



# New Development Paradigms:

Building Regulatory Confidence for  
the Early Release of Medicines

WORKSHOP  
11- 12 October 2010  
Surrey, UK

## Workshop Synopsis

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The following is a high-level summary of key points from a Workshop conducted by the CMR International Institute for Regulatory Science on October 11-12, 2010, in Surrey, UK. A complete report will be available in January 2011.

## Background

Over the last 5 years the 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 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 Mitigation Strategies (REMS). Now the question is what would be needed, pre- and post-release to provide confidence to the regulators to apply early-release models to a wider set of medicines?

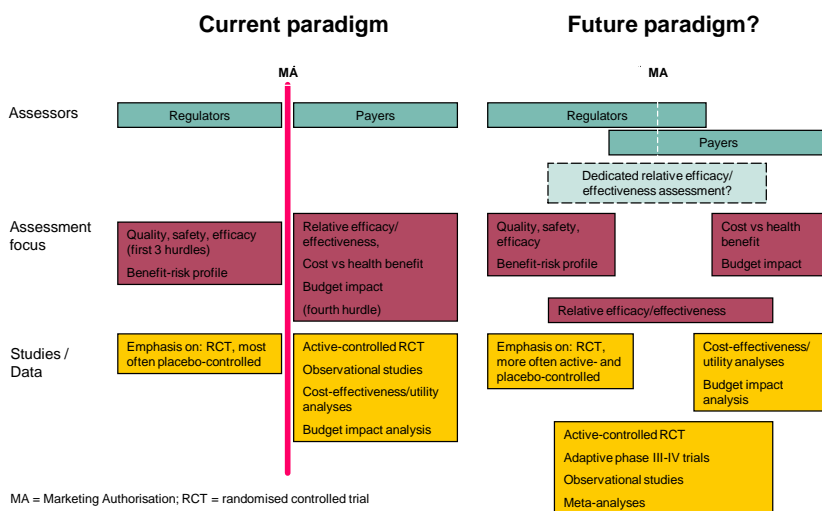
## Key points from Workshop presentations

**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 such as that illustrated in the adjacent figure 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?

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, improving efficacy and 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 forward, and the progressive authorisation of medicines allows us to work with a flexible and dynamic mechanism to collect downstream information about how a medicine really is used.



Explaining that system transformation requires concerted participation of 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, demonstration pilots and 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 with limited efficacy experience. This model requires shared risk taking by both regulators and industry and should include alignment 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 a novel 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 in which 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 (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?

The 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 that proposed by organisation such as the Athenaeum Group and others 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.

#### Reference

1. *CIS announces joint EMA-NEWDIGS research project*. Press release. Found at [http://web.mit.edu/cis/press\\_release/EMA\\_NEWDIGS.html](http://web.mit.edu/cis/press_release/EMA_NEWDIGS.html). Accessed November 2011.

## SYNDICATE DISCUSSION

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

### Syndicate Chairs

**Dr Supriya Sharma**, Director General, Therapeutic Products Directorate, Health Canada; **Prof Hubert Leufkens**, Chairman, Medicines Evaluation Board, The Netherlands; **Dr David Jefferys**, Senior Vice President, Global Regulatory and Government Relations, Eisai Europe Ltd, UK

### Syndicate Rapporteurs

**Dr Kian Ming Lam**, Director, Corporate Development and Operations Division, Health Sciences Authority, Singapore; **Mark Hope**, Head of EU/ROW Program Management and EU/ROW Head of Oncology, F. Hoffmann-La Roche Ltd, Switzerland; **Dr Steve Caffè**, Senior Vice President, Global Regulatory Affairs and Pharmacovigilance, Baxter Healthcare Corporation, USA

### Topics

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

### Key Discussion Points

**Early release:** It was considered important that a common definition of this term be understood by all stakeholders. Whether it refers to time of market authorisation or patient access, initiation of patent period, or controlled release, the definition may be a reflection of an evaluation process that is continually evolving to meet the changing needs of the development of new medicines.

**Synergies:** A number of ongoing initiatives are underway to improve or reduce the barriers to efficient and effective drug development by organisations such as the Center for Policy Analysis on Trade and Health (C-Path), the Innovative Medicines Initiative (IMI), the Athenaeum Group, and NEWDIGS. It is critical that information and activities developed by these groups be shared and understood, synergies explored and duplication avoided.

**Current tools:** To build confidence around early-release models, it is essential that they are not perceived as being associated with increased risk. A number of current tools and methodologies such as benefit-risk assessment, registries, companion diagnostics, and early discussion between agencies and companies around post-marketing risk management plans and adaptive trial designs can be optimised to minimise uncertainties, although it is also important that these methods add value and produce a good return on investment.

**Regulatory frameworks:** Because of the length of time required to enact legislative changes, it is important that agencies and companies looking to implement a more proactive approach to “bespoke development” determine the opportunities within the current regulatory frameworks. This includes defining the quantity and type of data that are appropriate pre- and post-approval to address the benefit-risk issues of products targeted to particular patient types.

**Patient needs:** A number of ideas were discussed to advance the consideration of patient needs early in the medicine development process such as a systematic method of assessing patient acceptance of risk and the influence this acceptance has on development and regulatory decisions as well as the use of patient-reported outcomes in clinical trials. Strong education and communication tools will be required to advise all stakeholders regarding unmet medical needs and to fully explain the role of benefit and risk in any early-release model.