we can communicate these aspects effectively to clinicians and patients who are using the medicines?

### Risk communication

US regulators are now using a variety of risk communication platforms to communicate directly to patients. The EMA currently communicates to patients primarily through its website. In the future, additional methods of communication will need to be emphasised including podcasts, video broadcasts, or internet-based broadcasts of clinical experts talking to patients about the rationale behind the use of specific medicines.

Ninety percent of the REMS that have been introduced in the US are based on medication guides. Patients now may be provided with as many as three documents instead of a single consolidated summary document, adding complication and confusion as to the relative importance of each form of communication. Consolidation of this information in a clear nontechnical format would benefit users; this may improve compliance and ultimately improve a product's effectiveness. The new E2E Tripartite Pharmacovigilance Planning Guideline issued by the International Conference on Harmonisation of Technical Requirements for Registration of Products for Human Use (ICH), specifies a single drug safety update report (DSUR) for each investigational product. The DSUR includes all indications, dosage forms and patient populations and incorporates an annual evaluation of safety information from all sources, new important safety issues, a summary of important identified and potential risks, a benefit-risk evaluation and the status of the clinical development programme.

### Benefit-risk tools

In addition to therapeutic guidelines to determine benefit-risk analyses for new medicines, we currently have clearly prescribed biostatistical methods and analysis and a multitude of guidelines for the conduct of randomised controlled trials. Tools such as new benefit-risk models are also emerging as we work to better define regulatory science and determine the best way to use predictive science. Biomarker development is going on in parallel with drug development, but the tendency has been to focus on the efficacy

## So what could industry do?

- **Personalized and stratified health care clinical trials**
- **Increasing use of seamless and adaptive product-specific clinical trial designs**
- **More radically, the introduction of conditional approvals based on appropriate safety but limited efficacy data**
  - Step 1: FTIM/Dose Selection one umbrella protocol
  - Step 2: Expanded Proof of Concept Trial based on surrogates
  - Step 3: Conditional approval (Risk sharing approval)
  - Step 4; Confirmatory Trial including biomarker if not yet validated.
  - Step 5: Full approval with continued determination of Risk/Benefit



## Regulators Role

- **Change Clinical Trial review and approval process to support new study designs**
- **Excellent and clear advice at possibly every step of the development**
- **Increased confidence and reliance on adaptive study designs**
- **Option of “rolling submissions” building on DSURs**
- **Optimizing the life cycle management of drugs**
- **Partnering with HTA bodies on comparative effectiveness**
- **Risk sharing**



rather than safety biomarkers. For example, safety and predictive biomarkers can be better used to determine the early signals of long-term chronic liver and renal disease. While measuring safety has become more absolute and precise, the determination of benefit continues to depend on stakeholder perspective and is subject to debate.

### Early-release paradigms

Is the “early release” of a new medicine a possibility, or should we concentrate, as Professor Eichler said in his presentation, on protecting our assets in the market and making sure they are used more effectively, thereby improving their overall value? We must move away from the blockbuster drug development model and from trying to develop a single regulatory framework that will fit every disease area, type of drug and patient, which is why pragmatic rather than legislative methods may be the best way to effect a change in the review and approval process.

Industry should begin to think much more about personalised and stratified healthcare clinical trials and to develop clear criteria for the co-development of devices and drugs. The increasing use of seamless and adaptive product-specific clinical trial designs is unfortunately not yet fully supported in the European environment in which each change in design requires a separate approval process in multiple countries. Conditional approvals based on appropriate safety data may be possible, but any conditional approval would have to be based on risk sharing, and involve a comprehensive process to communicate that risk to stakeholders.

An initial step can be taken by regulators to help change the clinical trial review and approval process to support the use of new study designs. We must increase confidence in consistent use of adaptive study designs and use these approaches to optimise product life cycle management. Excellent and clear scientific advice is required at every step of the development process as well as an open debate around safety profiles that evolves from ongoing drug safety update reports. The current debate in the US surrounding evolving diabetes guidelines through data analyses from 18,000 multiregional studies demonstrates that the collection of benefit and risk data post-approval through meta-analysis must be approached carefully and focus on truly relevant data. To make new options a reality, industry and regulators have a shared responsibility to develop a risk framework that provides for incentives with clear and enforceable post-approval regulatory oversight.

As healthcare changes continue to advance globally, the information needs of legislators will also be considered and benefit risk extended into life cycle management.

## Healthcare Databases – Are these ready to be harnessed for assessing post-marketing benefit and risks?

**Dr Michael Devoy**

*Senior Vice President, Global Medical Affairs and Pharmacovigilance, BayerSchering Pharma AG, Germany*

The paradigm of randomised control trials (RCTs) has been with us for quite some time. This study design is associated with a high level of confidence, despite its potential limitations. The use of observational data sets, however, particularly in their current form, is a much more immature science, which needs to be nurtured so that its applications can be fully understood and not discredited because of a lack of basic knowledge about the strengths and weaknesses of these study designs.

RCTs have been and continue to be the preferred source of evidence of a medicine's benefit and risk. The key advantage of randomised treatment assignment is that it ensures, on average, balance of treatment groups with respect to baseline characteristics (covariates). Also, RCTs are generally conducted in a double-blind fashion in an effort to ensure that knowledge of the treatment assignment either by the study subjects or the investigators does not affect the observed outcomes. Thus, any observed difference in outcome between

subjects randomised to treatment and those randomised to the control can be attributed to the treatment assignment. Randomised trials also have their limitations. They usually enrol a relatively homogeneous group of patients with a narrower range of characteristics than the general population, including fewer co-morbidities and concomitant medicines who may not reflect how the therapy is used in the real world.

Currently, observational databases can be derived from insurance claims/ payer databases, medical record databases, and survey databases. Because technology has made databases easily available, a danger is that users will rush to analyse these data sets without fully understanding their limitations. For example, an expert group wanted to use an observational data set to compare effects on joint damage associated with two options in the treatment of haemophilia in children, the traditional on-demand treatment, and a scheduled three-times-weekly regimen. However, when clinical haemophilia experts were consulted, it emerged that in addition to treatment, one of the key issues in determining joint damage is how these children behave in school or during active play and contact sports, data which were not included in any of the target databases.

Moreover, confounding baseline conditions (covariates) are frequently unaccounted for. A recent study using a claims database concluded that a drug used in cardiac surgery was associated with increased risk of renal failure or death. However, a secondary analysis using ten additional covariates that were not included in the original analysis, such as pre-operative history of angina, dialysis, heart failure, and use of antiplatelet agents, demonstrated that the reported treatment differences moved toward the null when these covariates were considered.

In a third example, a multi-national observational study had concluded that among patients surviving MI with ST-segment elevation [STEMI], the mortality rate between 6 months and 2 years in patients treated with drug-eluting stents was higher than in patients treated with bare metal stents. However, another study conducted by Harvard investigators in Boston addressed the same question. The Boston study used an electronic registry mandated by the state of Massachusetts that recorded in PCI patients detailed cardiovascular risk factors and outcomes that could be linked to government death records. The Boston investigators concluded that

### Typical Post-market “real world” database studies compared with typical RCTs

	Pivotal RCTs	Real World Database Studies
<b>Inclusion/Exclusion</b>		
Diagnosis	Narrow	Broad
Co-morbidities	Few	Many
<b>Controlled Conditions</b>		
Compliance	Generally good	Variable
Concomitant Drugs	Controlled by protocol	Not controlled
Concomitant Therapy	Controlled by protocol	Not controlled
<b>Level of Care</b>		
	More intense	Less intense

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## Conclusion

- Assessment of benefit and risks in observational studies using healthcare databases requires dealing with non-randomized treatment assignment, absence of blinding, and data collection not tailored to the research question. This requires both identification of a suitable database (where possible) and use of appropriate methodology.
- The value and utility of a Healthcare database is determined by its suitability to the specific research question at hand.
- For most, but not all, research questions EMR databases are more suitable than claims databases.
- *In an 'early release scenario' database studies may be used to supplement and complement data from RCTs.*

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in patients with myocardial infarction, treatment with drug-eluting stents was associated with reduced 2-year mortality as compared with bare metal stents. This result underscores the need for a rigorous examination of potential database limitations.

## Conclusions

Although observational studies are not intended to replace well-designed randomised trials in the context of early release of medicines, they will play a role in defining the real-life perspective of treatment effects in larger, more heterogeneous populations. To be useful to examine benefit and risk in the context of market use, a healthcare database must contain detailed patient-level treatment information, relevant covariate data, clear timing of events (in order to distinguish baseline conditions from outcomes), means to evaluate adherence to treatment (how and why patients discontinue treatment), and accurate measurements of outcomes.

Generally, electronic medical record databases may be more suitable than claims databases because they generally contain more complete clinical records. Maintaining patient confidentiality will be a critical aspect of the analyses of these comprehensive data sets. Observational databases will be increasingly used as a complement to randomised control trials. Therefore, a thoughtful approach to the design and conduct of these analyses will be required.

## **An alternative model to enable early patient access: Proposal for an orphan drug and implications for real world data**

### **Dr Tony Hoos**

*Senior Vice President, European Medical Affairs,  
GlaxoSmithKline, UK*

Duchenne muscular dystrophy is a rare disease affecting one in 3,500 young boys. The disease typically initially manifests as difficulty in walking and eventually progresses to the point at which patients have no muscle use. No curative treatment is available, and those who contract the disease eventually die by age 30, usually of respiratory infection or respiratory or cardiac failure.

GlaxoSmithKline (GSK) is developing the first of a family of compounds that targets Exon 51, a gene which is mutated in a subset of patients with Duchenne. In November 2009, GSK proposed a compound from this family be

used as a pilot for accelerated development. This project met the criteria for Development Model set by the Athenaeum Group, that is, it was a novel compound, in a situation of high need, which because it has been designed for patients with a specific mutation, is an example of personalised medicine. Because the target population consists of just 250 to 300 boys, patient accrual is a tremendous challenge and enrolling 180 patients who would have been typically required for trial results to achieve significance would have been near impossible.

Various options were presented within the company for an accelerated development study design including using dystrophin levels in muscle as a surrogate endpoint for efficacy. Parallel regulatory and HTA evaluation and a single unified HTA approval and pre-approval access programme were also considered. Finally, it was proposed that flexibility in the design of the pivotal study could include a reduced or omitted placebo arm requirement and that the demonstration of efficacy in the subpopulation of boys who were most likely to show benefit could perhaps be extrapolated as evidence of the treatment's efficacy in all boys with the disease.

An initial trial has begun in 12 young boys who receive weekly injections of the drug and is now in its extension phase. Discussions regarding a change in the development plan were initiated with the European Medicines Agency (EMA) and the National Institute for Health and Clinical Excellence (NICE), but there appears to be little flexibility at this time for this product. Although there have been some signs of efficacy, unfortunately, it seems that the classical model for medicine development and regulatory approval is not likely to work for treatments for rare diseases because of limitations in the number of patients available for testing.

For future compounds targeted to the management of rare diseases or for personalised medicine approaches, several strategies could be considered. Because of the limited number of target patients and the need to provide new medication rapidly around the

world, a single global development plan is essential. Harmonisation of review requirements between different regulatory authorities and approval based on smaller numbers of patients would be ideal. Because rare diseases often represent uncharted territory, there is a greater need for frequent dialogue between the sponsor, regulators and HTA bodies during the development programme.

Looking at therapies for these extremely rare diseases with “conventional” eyes will not work. Although there is a potential increase in risk associated with giving these patients early access to these novel therapies, individual patients are likely willing to share that risk. GSK is willing to share this development experience, to share its knowledge of the compound and to share the development program to improve the process of review and ultimately, accelerate patient access to therapies for rare disease.



### Lessons learnt from “live license” or life cycle regulatory management for oncology /niche medicines – How could these be translated to a wider set of medicines?

**Dr Eric Abadie**

*Chairman, Committee for Medicinal Products for Human Use, European Medicines Agency, France*

For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required. In such cases, it is possible for the Committee for Medicinal Products for Human Use (CHMP) to recommend the granting of a marketing authorisation subject to certain specific obligations to be reviewed annually. A “conditional marketing authorisation” may be granted where the CHMP finds that, although comprehensive clinical data describing the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met: the risk-benefit balance of the medicinal product is positive; it is likely that the applicant will be in a position to provide the comprehensive clinical data at a later date; unmet medical needs will be fulfilled; and the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required to gain complete confidence in the benefit-risk profile of the product.

This legislation aims to provide both an early access mechanism and a more rigorous framework for the fulfilment of follow-up measures. The legislation is not a tool for compromise but is a formalised framework for products accepted with conditions, because of incomplete development programmes, but

**How to build regulatory confidence for the early release of medicines ?**

- 1) By strengthening the assessment of the B/R balance in pre and post MA (quantitative aspect, PROTECT)
- 2) By strengthening the post marketing monitoring, not only for safety (New EU regulation on pharmacovigilance, ENcEPP)
- 3) By convincing regulators and HTA bodies in some specific cases early release is the best option (early dialogue is key !)

Slide 1

Slide 2

**Is early release of medicines the « new » necessary paradigm ?**

1) Early release, at any price: not a good solution

2) For regulators, and probably HTA bodies: increase the « learn » phase, accept to lose time at beginning to gain time afterwards, may permit an earlier MA provided « only » one pivotal trial is supported by a strong exploratory phase

where benefit-risk is clearly positive. Possible models for conditional approval include instances in which:

- The endpoint used is not typical
- An earlier-than-typical time point for assessment of clinical outcome is specified
- Relevant clinical settings are not adequately represented
- There has been an inadequate investigation of posology
- There are incomplete data to fully characterise the product's safety profile

Three types of challenges have emerged with the granting of conditional marketing authorisations. The first centres on demonstrating a positive benefit-risk prior to having a comprehensive clinical package. The question behind this difficulty is how to change the legislated requirements "to demonstrate a positive benefit-risk profile" while clearly being able to communicate what level of uncertainties can be accepted? The second challenge lies in completing a comprehensive clinical package after conditional approval when the implications for continuing or initiating controlled pivotal trials must be considered. The third challenge is methodologic and includes such considerations as:

- The qualification of new surrogates / biomarkers to better define the product's characteristics
- How to best benefit from the Scientific Advice Working Party procedure

- The role and limitations of interim data analyses following authorisation
- Type I error control in these analyses
- The feasibility of implementing and carrying out specific post-authorisation obligations

### Lessons learned from CHMP experience

Between 1995 and 2010, sixteen oncology drugs were granted marketing approval under exceptional circumstances. Ten were granted "conditional" and six "under exceptional circumstances/orphan." Out of ten "conditional approvals", five converted to "full" approval within a median four years. Between 2005 and 2010, five oncology products were granted conditional marketing approval. Four out of five were "promising" drugs with suboptimal development, but were ultimately difficult to reject outright.

Early release could be envisioned for a wider set of medicines beyond oncology, provided the prerequisites noted above are met. Confidence for the early release of medicines can be achieved by strengthening the assessment of the benefit-risk balance before and after marketing approval, by strengthening post-marketing monitoring, and by convincing regulators and HTA bodies that in some specific cases early release is the best option for the patient and the health care system overall. Early release, at any price, however, is not a good solution to expediting patient access to new medicines. For regulators and HTA bodies, the knowledge gained from a single pivotal trial may form the basis for an earlier marketing authorisation, provided the development programme is supported by a strong real-world exploratory phase.

Because CHMP's experience of conditional marketing authorisation for oncology products has not been altogether satisfactory, a cumulative approval process different from the current conditional marketing authorisation could be envisioned provided that post-marketing activities evolve from risk management to benefit-risk management, that the methodology of benefit-risk assessment is enhanced, that uncertainties at the marketing authorisation level are mitigated through approaches such as robust risk management programmes, and that there is ongoing collaboration between industry, regulators and payers from the beginning of development to support the product's gradual entry to market with a resultant steady, controlled market penetration.

## Early access scenarios – the patient perspective on the concept

**Dr Mary Baker**

*President, European Federation of Neurological Associations*

### Offsetting rising costs

As the cost of producing medicine continues to rise, disagreement and uncertainty surrounding the therapeutic value of these medicines also

mounts. Patients find themselves at the centre of this controversy, because often the potentially life-saving medicines they require are those with small target populations and high per-patient costs.

This disagreement and uncertainty has in turn given rise to a variety of payer schemes to meet the challenge of escalating costs of these new therapies. One such scheme, known as portfolio deals, are a trade-off between price or reimbursement on one product versus prices of other products or discount on joint volumes. In the one-price-per-patient plan, price is calculated per patient or population for a given period and includes as much drug as required. In another plan, pharmaceutical companies offer solutions to decrease the patient out-of-pocket burden of prescription medicines, while in yet another, industry manages disease or diseases in a certain population of patients and guarantees budget savings in return for favourable pricing and coverage. Finally, risk sharing includes coverage with evidence development, conditional coverage, outcome guarantee and price and volume agreements.

### New paradigms

The desire of regulators, clinicians, and many patients to be in a position to fully characterise a new product's safety profile at the time of its initial approval is stifling innovation in medicine development, and we must progress from a situation in which the general public expects every medicine to meet the unrealistic standard of "absolutely safe." However, the average person does not fully understand how to interpret a product's benefit and risk. Patient information leaflets, often a primary source of benefit and risk information, are not written in easy-to-understand language, and communication and education in this regard at the patient level must improve. Patients want to see a new approach to the use of novel clinical trial designs, and the inclusion of validated patient-reported outcomes would ensure that patients' voices were heard in relation to a medicine's effect on their quality of life and other meaningful endpoints.

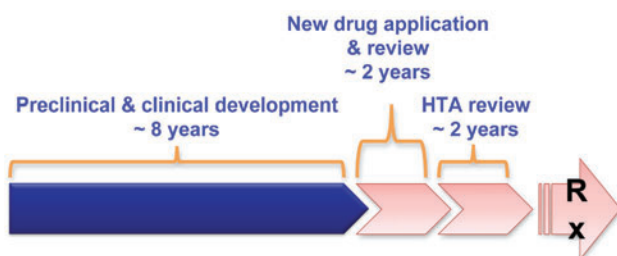
The movement of medicine from the bench to the bedside takes far too long in the eyes of sick patients, with eight years preclinical and clinical development, two years to go through the regulatory review, and two years to be reviewed by health technology assessment. Then, following approval, a conservative doctor may still tell a patient "I'm sorry, but the clinical trials were so narrow, the exclusion criteria so great, that we'll have to wait and see just how safe and

## Safety versus innovation



*"I am already in an unsafe world, a little more unsafeness doesn't worry me" Albert Jovell, Barcelona*

## From the bench to the bedside



effective this medicine is for patients with your condition”, which can amount to another year of real-world experience. So at the end, it may take 13 years for a drug to reach patients in the UK. Management of the chronic disabling diseases of the elderly such as cancer, brain disease, diabetes and COPD is a very expensive challenge to a health system, and the health system must adapt

to this challenge. It is after all as Darwin says, that the surviving species is not the strongest or most intelligent, but the one most adaptable to change. Patients can help to contribute needed improvements in the medicine development process by providing the perspective and expertise achieved by living with disease.

### Early Access Models: What is the perception of those organisations responsible for health technology assessment?

**Meindert Boisen**

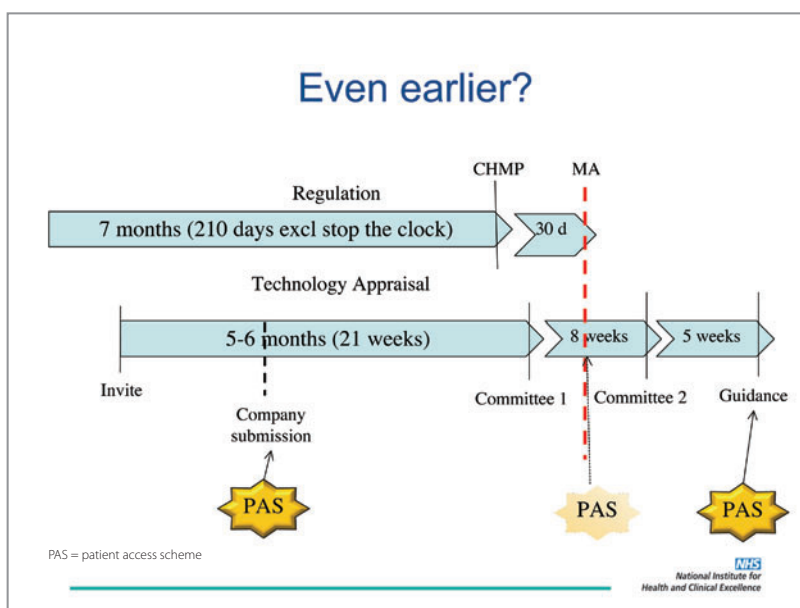
*Programme Director Technology Appraisals, NICE*

#### What does NICE do?

The National Institute for Health and Clinical Evidence (NICE), together with National Health Service (NHS) provides clinical and non-clinical evidence and offers guidance for best medical practice. It is the goal of NICE to help the NHS and other organisations to ensure not only that the money they spend improves health for their communities but also, just as importantly, that they do not spend money on ineffective care. NICE guidance promotes better outcomes for patients and effective use of NHS resources, provides new knowledge for NHS professionals and patients, and can help medicine developers access the NHS market.

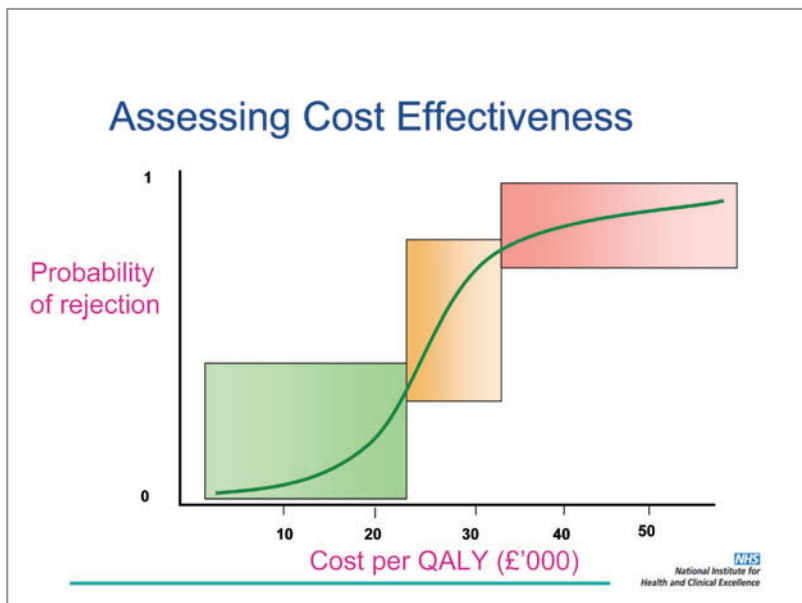
Since an important social objective is to improve health outcomes across the NHS, a new medical technology (be it a drug, device or other intervention) can be regarded as valuable if its approval is expected to increase overall population health. It is not sufficient to establish whether a technology is more effective than the alternative interventions available because approving a more costly technology will displace other health care activities that would have otherwise generated improvements in health for other patients at perhaps a lower cost. Therefore, the health expected to be gained must be compared to the health expected to be forgone elsewhere as a consequence of additional NHS costs. The social objective of health improvement and an ethical principle that all health impacts are of equal significance, whether they accrue to those who might benefit from the technology or other NHS patients, is an established starting point for the NICE appraisal process.

A medicine’s cost-effectiveness is determined through its impact on quality-adjusted life year (QALY) and opportunity costs, and a technology costing less than £20,000 per QALY gained is normally approved. Above that figure other factors such as the degree of certainty surrounding the calculation of cost-effectiveness, changes in health-related quality of life and the innovative nature of the technology are considered. Our committees have flexibility to make judgements and listen to the public, especially in considering life-extending treatments, allowing drugs with a higher cost-effectiveness ratio to be approved on a great number of occasions.



#### What role can a HTA agency have in early access models?

NICE has benefitted from a decade of process refinement, and now performs single technology appraisals faster and earlier than ever before. New expectations for speed include the goal of having all single technology appraisals of oncology drugs in 2011 completed within six months of the marketing authorisation. The



result of earlier engagement has been that NICE spends much more time communicating with companies and sending clarification requests, with the result of more approvals supported by more complete evidence. From 2000 to 2010, 65 percent of applications could be categorised as recommended, 18 percent as optimised, 6 percent designated only for research and only 11 percent as rejected.

**Is coverage with evidence development viable for NICE?**

Obtaining more information through a conditional licensing process might reduce but not resolve uncertainty – and not just about efficacy or effectiveness. Consider that the cost-effectiveness ratio changes that are observed by using different assumptions in the economic model present a much more complex decision

than simply requiring more effectiveness evidence. Furthermore, manufacturer cost-effectiveness analysis always differs from academic analysis of the same technology, not because of bias but because of differences in assumptions (such as the worth of innovation) and interpretation and value judgements. The economic aspect of conditional licensing, that is, the ongoing cost of research to industry versus the chance of eventual approval must also be considered.

**If we would engage in earlier access, can we then find a way of talking to regulatory bodies to talk about the methodologic needs?**

When NICE needs to make a comparative judgement, evidence from historical controls is often used, involving a whole new area of methodologic considerations, when comparators are not obvious or sometimes not even licensed. For example, lapatinib might be cost-effective versus trastuzumab, but if trastuzumab was never cost-effective, how is that relevant? What techniques of crossover accounting should be used? Interpretation of the technique can also vary with perspective as well; for example, indirect comparisons for technology approved with no head-to-head comparison can be problematic. All of this contributes to uncertainty. Earlier access or approval will inevitably be associated with higher uncertainty, but we as HTA organisations or payers are geared towards handling uncertainty. We can work towards a way to agree on how to resolve uncertainty through earlier access with evidence development, and how to quantify whether investing in that evidence is an efficient use of resources that will make a difference.

## Appendix: Workshop Attendees

Regulatory agencies		
<b>Dr Eric Abadie</b>	Chairman, CHMP	European Medicines Agency
<b>Dr Mary Baker</b>	President	European Federation of Neurological Associations
<b>Meena Ballantyne</b>	Assistant Deputy Minister	Health Canada
<b>Meindert Boysen</b>	Programme Director, Technology Appraisals	National Institute for Clinical Excellence, UK
<b>Prof Sir Alasdair Breckenridge</b>	Chairman	Medicines and Healthcare products Regulatory Agency, UK
<b>Agnes Ket Yee Chan</b>	Regulatory Consultant	Health Sciences Authority, Singapore
<b>Dr Petra Doerr</b>	Head of Management Services and Networking	Swissmedic
<b>Prof Hans-Georg Eichler</b>	Senior Medical Officer	European Medicines Agency
<b>Dr David Guez</b>	R&D Strategy Director	Institut de Recherches Internationales Servier, France
<b>Margaret Jackman</b>	Group Manager	Medicines and Healthcare Products Regulatory Agency, UK
<b>Dr Kian Ming Lam</b>	Division Director, Corporate Development and Operations Division	Health Sciences Authority, Singapore
<b>Prof Hubert Leufkens</b>	Chairman	Medicines Evaluation Board, The Netherlands
<b>Dr John Lim</b>	Chief Executive Officer	Health Sciences Authority, Singapore
<b>Thomas Lönngren</b>	Executive Director	European Medicines Agency
<b>Dr Hwei-Xin Lou</b>	Acting Director, Pharmaceuticals and Biologics Branch	Health Sciences Authority, Singapore
<b>Prof Robert Peterson</b>	Executive Director, Drug Safety and Effectiveness Network	Canadian Institutes of Health Research
<b>Dr Supriya Sharma</b>	Director General, Therapeutic Products Directorate	Health Canada
Industry		
<b>Dr Steve Caffè</b>	Senior Vice President, Global Regulatory Affairs and Pharmacovigilance	Baxter Healthcare Corporation, USA
<b>Dr Nicola Course</b>	Vice President, Global Regulatory Affairs, Europe	GlaxoSmithKline, UK
<b>Moira Daniels</b>	Global Head Regulatory Policy Intelligence and Labelling	AstraZeneca, UK
<b>Dr Paloma De Miguel</b>	Vice President, Regulatory Affairs and Pharmacovigilance EMEA	Baxter Healthcare Corporation Inc, Spain
<b>Dr Michael Devoy</b>	Head of Global Medical Affairs and Pharmacovigilance	Bayer Schering Pharma AG, Germany
<b>Ed Geuns</b>	Head of Global Regulatory Affairs Liaison Vaccines	Abbott Biologicals BV, The Netherlands
<b>Dr Tony Hoos</b>	Senior Vice President, European Medical Affairs	GlaxoSmithKline, UK
<b>Mark Hope</b>	Head of EU/ROW Program Management and EU/ROW Head of Oncology	F. Hoffmann-La Roche Ltd, Switzerland
<b>Dr Paul Huckle</b>	Senior Vice President, Global Regulatory Affairs	GlaxoSmithKline, USA
<b>Dr David Jefferys</b>	Senior Vice President, Global Regulatory and Government Relations	Eisai Europe Ltd, UK

<b>Mark Jungemann</b>	Executive Director	Eli Lilly and Company, USA
<b>Prof Trevor Jones</b>	Director	Allergan Inc, USA
<b>Sukhwinder Jossan</b>	Associate Vice President, Global Regulatory Affairs, Development Projects	Ferring Pharmaceuticals, Denmark
<b>Diane Mackleston</b>	Senior Director, Global Regulatory Affairs Europe, CNS and General Medicine Therapeutic Areas	Eli Lilly and Company Limited, UK
<b>Dr Birger Ohlrogge</b>	Head of Global Regulatory Oncology EU II	Merck KGaA, Germany
<b>Dr Joseph Scheeren</b>	Senior Vice President, Head of Global Regulatory Affairs	Bayer Healthcare Pharmaceuticals Inc, USA
<b>Mark Smyth</b>	Senior Regulatory Process Manager, Global Processes	Novo Nordisk A/S, Denmark
<b>Dr Deborah Szafir</b>	Head of EU Regulatory Liaison	Roche, France
<b>Dr Thomas Unger</b>	Executive Director, Worldwide Regulatory Strategy	Pfizer Inc, USA
<b>Dr Catherine Weil</b>	Associate Director, Global Regulatory Sciences EMA	Bristol-Myers Squibb, Belgium
<b>Dr Laura Wolf</b>	Head of Regulatory Affairs/Liaison	Abbott Products GmbH, Germany
<b>Dr Dmitry Zamoryakhin</b>	Manager, Clinical Development	Daiichi Sankyo Development Ltd, UK
<b>Academic Institutions and Associations</b>		
<b>Dr Richard Barker</b>	Director General	Association of the British Pharmaceutical Industry, UK
<b>Dr Pieter Stolk</b>	Project Manager, Escher Project	Utrecht University, The Netherlands
<b>CMR International Institute for Regulatory Science</b>		
<b>Patricia Connelly</b>	Manager, Communications	CMR International Institute for Regulatory Science
<b>Lawrence Liberti</b>	Executive Director	CMR International Institute for Regulatory Science
<b>Dr Neil McAuslane</b>	Director	CMR International Institute for Regulatory Science
<b>Dr Franz Pichler</b>	Manager, HTA Programmes	CMR International Institute for Regulatory Science
<b>Prisha Patel</b>	Portfolio, Manager, Emerging Market Programme	CMR International Institute for Regulatory Science
<b>Prof Stuart Walker</b>	Founder	CMR International Institute for Regulatory Science
<b>Tina Wang</b>	Research Analyst	CMR International Institute for Regulatory Science