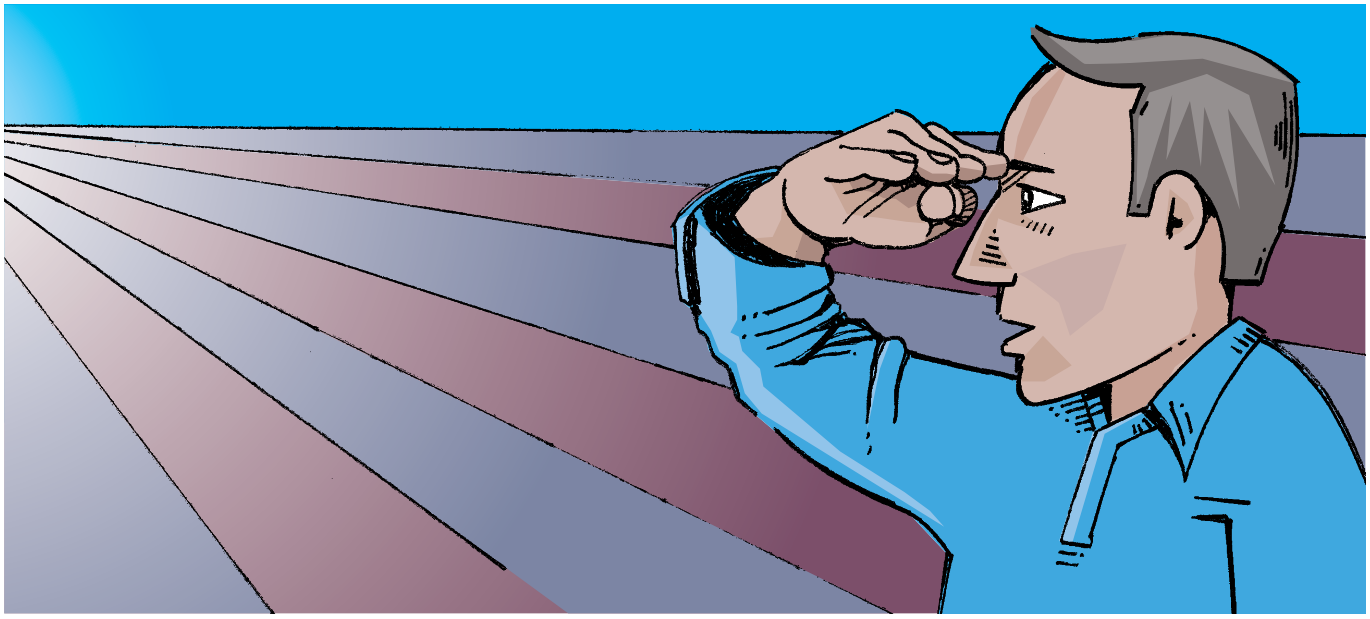

MEDICINES ADAPTIVE PATHWAYS:

A PRACTICAL STRATEGY TO IMPROVE PATIENT ACCESS TO MEDICINES?

1-2 OCTOBER 2014
HEATHROW, UK

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards and its funding is derived from membership dues, related activities and grants.

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Section 1: Executive Summary

Background to the Workshop

Different approaches to meet unmet medical needs and make new medicines available to patients more rapidly have been adopted by regulatory agencies. The advantages of these models are:

- A streamlined regulatory review process enhanced by more frequent formal sponsor-agency interactions during development resulting in a more rapid availability to patients than standard approaches
- The possibility to integrate the scientific requirements of health technology assessment (HTA) and payers into the development process
- The use of innovatively designed studies incorporating predictive endpoints to aid in answering questions around benefits, harms and effectiveness of the new medicine with smaller study cohorts than previously assessed
- Ability to address regulatory uncertainty associated with an early-release model through the collection of real world data
- The ability to manage the product in the post-approval period including implementing ways to reduce its availability if benefits and harms are not as expected in early development

It is therefore important that these models also dynamically assess the benefits and harms in the post-approval phases. For these regulatory pathways to successfully deliver safe and effective new medicines to patients more quickly it is also necessary for the HTA or reimbursement bodies to be an integral part in the development and acceptance of any new approach.

This Workshop built on previous CIRS Workshops in which recommendations to advance this concept have been identified. In addition to providing a current overview of the different medicines adaptive pathways being discussed, designed, piloted and implemented around the world this Workshop provided perspectives on the opportunities and hurdles from the points of view of the sponsor, the HTA and the licensing bodies and focused on specific building blocks needed to refine and implement these paradigms. The focus of this workshop was to:

- Consider whether new approaches to medicines availability are needed and how will they be valued by companies, patients, HTA and licensing agencies
- Identify the commonalities among the various medicines adaptive licensing pathways and related facilitated regulatory pathways and to explore common elements in detail
- Explore which new methodologies, including novel clinical designs, are being considered and what the opportunities and challenges are to different stakeholders

Workshop Objectives

- Discuss the new regulatory approaches to accelerating medicines availability and the role of HTA and coverage bodies in enabling access
- Recommend how to best ensure the success of new facilitated regulatory pathways and what will be the critical success factors to manage uncertainty, ensure proper use and to interpret continuity with evidence generated during early phases of study.
- Identify the possible pathways for an integrated approach that are acceptable to all stakeholders for adaptive routes and discuss the challenges and opportunities for the regulatory and HTA agencies and the sponsor.

Key points from presentations

SESSION: MEDICINES ADAPTIVE PATHWAYS: WHAT ARE THE CRITICAL ELEMENTS, CHALLENGES AND OPPORTUNITIES?

CIRS Executive Director, **Lawrence Liberti** set the stage for the Workshop by presenting the results of a survey of 78 members of pharmaceutical companies, regulatory and health technology assessment agencies, patient groups and other organisations to gain insights into personal opinions regarding facilitated regulatory pathways (FRPs) and adaptive licensing (AL). The survey helped to characterise the key elements of AL pathways, understand the barriers to their implementation and to provide guidance to those who are developing and seeking to implement these novel systems. Whilst 62% of survey participants indicated that US FDA FRPs are fit for purpose, EMA pathways and Japanese PMDA pathways were regarded as useful by only 11% and 7% of respondents respectively. Ultimately, only 22% of respondents felt that it is likely that an AL approach will be fully implemented within the next 5 years, with the principle barriers to implementation seen as a lack of definitions, alignment and international standards; evidentiary requirements and adaptive development; and problems with exit strategies and disinvestment. Possible solutions to these barriers offered by survey participants included convergence of legislative requirements, early involvement of all important stakeholders in designing the process, collaboration on policy and process and beginning with the end in mind, all of which provided a direction for the presentations and discussions that would take place during this meeting.

To address the trade-off between timely access and complete scientific evidence for benefits, risks and relative effectiveness and to provide an environment that supports innovation, the European Medicines Agency launched the Adaptive Licensing Project (ALP) in March 2014. The project, which involves sponsors, health technology assessment (HTA) organisations, patient representatives and healthcare professionals, seeks to provide early access for patients, starting from approval in a niche indication with a high unmet medical need. Once an initial, limited approval is granted, collection of efficacy and safety data will continue in the niche indication and be extended to broader patient groups. **Prof Tomas Salmonson**, *Chair, Committee for Medical Products for Human Use, European Medicines Agency* reported that seven applications for the project were selected from 28 industry submissions. The project includes an iterative development pathway with expansion of the target population and/or progressive reduction of uncertainty around the initial decision; the potential for real-world data collection and use; engagement of HTA organisations and other stakeholders; unmet medical need that potentiates more regulatory options and acceptance of uncertainties; the opportunity to influence clinical development and the choice of 'large' and 'small' indications.

Dr Amy G. Egan, *US Food and Drug Administration Liaison to the European Medicines Agency* detailed the provisions of the US Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA), which enhances the authority of the FDA to consider appropriate scientific data, methods and tools and to expedite development of and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions. FDASIA broadened the scope of accelerated approval and fast-track provisions, while maintaining safety and effectiveness standards. The act established a programme to encourage the development of surrogate and clinical endpoints, including biomarkers and other scientific methods and tools that can assist in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist. It additionally provided incentives for the development of antibacterial and antifungal drugs intended to treat serious and life-threatening infections.

Despite the advantages that may accrue from the use of adaptive licensing such as earlier access to promising therapies and the potential to maximise the positive impact of new drugs through more targeted prescriptions, payer concerns include its potential to increase the off-label use of drugs unless safeguards are put into place, ensuring the adequacy of systems for gathering and analysing real-world data, managing multiple agreements for risk sharing, access and coverage with the development of new evidence, developing methods for delisting medicines that do not perform as expected and the need for an adaptive pricing model. **Brian O'Rourke**, *President and CEO, Canadian Agency for Drugs and Technologies in Health* forecast that it is likely that AL will be well accepted by

clinicians and patients; however, while industry will need to understand AL advantages, payers are likely to remain sceptical and it is not certain that there will be international regulatory consensus on the concept. Given current developments, real-world evidence will become the norm in decision making about new drugs but appropriate contextualisation will be critical to effective decisions.

Dr Tony Hoos, *Core Member of NEWDIGS & President M4P Consulting, UK* reported on four years of work in adaptive licensing by the Massachusetts Institute of Technology New Drug Development Paradigms (NEWDIGS) team. Eichler and colleagues from NEWDIGS established a framework for a discussion of individual AL pilot studies in a 2012 publication. This work set out the multiple important differences between AL and traditional licensing paradigms but emphasised that AL is not another new regulatory or reimbursement pathway but rather a process to facilitate broader and more coordinated application of existing flexibilities. After Oye and associates established that AL could therefore be employed using existing legislation, the European Medicines Agency (EMA) initiated the pilot programme that was detailed by Prof Salmonson, inviting companies to submit development plans for new medicines for consideration for a prospective AL study. Generalised learning from NEWDIGS AL work to date include the fact that the success of adaptive proposals depends on an acceptable benefit-risk balance, which may be easier to achieve with products developed to fulfil a highly unmet medical need and the confidence of regulators and payers in post-authorisation control can be facilitated by identification of a well-defined patient population.

Donald A. Berry, *Professor, Department of Biostatistics, University of Texas Anderson Cancer Center, USA* pointed to the success of trials that employed longitudinal modelling such as the Critical Path Initiative phase 2/ 3 adaptive clinical trial in type 2 diabetes to demonstrate that surrogacy is not necessary to establish confidence in a predictive endpoint. Rather, modelling should be used during a trial to learn how well an endpoint predicts a desired outcome, with uncertainty incorporated into predictions through techniques such as the use of multiple imputations and model updates to reflect actual trial data. Additionally, through the use of multi-sponsor, multi-therapy platform trials such as ISPY-2, experimental drugs are matched with biomarker signatures and a common control is used, resulting in significant cost and time savings. The result is that better therapies are approved more quickly and successful drug-biomarker pairs graduate to small, focused, more successful phase 3 trials that are based on Bayesian predictive probabilities.

Cystic fibrosis is a complex disease caused by gene mutations that fall into five main classes. Orally bioavailable small-molecule CFTR modulators used alone or in combination for the treatment of CF have the potential to eventually allow treatment of up to 90% of patients with CF but experience indicates that a mutation-by-mutation research approach delays access to potentially beneficial therapy. The CFTR modulator Kalydeco (ivacaftor) was granted an EU orphan designation in 2008 for treatment of cystic fibrosis due to unmet medical need and its novel mechanism of action. The ivacaftor development programme illustrates the potential to gain approval for a very small population and subsequently expanding to progressively larger populations. **Mark Higgins**, *Senior Clinical Director, Cystic Fibrosis, Vertex Pharmaceuticals, UK* relayed important learnings acquired through the ivacaftor programme included the use of system flexibilities, such as an orphan designation to reduce fees, the protocol assistance process to gain access for advice and accelerated review to reduce review time.

Kelly Robinson, *Director, Bureau of Metabolism, Oncology and Reproductive Sciences, Health Canada* explained the management of uncertainty in Health Canada through use of the Notice of Compliance with Condition (NOCc). An NOCc is granted by Health Canada to facilitate earlier access by physicians and patients to a drug for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease or condition for which there is no alternative therapy available on the Canadian market or where the new product represents a significant improvement in the benefit-risk profile over existing products. In addition the drug must, be of high quality and demonstrate an acceptable benefit-risk profile and promising evidence of clinical effectiveness in clinical trials. Like a priority review, submissions granted advanced consideration for NOCc status are subject to a shortened review period of 200 days compared with 300 days for a normal review. A variety of conditions are associated with an NOCc. These include restrictions on advertising and labelling, an agreement to carry out additional clinical trials to verify the

clinical benefit of the drug and a requirement to undertake increased monitoring of the drug and reporting to Health Canada. Health Canada is experiencing significant increases in the use of the NOCc pathway, with corresponding increases in demands for time and resources but greater opportunities for dialogue among all stakeholders. How the agency responds to this will be affected by the changing regulatory landscape in Canada.

The management of uncertainty from an HTA perspective through the use of Medicines Adaptive Pathways to Patients (MAPPs) was discussed by Wim Goettsch, Advisor, National Health Care Institute, The Netherland, who said that health technology assessors may wish to use the term MAPPs rather than adaptive licensing (AL). The primary differences between these two terms may lie in the MAPPs focus on life cycle approach for new technologies and the essential collaboration between regulators and health technology assessors and payers. Some health technology agencies may be sceptical about the use of MAPPs to resolve uncertainties, however, because of the challenges that are involved in the continuing assessment of medicines. Comparative effectiveness research studies can create extra tasks for healthcare professionals, typically have small sample sizes and may lack consistency in data collection methods. In addition, there are differences in patient characteristics between treatment groups and quality of life is often measured for a given health state rather than for those different treatment groups. Finally, when new drugs are introduced to existing treatment paradigms over time, comparisons become more difficult. However, MAPPs may provide for stricter definition of the exact population that will be treated with a drug and thus may avoid "indication-creep.": MAPPs may also make it possible to better organise patient registries, with collaboration between regulators and HTA organisations, as well as between countries. In addition, MAPPs may provide more influence for HTA organisations in priority setting and selection of new pharmaceuticals.

SESSION: MEDICINES ADAPTIVE PATHWAYS: WHAT ARE THE MAIN BUILDING BLOCKS AND PRACTICAL HTA AND REGULATORY STRATEGIES FOR ADOPTION?

Elements of an adaptive pathway fit well into current regulatory approaches, which have undergone a significant evolution since the earlier time of binary decision making. This regulatory evolution has encompassed more proactive pharmacovigilance since the introduction of risk management plans, with strengthened methodologies for investigating drug safety and monitoring the benefit-risk balance in real-world populations. **Dr Almath Spooner**, *Pharmacovigilance and Risk Management Lead, Health Products Regulatory Agency, Ireland; Vice Chair European Medicines Agency Pharmacovigilance Risk Assessment Committee*, detailed the ways in which the regulatory toolbox has expanded and EU regulators are incorporating new methodologies, building on best practices and increasing the level of engagement with stakeholders. Risk management plans have become established as a mechanism for planning data collection to reduce uncertainties and manage post-marketing risk and with the use of tools such as post-authorisation efficacy studies have the potential to become benefit-risk management plans. The lifecycle approach is already in operation with the use of signal management and periodic benefit-risk reviews, leading to better product information. Finally, there is evidence of increasing regulatory and industry experience in responding to emerging information on safety and efficacy throughout the product lifecycle and in communicating updated recommendations promptly.

Andrew Mitchell, *Strategic Adviser, Evaluation, Department of Health and Ageing, Australia* provided the HTA perspective on required decisions when post-approval evidence does not support the initial potential of new medicines, stating that health technology assessment organisations recommend early access to innovative medicines approved through adaptive pathways when these products promise efficacy and safety. When post-authorisation evidence does not support the expected potential of a product, its use can be continued if the price is still justified as being acceptably cost effective but if the lower price is no longer justified, mitigation is needed. Mitigation can involve partial disinvestment, which may take the form of a decrease in price as occurred with cinacalcet, a treatment for secondary parahyperthyroidism that demonstrated effects against surrogate outcomes but did not provide clinical benefits. Mitigation can also involve a decrease in the eligible population by removing patients experiencing lesser benefit or increased harm, as occurred with anti-epidermal growth factor receptor (EGFR) antibody treatment for

colorectal tumours, which was not effective for patients with a KRAS mutation. Full disinvestment is a more drastic mitigation, in which the product is removed entirely from reimbursement. An understanding of the challenges of disinvestment should guide the development of adaptive pathways.

Dr Indranil Bagchi, *Vice President and Head, Payer Insights and Access, Global Health and Value, Pfizer Inc, USA* proposed an ideal scenario for the development of post-approval evidence in which reimbursement coverage would be provided at mutually agreed terms while additional evidence is generated over a mutually agreed timeline. In this scenario, coverage should be agreed at a price reflecting the value of innovation, as if the data had been available at the time of product approval and launch. At the end of the evidence generation period, reimbursement terms may be altered pending an analysis of the expected value at the time of agreement versus the determined value following the analysis of the additional clinical evidence. The schedule of such a review, the analyses to be conducted and the implications should be established a priori by agreement. If the evidence supports the expected value, there should be no price reduction or imposition of additional restrictions to reimbursement. If the target population was initially restricted by agreement for evidence development, reimbursement should be expanded to the full target population. If the evidence is negative, there may be conditions for re-examination or further development of evidence. If the extreme action of drug withdrawal is required, it may be implemented immediately or phased in over time. Less extreme measures would include increased restrictions on the reimbursed patient population, start-stop rules, dosage caps, pricing adjustments going forward and rebates on past sales.

A number of key challenges face expedited regulatory pathways. **Merete Schmiegelow**, *Senior Director, Regulatory Policies and Intelligence, Novo Nordisk, Denmark* discussed proposed adjustments to meet these challenges. Among these recommendations she said that unmet medical needs should be more precisely defined, taking patient perspectives into account; a new medical marketing authorisation application should be developed to include provisions for Type 2 variations and extensions of indications; the definition of a positive benefit-risk balance should be revised to accommodate both a reduction in risk aversion by regulators and health technology assessors and the incorporation of the patient perspective for medicines having a substantial advantages over current alternatives within unmet medical needs; more transparent criteria are needed both for justifying accelerated assessment and for decisions by the Committee for Medicinal products for Human Use (CHMP) to withdraw approval for acceleration. Other recommendations included a resetting of the clock for patent expiration once a full data package for a product is approved to accommodate industry concerns about intellectual property rights and patent expiration when an adaptive pathway is used and consideration by HTA agencies and payers for increases in prices and reimbursement as more data for conditionally approved medicines accumulate.

Dr Sarah Garner, *Associate Director, R&D, National Institute for Health and Care Excellence, UK* detailed NICE experience with non-RCT evidence including its use for the appraisal of retigabine for adjunctive treatment of partial onset seizures in epilepsy, because clinical trials mandated forced titration, rather than titration tailored to the individual patient as is seen in practice. Non-RCT data were also used for estimating clinical efficacy through modelling such as occurred in the appraisal of insulin pumps for diabetes in which an estimate of clinical efficacy was derived from the Insulin Pumps Clinical database, which was much larger, of longer duration and more representative of people likely to be considered for therapy in routine clinical practice than the populations in the RCTs available. Appraisals have also been conducted through the use of non-RCT data for long-term use as was done for alitretinoin for eczema and observational data as was done for omalizumab for severe persistent allergic asthma, when these data were used for extrapolation of treatment effect and for health-related quality of life in children.

Providing a patient viewpoint on adaptive licensing and early access schemes, **Alastair Kent**, *Chair of Rare Disease UK and Director of Genetic Alliance UK* said that an adaptive licensing approach has a number of strengths including the fact that it allows people with unmet health needs and life-limiting conditions to participate in the development of medicines at an earlier stage, permitting a focus on what matters to patients. Furthermore, AL allows for the development of unexpected insights, both good and bad and creates an opportunity for a genuine partnership across healthcare

stakeholders. Potential deal-breakers for these pathways, however, include a lack of willingness on the part of regulators to participate in the system, industry to expose assets and clinicians to accept the additional burden of new trials. Early Access Schemes (EAS) also have strengths including possible health gains, the potential for industry to rescue assets, the capacity to produce breakthroughs in intractable conditions and the enhancement of patient participation in decision making. Potential deal-breakers with an EAS include the questions of who pays for a drug and how to monitor and evaluate it, the later channelling of EAS-approved medicines into the standard regulatory system and the continuity of these medicines in a clinical development context. In addition the use of EAS may be complicated by the vulnerability of desperate patients and the damage to proper clinical development, particularly in small populations with rare diseases.

SESSION: CRITICAL SUCCESS FACTORS FOR ADAPTIVE PATHWAYS AND HOW CAN THIS PRINCIPLE BE USED TO FACILITATE MEDICINES AVAILABILITY?

Modelling suggests adaptive licensing can improve expected net product value for industry and increase the overall numbers of patients treated compared with traditional licensing and it may also have the opposite effect. Industry is interested in the use of adaptive pathways but is concerned about the lack of HTA and payer buy in, recognising that a coordinated European Medicines Agency- and health technology assessment-invested approach is needed. **Professor Adrian Towse**, *Director, Office of Health Economics, UK* reported the results of research performed by the Office of Health Economics and the Centre for Medical Technology Policy in which the future scenario most conducive to determining relative effectiveness in the EU involves both pre- and post-launch coordination between HTA and EMA, collaborations across large registries, with full use of electronic health records, good progress in methods and a major role for public-private partnerships. The key drivers for these events are HTA coordination, regulatory innovation, regulatory/HTA interaction, data availability and the evolution of methods. In the US, the scenario most conducive to comparative effectiveness research will require changing the locus of decision making, providing opportunities for new partnerships and increased willingness to invest in electronic health records and a desire to reduce systems costs. The two critical points that affect the situation are that there is currently no regulatory reform and no interaction between the FDA and payers.

Dr Jens Grueger, *Vice President, Head of Global Pricing & Market Access, F. Hoffmann-La Roche, Switzerland* discussed the potential for a viable commercial strategy for adaptive licensing, including early dialogue with regulators and health technology assessment agencies and payers. Points of discussion must include the acceptability of study endpoints and the patient population, a lifecycle perspective on evidence and value and mechanisms to adjust price on the basis of value. An efficient infrastructure to collect utilisation and outcomes data after launch is also required and treatment registries like those of the Agenzia Italiana del Farmaco (AIFA) in Italy and the Systemic Anti-Cancer Therapy database in the UK, can fulfil this function with their potential to add disease- and treatment-specific endpoints with a focus on early response, progression and toxicity. Treatment registries can also be used to manage the entry of medicines but disinvestment procedures also have to be established to manage a drug's exit, if needed. In the collection of real-world data, it will not be possible to monitor off-label use in every jurisdiction in which a drug is licensed and agreement is needed on reference countries to be used for evidence generation. In addition, there must be accord on the appropriate identification of evidence needs, with care taken to distinguish parameter uncertainty from decision uncertainty.

Dr David Jefferys, *Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK* outlined the UK Early Access to Medicines Scheme (EAMS). The goal of the EAMS is to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Candidate drugs must have a positive benefit-risk profile and must represent a significant advance in treatment. The MHRA is responsible for the scientific aspects of this adaptive licensing programme and the scientific opinion is provided after a two-step evaluation process, bringing the decision point for these medicines to the end of phase 3 or, in very exceptional cases, to the end of phase 2B, making potentially life-saving treatments available one year earlier than is possible with traditional review. Amidst rising demands for patient inclusion in the development and decision-making processes for

new medicines, implementation of EAMS may help to overcome the public perception that regulatory agencies and systems are risk averse

In the first of four of presentations on the factors and methods necessary for healthcare stakeholders to develop an adaptive "mindset' for pharmaceutical development, regulation and reimbursement, **Prof Sarah Garner**, *R&D Associate Director, National Institute for Health and Care Excellence* provided the health technology assessment perspective, explaining that for new, extremely expensive medicines to be of optimal value for public funds, a new social contract and shift in perceptions are required. However, the willingness of stakeholders to advocate for change depends on their perspectives and whether they feel change is needed. It is true that public awareness needs to be raised regarding the fact that regulatory approval does not mean that drugs are completely safe and the users of medicines need to be especially and explicitly aware of the additional uncertainty surrounding medicines that receive early approval. These are joint challenges to implementing adaptive pathways that require joint solutions and opportunities and enablers abound if all stakeholders make the best use of prospects for group discussion and pathway design.

In a regulatory perspective of this topic, **Prof Alasdair Breckenridge**, *Former Chairman, MHRA*, proposed the consideration of two ideas to move healthcare stakeholders into an adaptive mindset. It may be appropriate to consider adaptive pathways as potential "disruptive regulatory pathways" for the regulation of new medicines for which a regulatory paradigm has not yet been developed and for which novel facilitating processes may be required such as custom-made RNA antisense oligonucleotides for specific patients, new cancer drugs based on novel gene sequences or non-biological complex drugs such as amino acid sequences used to treat multiple sclerosis. In addition, because social media have emerged as an important data collection resource whose full utility remains to be determined, Professor Breckenridge recommended further research into the most effective use of these media to acquire post-authorisation data.

From an industry regulatory point of view, **Sharon Olmstead**, *Global Head, Development and Regulatory Policy, Novartis Pharmaceuticals, USA* said that changing mindsets would require the establishment of methodologies for real-world evidence development, including the use and linkage of databases and the creation of database infrastructure, the engagement of internal stakeholders such as research, clinical, technical and market access teams, the consideration of the labelling implications of adaptive licensing, the shifting of development costs, the convergence of adaptive and traditional pathways for global development programmes and deliberation regarding the potentially competing interests of public health benefit versus pricing models. Ultimately, however, new regulatory pathways provide all stakeholders the opportunity to develop a better understanding of national and local priorities and to rethink approaches for delivering new therapies to patients.

Maximising the positive impact of new medicines through timely access to patients is the central rationale behind adaptive licensing. It remains to be determined, however, if all stakeholders are ready for the changes necessitated by the adoption of the adaptive licensing model. In his presentation of the industry HTA outlook on changing mindsets, **Dr Eric Giesen**, *Director, Market Access Policy, Bayer Pharma AG, Germany* detailed the specific steps that companies can take to fully engage in an adaptive licensing model such as taking a proactive rather than reactive position in moving toward continuous evidence generation and using new study designs. Company knowledge and capabilities should be enhanced through an education programme for adaptive approaches and new trial designs and company teams must be aligned around these approaches. Capabilities in post-licensing study design and implementation need to be strengthened and action scenarios built around different potential outcomes. Finally, a business model should be adopted that accepts certain levels of uncertainty and alignment with external stakeholders must occur.

Recommendations from across the Syndicates

1. **It is critical that the EMA openly shares learnings from its adaptive licensing pilot.**
2. **A forum for HTA discussion should be developed in which common approaches for evaluating necessary evidence at appropriate time points and life-cycle management are discussed.**
3. **CIRS should follow up their Adaptive Licensing Survey with a series of structured interviews to capture the perspectives of respondents to the first survey with dissenting views.**
4. **CIRS should conduct an adaptive licensing discussion meeting specifically with stakeholders who are not typically represented.**
5. **Develop retrospective and prospective case study pilots of adaptive licensing for new compounds**
6. **Assess ways to educate all stakeholders on the pros and cons of adaptive licensing approaches and execute these programmes as appropriate.**
7. **CIRS should complete an assessment of current facilitated regulatory pathways to assess effectiveness in terms of resources and development and review time.**
8. **CIRS should build on its recently completed perception survey and conduct an expanded survey of global payer perspectives regarding adaptive pathways.**
9. **CIRS should assess current monitoring systems and methods for the acquisition of patient input for outcomes assessment to create data sets to support new study methodologies.**
10. **Assess methods that are in place to monitor current drug utilisation as a way to ensure that appropriate patient populations are being targeted.**
11. **CIRS should create a roadmap of adaptive pathways and payer data requirements to enhance the ability of stakeholder to move towards harmonisation.**

Workshop Programme

Day One: Wednesday, 1 October 2014	
SESSION: MEDICINES ADAPTIVE PATHWAYS: WHAT ARE THE CRITICAL ELEMENTS, CHALLENGES AND OPPORTUNITIES?	
Chairman's welcome and introduction	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
Are new facilitated approaches to medicines availability needed and what are the major challenges? Perspectives from key stakeholders (patients, companies, HTA and licensing agencies)	**Larry Liberti**, *Executive Director, CIRS*
What approaches or initiatives are used or being considered by regulatory and HTA agencies to provide flexible and/or adaptive pathways to gain regulatory approval and reimbursement?	
EMA Framework development and pilot study for adaptive licensing: What are the key considerations and aspirations?	**Prof Tomas Salmonson**, *Chair, CHMP, European Medicines Agency*
Building flexibility for regulatory approval in the US. What is being used or considered and what are the perceived advantages and barriers?	**Dr Amy Egan**, *Deputy Director, Office of New Drug Evaluation III and Acting FDA Liaison to European Medicines Agency*
What are the possible pathways to adapt coverage decisions as new evidence comes in: What can be practically considered and what are the main hurdles and possible solutions?	**Dr Brian O'Rourke**, *President and CEO, Canadian Agency for Drugs and Technologies in Health*
Adaptive licensing: Lessons learned from four years of evaluation by MIT NEWDIGS	**Dr Tony Hoos**, *Core Member of NEWDIGS & President M4P Consulting, UK*
What would practical study designs look like in generating the evidence for the initial approval and how should these be linked to post-approval evidence generation - How do we know when we can be confident of a "predictive endpoint"?	**Dr Donald Berry**, *Professor, Department of Biostatistics, University of Texas Anderson Cancer Center, USA*
Case study: Adaptive trial designs, or other "seamless" ways of ensuring continuing generation of evidence	**Dr Mark Higgins**, *Senior Clinical Director, CF, Vertex Pharmaceuticals UK*
How can uncertainty be managed in practice to meet the needs of different stakeholders?	
Agency perspective	**Kelly Robinson**, *Director, Bureau of Metabolism, Oncology and Reproductive Sciences, Health Canada*
HTA perspective	**Dr Wim Goettsch**, *Advisor, National Health Care Institute, The Netherlands*
SESSION: MEDICINES ADAPTIVE PATHWAYS: WHAT ARE THE MAIN BUILDING BLOCKS AND PRACTICAL HTA AND REGULATORY STRATEGIES FOR ADOPTION?	
What sort of decision (withdrawal and exit strategies, adaptive disengagement and orchestrated safeguards) is required when the post-approval evidence does not support the initial potential?	

Agency perspective	**Dr Almath Spooner**, *Pharmacovigilance and Risk Management Lead, Health Products Regulatory Agency, Ireland*
HTA perspective	**Dr Andrew Mitchell**, *Strategic Adviser, Evaluation, Department of Health and Ageing, Australia*
Company perspective	**Dr Indranil Bagchi**, *Vice President and Head, Payer Insights and Access, Global Health and Value, Pfizer Inc, USA*
Case studies	
How should a company address opportunities to use facilitated regulatory approaches?	**Merete Schmiegelow**, *Senior Director, Regulatory Advocacy, Novo Nordisk, Denmark*
How do HTA use models and simulation to extrapolate efficacy data and how these could be used effectively in a facilitated or adaptive pathway?	**Prof Sarah Garner**, *R&D Associate Director, National Institute for Health and Care Excellence*
How do patients perceive early access schemes and adaptive licensing approaches – with hope or concern?	**Alastair Kent**, *Chair of Rare Disease UK and Director of Genetic Alliance UK*

Syndicate sessions

Syndicate 1: Managing uncertainty and ensuring appropriate utilisation post-initial approval - Are the systems in place?

Chairperson: Prof Angela Timoney, *Director of Pharmacy, NHS Lothian*

Rapporteur: Jesús Muñiz, *Senior Director, Regulatory Policy and Intelligence, Shire, USA*

Syndicate 2: What type of management plans need to be developed for implementation at the front end to manage questions that arise post-initial approval?

Chairperson: Dr Andrew Mitchell, *Strategic Adviser, Evaluation, Department of Health and Ageing, Australia*

Rapporteur: Dr Michiel Hemels, *Director, EMA HEMAR, Janssen, Denmark*

Syndicate 3: Incentives for using an facilitated approach: What are they and how can this best be achieved? – Company, HTA, Regulatory perspective

Chairperson: Barbara Sabourin, *Director General, Therapeutic Products Directorate, Health Canada*

Rapporteur: Andrew Storey, *Vice President, Regulatory Affairs, US/Canada, AbbVie, USA*

DAY 2: Thursday, 2 October 2014	
SESSION: CRITICAL SUCCESS FACTORS FOR ADAPTIVE PATHWAYS AND HOW CAN THIS PRINCIPLE BE USED TO FACILITATE MEDICINES AVAILABILITY?	
Chairman's introduction	**Prof Richard Barker**, *Director, CASMI*
Feedback of Syndicate discussion	
Is there a viable commercial strategy for the use of adaptive approaches, now and in the future?	
Academic perspective	**Prof Adrian Towse**, *Director Office of Health Economics, UK*
Company perspective	**Dr Jens Grueger**, *Vice President, Global Pricing and Market Access, F. Hoffmann-La Roche, Switzerland*
UK early access scheme: What is it and how will it work?	**Dr David Jefferys**, *Senior Vice President, Eisai, UK*
How to move from current mindset to an "adaptive mindset": What do companies, regulatory agencies, HTA and payers need to adopt?	
HTA perspective	**Prof Sarah Garner**, *R&D Associate Director, National Institute for Health and Care Excellence*
Regulatory perspective	**Prof Alasdair Breckenridge**, *Former Chairman, MHRA*
Company regulatory perspective	**Sharon Olmstead**, *Global Head, Development and Regulatory Policy, Novartis Pharmaceuticals, USA*
Company HTA perspective	**Dr Eric Giesen**, *Director, Market Access Policy, Bayer Pharma AG, Germany*

Section 2: Syndicate Discussions

Syndicate Discussions

The three Syndicates that met during this Workshop were all asked to discuss different aspects of medicines adaptive pathways. For the purposes of these discussions, all groups were asked to use the following definition of adaptive licensing (AL):

Adaptive licensing is a novel pathway that transforms the medicines development process and that has the following elements:

- An early and controlled initial release following a short testing period in a limited number of patients;
- A period of intensive real-world monitoring with progressive data collection to more completely define the medicine's profile and manage the uncertainty about the product's benefits and risks;
- A follow-on full approval, an approval restricting use in a selected population or a withdrawal. Active involvement of regulators, prescribers, patients and health technology assessment (HTA) agencies/payers is a hallmark of AL pathways.

Syndicate Discussion A

Managing uncertainty and ensuring appropriate utilisation post-initial approval – Are the systems in place?	
Chair	**Prof Angela Timoney**, *Director of Pharmacy, NHS Lothian*
Rapporteur	**Jesús Muñiz**, *Senior Director, Regulatory Policy and Intelligence, Shire, USA*

Background

Different approaches to fulfil unmet medical needs and make new medicines more rapidly available to patients have been adopted by regulatory agencies worldwide. However, there are two key aspects of an AL licensing approach that trouble both licensing and HTA evaluators: the methodologies employed by companies and healthcare systems to ensure appropriate utilisation of the new medicine after approval and to manage the uncertainties surrounding effectiveness and safety.

In principle, any adaptive approach should provide the ability to manage a product in the post-approval period, including the reduction of the product's availability if its benefits and harms are not as expected. It is therefore important that these models dynamically assess those parameters during this time. In addition, for new regulatory pathways to successfully deliver safe and effective new medicines to patients more quickly it is also necessary for the HTA or reimbursement bodies to be an integral part in their development and acceptance.

Many jurisdictions already have some method for licensing a medicine based on a conditional approval or reimbursement decision. It must be determined if these methods can be used effectively within the AL scenario, if they need to be adapted or if entirely new systems are required. If new or adapted systems are needed, it should further be determined what requirements must be implemented to provide confidence to all stakeholders that patient safety is not being compromised and that HTA and licensing agencies will be able to obtain necessary information in an efficient and effective way.

This Syndicate was asked to discuss and make recommendations regarding the approaches that can be undertaken in an AL scenario to provide confidence to patients and HTA and regulatory agencies that any uncertainties can be managed and that the medicine will be used appropriately after the initial approval.

Objectives

The objectives of this Syndicate group were to:

- Determine if the current methodologies and post-approval toolbox available to HTA and regulatory agencies are robust enough to

provide the agencies the necessary systems and processes to manage the initial post-approval period following the grant of an adaptive license

- Discuss the key challenges and potential opportunities for current methodologies to be simplified, evolved or utilised in a wider way without losing regulatory strength, which can enable HTA and regulatory agencies to manage potential known and unknown risks and provide the evidence of safety and effectiveness as required
- Recommend how current methodologies can be utilised or identify new methodologies that can be developed to provide the information as to what needs to be considered and by whom

Questions for consideration

1. How do HTA and regulatory agencies reduce the risk of an AL approach and ensure that they have the ability to develop a rigorous evidence base after the initial approval?
2. Are the methods for managing uncertainty and utilisation of medicines currently in place in the post-approval period?
3. Are the methodologies sufficiently robust for regulatory and HTA agencies and companies to agree that they are fit for purpose to measure both effectiveness and safety?
4. Do new methodologies need to be developed in order for jurisdictions to be confident in managing both uncertainty and utilisation post-approval? If so:
   - Will it be possible to produce methodologies to adequately provide the answers that HTA and regulators will be seeking, post-initial launch and if so what will these entail?
   - Will these be within current laws and regulation?

RESULTS

Critical issues

Currently, there are multiple challenges for various stakeholders in the use of adaptive licensing and the resolution of uncertainties surrounding medicines. Medicines are typically evaluated against outcomes that are more important to physicians than patients. There are different criteria among HTA bodies regarding the evaluation of evidence and different ways of generating evidence throughout the life of the drug. Moreover, an acceptance of alternative evidence at regulatory review level is still needed and payers will require an incentive to accept any harmonised plans for adaptive licensing.

This Syndicate agreed that there is a global need for proactive, prospective planning for the life-cycle of medicines. This must be a collective plan that includes an overall communication strategy and that has been prospectively planned and developed by all healthcare stakeholders, including payers. Additionally, it must be determined which of the stakeholder groups has committed to the success of adaptive licensing and which group is leading the overall plan.

It is critical that the benefits of medicines as well as their surrounding uncertainties are clearly articulated to all these participants, including patients and payers. However, these activities must be operationalised and the forum for this communication does not currently exist. Such a forum could be a platform to agree on an integrated plan for adaptive licensing for health technology and regulatory agencies, industry and patients. The EMA pilots for adaptive licensing and patient input and the US FDA Patient-Focused Drug Development Programme may serve as models for this forum.

Recommendations

1. It is critical that the EMA openly shares learnings from its adaptive licensing pilot.
2. A forum for HTA discussion should be developed in which common approaches for evaluating necessary evidence at appropriate time points and life-cycle management are discussed.
3. CIRS should follow up their Adaptive Licensing Survey with a series of structured interviews to capture the perspectives of respondents to the first survey with dissenting views.
4. CIRS should conduct an adaptive licensing discussion meeting specifically with stakeholders who are not typically represented.

Syndicate Discussion B

What type of management plans need to be developed for implementation at the front end to manage questions that arise after initial approval?	
Chair	**Dr Andrew Mitchell**, *Strategic Adviser, Evaluation, Department of Health and Ageing, Australia*
Rapporteur	**Dr Michiel Hemels**, *Director, EMA HEMAR, Janssen, Denmark*

Background

Consideration of the adoption of an AL pathway raises concerns for health technology assessors, regulators, payers, healthcare providers and patients regarding the adequacy of the dataset on which the early approval would be based. However, these concerns could be overcome by an advance agreement among the stakeholders on an AL approach to ensure the continuing generation of appropriate evidence from the time of clinical development through real-world use.

Despite the uncertainties of early clinical development, stakeholders must ensure that evidence standards are not lowered for medicines using AL pathways and that there is reasonable confidence in the predictive value of the development endpoints. Pre-defined criteria should be agreed early in development so that there is clarity regarding how a product becomes eligible for an adaptive pathway, what must be undertaken pre- and post-approval, what must be confirmed and what the expectation is when the later evidence does not support the initial potential.

This Syndicate was asked to discuss and make recommendations on what types of agreements must be in place before a product can take an AL pathway and how the different stakeholders ensure that they are part of the discussion and outcome.

Objectives

The objectives of this Syndicate group were to:

- Discuss what issues companies and HTA and regulatory agencies need to consider prior to products being chosen for an AL pathway
- Identify the key challenges for companies and agencies in agreeing to upfront management plans to ensure confidence in the development of medicines after initial approval
- Recommend which areas companies and HTA and regulatory agencies will need to agree upon before the adoption of an AL pathway in order to provide confidence in the management of a new medicine after initial approval

Questions for consideration

- What type of management plans should be developed upfront to ensure they address patients', HTA assessors' and regulators' expectations?
- What are the questions that need to be considered from each of the stakeholder's perspectives?
- How should upfront management plans be designed to help ensure no lowering of current evidence requirements or of the quality of decision making?
- Who should be part of the discussion around the post-initial approval management plan, when should these discussions be held and how binding should they be required to be for all stakeholders?
- Do agencies need to be confident of a "predictive endpoint" or do they just require the ability to take action if the potential of the predictive endpoint is not reached?
- What sort of disinvestment decision is required if a medicine does not meet its predictive endpoint?
- Do agreements need to be in place if a product exceeds the agencies' expectation?

RESULTS

Critical issues

Healthcare stakeholders, who have the common interest of expediting patient access to medicines, need to identify common incentives to use adaptive licensing to meet that goal. For industry, incentives include the management of risk for return on investment; that is, clear price agreements require demonstrated value for sustainable business. Regulators, meanwhile,

need to oversee the safe use of medicines while providing incentives for development of medicines that might fulfil unmet medical needs. For their part, health technology assessors must evaluate the appropriateness of data for an assessment of value and to prioritise workloads.

It is important to select a compound for adaptive licensing with the highest chance for success, balancing technical requirements such as endpoints, population of interest and scientific rationale versus unmet medical need. In fact, adaptive licensing may be considered as an incentive for product development for rare disorders and perhaps be considered to reduce the risk of medicines being tested for second indications.

Issues that remain to be decided include how to judge the intermediate value of a medicine, the value of surrogate versus hard outcomes, the willingness to pay for those outcomes and the implication of small patient numbers for benefit-risk assessment. It also remains to be determined if adaptive licensing will provide information more efficiently for decision making and how new competitive entrants not using adaptive licensing will be handled. Finally, stakeholders need to understand if necessary systems are in place to employ adaptive licensing and if the resource burden for their use will outweigh the benefits.

Challenges

Adaptive licensing can present a challenge to existing management plans and requires agreement across and within stakeholders, whose response to new ways of thinking about approval and reimbursement may be unpredictable.

Change management will be necessary to deal with the implications of potential disruptive events such as the entry of new products and the evidence for those products, which are not being approved under adaptive licensing agreements. These implications include changes in benchmarking pricing.

Infrastructure must be developed to agree on the necessary evidence generation to quantify and measure future outcomes as well as reaching clear agreement on appropriate assessment methods. These methods extend beyond the apparent divide that already exists between randomised trials and real-world evidence. Surrogates will need to be validated for the size of the effects expected in future outcomes. Stakeholders must acknowledge the consequences of possible disinvestment in some medicines and the implications for international reference pricing and the realities and consequences of different prioritisation, economics and patient management.

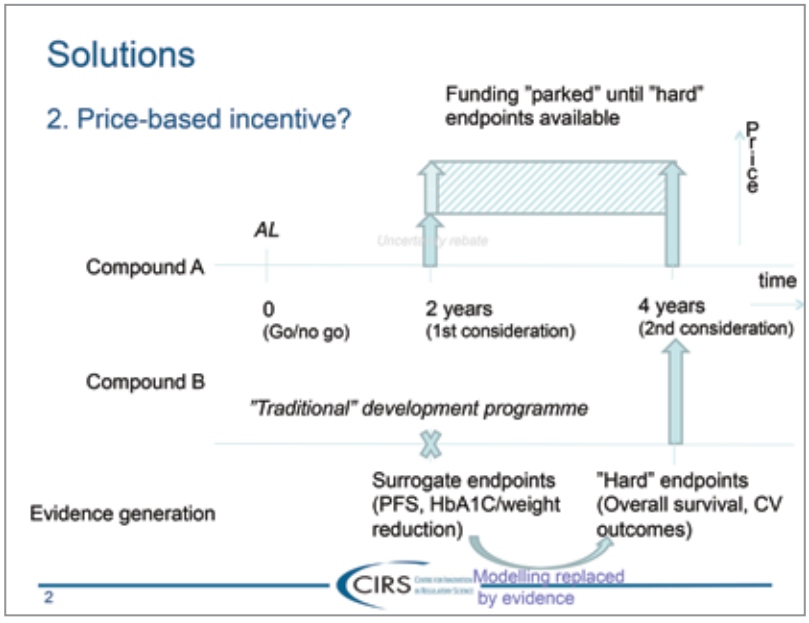
Strategies

There are two options to provide incentives to bring stakeholders together. In the first volume-based option, indications for a new medicine would move from narrow to broad, for example, a product would be granted licensing for use in severe schizophrenia, with a development plan to extend later to moderate schizophrenia; or a product would receive approval for weight reduction among those with a body mass index (BMI) greater than 40, with a development plan to extend later to those with a BMI greater than 28.These licenses would be granted under conditions of adequate reinforcement of limited access to initial, restricted populations.

In the second option, funding for new medicines is deferred until modelling is replaced with hard evidence (Figure 1).

Pilots of early involvement and collaboration among appropriate stakeholders can provide insight into potential solutions for the challenges surrounding adaptive licensing (Figure 2). These pilots would be distinct from the existing EMA pilot, with self-selected participants and address unanswered questions and serve to engage other stakeholders. A pilot study of adaptive licensing could demonstrate its feasibility with respect to timeliness, its ability to address the

Figure 1. Deferring funding of new medicines would provide a price-based incentive for adaptive licensing.



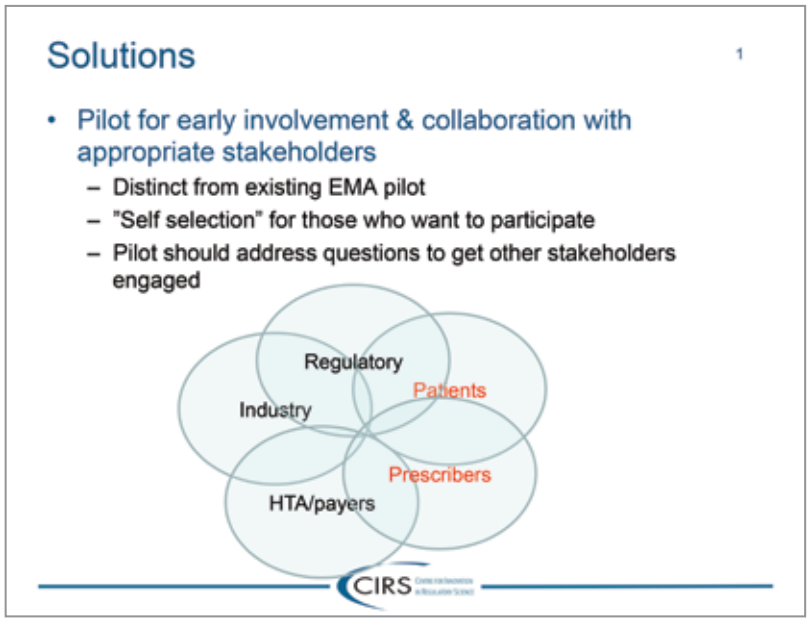


Figure 2. Pilots of early involvement and collaboration can provide insight into potential solutions for the challenges surrounding adaptive licensing.

needs of patients, its acceptability, practicality and appeal to all stakeholders, the validity of its endpoint assessments, acceptability of associated price setting and return on investment, the manageability of resource use and the feasibility of building on the treatment of small populations with unmet medical need toward use in a larger population.

Recommendation

- Develop retrospective and prospective case study pilots of adaptive licensing for new compounds

Syndicate Discussion C

What are the incentives for using a facilitated approach and how can this best be achieved? – Company, HTA and regulatory perspectives	
Chair	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
Rapporteur	**Andrew Storey**, *Vice President, Regulatory Affairs, US/Canada, AbbVie, USA*

Background

Although there is a clear understanding by companies, regulatory and HTA agencies and patients that flexible pathways can expedite the access of valuable medicines to patients and fulfil unmet medical need, discussion of the adaptive licensing model raises issues regarding the necessary incentives for the different stakeholders to become involved and support use of these pathways.

Companies are concerned regarding intellectual property issues, the "patent clock", liabilities, the mechanisms for reimbursement after initial approval and shared risk among different stakeholders. HTA agencies are concerned that they will be paying for too much uncertainty and regulatory agencies worry about potential safety issues and the inability to control the medicine in the marketplace. These concerns raise the question for each of the stakeholders in terms of incentives. Companies especially must consider if there is a viable commercial strategy for the use of adaptive approaches and if so, what the right incentive signals are for them to engage in this type of pathway.

This Syndicate was asked to discuss and make recommendations regarding the incentives for the different stakeholders to engage in an adaptive licensing approach.

Objectives

The objectives of this Syndicate group were to:

- Discuss the key challenges and potential opportunities for the different stakeholders involved in an adaptive licensing approach
- Identify current or future incentives for engagement in the use of adaptive licensing
- Recommend appropriate incentives and how they could be best integrated into the development of medicines

Questions for consideration

The Syndicate was asked to consider these different perspectives

Stakeholders	Potential incentives for adopting AL	Disincentives to adopting AL	Ways to overcome the disincentive
Patients			
Companies			
Regulatory Agencies			
HTA agencies			
Payers			
Healthcare providers			
Others – Please specify			

What are the main advantages or potential incentives to each stakeholder (patient, healthcare provider, company, regulator, HTA assessor and payer) to engage in the AL approach and the main disincentives?

1. What are the types of positive incentives such as timely access to medicines, scientific advice, study and trial designs to meet real-world needs and stakeholder buy- in that should be considered?
2. What kind of tradeoffs will be needed to get past the disincentives such as intellectual property issues, patent clock initiation, reduced initial patient coverage, commercial issues and liability and how can these be best addressed?
3. Will the incentives be dependent on the type and cost of the medicine? Is the approach to price/cost the main incentive for companies or are there other incentives for taking an adaptive licensing approach?
4. Can there be true risk sharing in adaptive licensing and how can alignment to occur across jurisdictions?
5. What type of approaches could be put in place and what are the issues with the different incentive approaches?
   - Lower price after initial approval, because of reduced confidence and certainty and an increase in price later when new supportive evidence is generated
   - Premium price after initial approval with adaptive coverage for price and covered population as new evidence is generated
6. Are there societal incentives/tradeoffs for the adoption of AL as one of the flexible pathways open to jurisdictions?

Critical issues

Incentives

Incentives to the use of adaptive pathways include faster access to new drugs on a global basis, the potential for reduced cost of development, the reduced methodological risk presented by the failure of large trials, mechanisms to control the proper clinical use to reduce "unknown unknowns" or the so-called Rumsfeld effect. There would be earlier discussions and alignment of stakeholders with the greater efficiencies yielded by integrated processes and because of this alignment, products will be developed that will be appropriately reimbursed. Innovative studies with smaller cohorts will be conducted, more molecules can be tested and use among limited populations can be controlled.

"There are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns - the ones we don't know we don't know."

Donald Rumsfeld 2002

Disincentives

Industry may see pricing inflexibility, increased long-term costs of development weighted by post-authorisation requirements and endangerment of intellectual property rights as detriments for adaptive licensing while regulators may regard it as merely a faster approval route that presents an increased safety risk and may also be apprehensive regarding the potential for off-label use accompanied by a lack of confidence in the effectiveness of education regarding that use. Both groups may be concerned about the subjectivity and variability of benefit-risk assessments, the costs and required infrastructure for monitoring real-world data, which may present an insurmountable burden to the healthcare system and the issues that would surround the potential withdrawal of products.

This Syndicate prepared a table reflecting the incentives and disincentives for the use of adaptive licensing for each stakeholder group as well the potential solutions to those disincentives (Figure 3).

Multiple challenges to the use of adaptive licensing still exist, including concerns regarding pricing, ethics, consents and medical liability and the interface with the developing field of personalised medicine. Additionally, it must be determined which unmet medical needs can be appropriately addressed by adaptive licensing and the need for revisions to regulatory processes and additional skill development by all stakeholders to handle new methodologies should be considered. Diagnostic tools will need to be developed and a differentiation between current facilitated pathways versus those that may be developed in the future should be assessed. Finally, engagement and preparedness by health technology assessment agencies will be required.

Critical issues

Incentive	Disincentive	Solution
Patients		
Faster access	Potential perceived uncertainty about BR	Ensure risks are communicated
Reduced cost	Off label use – inadequate information	Maximize transparency and communication of available data
More involved	Additional data collection	Balance between burden and benefit of research
Treaters		
Faster access	Increased Safety Risk	Ensure additional risks are minimised and communicated
Earlier engagement	Burden of monitoring	Assess burden and minimise through design
	HR Burdens	Focus on efficiency
Payers		
Adaptive Pricing	Adaptive pricing Products listed sooner Increasing drug bill	Develop standardised principles
Paying for products developed	Off label use	Controlled utilisation
Reduced prices	HR burdens	
Regulators		
Integrated process Innovation	HR burdens	
Reduced Rumsfeld	Off label use	Controlled utilisation
Patient access Address unmet needs	Increased smaller Rumsfelds	
Earlier engagement		
Industry		
Adaptive Pricing	Adaptive Pricing	Develop standardised principles
Get paid for products developed	Challenge with PM studies	Do studies in near label indication and extrapolate
Integrated process	Uncertain costs of development	
Innovative studies	IP issues	Renew IP upon completion of confirmatory studies Advocate for IP changes data and patent
Reduced Rumsfeld (Gated risk)	HR burdens	

Figure 3. Incentives, disincentives and solutions for medicines stakeholders.

Recommendations

1. Assess ways to educate all stakeholders on the pros and cons of adaptive licensing approaches and execute these programmes as appropriate.
2. CIRS should complete an assessment of current facilitated regulatory pathways to assess effectiveness in terms of resources and development and review time.
3. CIRS should build on its recently completed perception survey and conduct an expanded survey of global payer perspectives regarding adaptive pathways.
4. CIRS should assess current monitoring systems and methods for the acquisition of patient input for outcomes assessment to create data sets to support new study methodologies.
5. Assess methods that are in place to monitor current drug utilisation as a way to ensure that appropriate patient populations are being targeted.
6. CIRS should create a roadmap of adaptive pathways and payer data requirements to enhance the ability of stakeholders to move towards harmonisation.

Section 3: Presentations

Adaptive licensing and facilitated regulatory pathways: A stakeholder perception survey

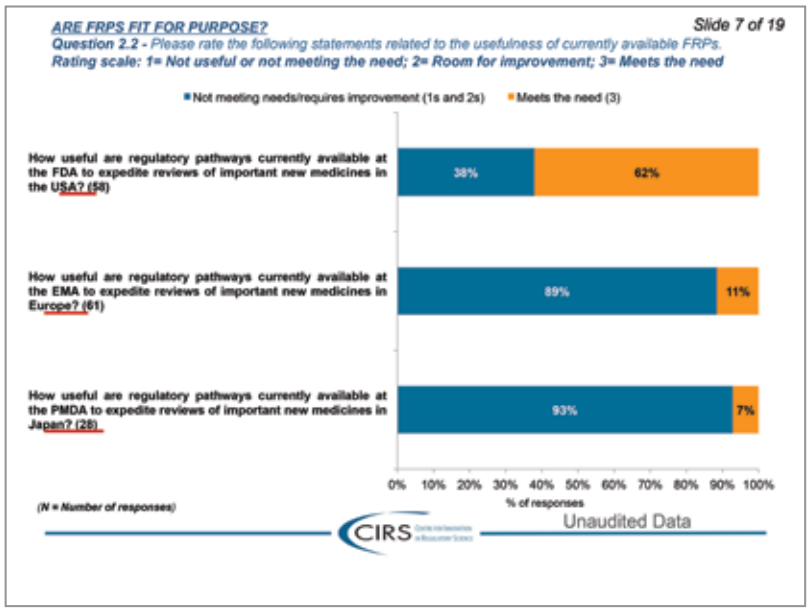
Lawrence Liberti

Executive Director, Centre for Innovation in Regulatory Science

CIRS conducted a stakeholder survey prior to this Workshop to gain insights into personal opinions regarding facilitated regulatory pathways (FRPs) and adaptive licensing (AL). This survey was also designed to characterise the key elements of AL pathways, understand the barriers to their implementation and to provide guidance about stakeholder interest, acceptance and concerns to those who are developing and seeking to implement these novel systems.

CIRS invited 252 individuals to participate in the survey and received 78 responses (31%), including 24 of 25 CIRS member companies. The greatest number of responses, 34, came from individuals in regulatory departments of pharmaceutical companies and the other two top categories of respondents were from pharmaceutical health technology assessment (HTA) or outcomes research groups (11) and regulatory agencies (10).

Figure 4. How fit for purpose are FRPs?



Facilitated regulatory pathways

For purposes of the survey, FRPs were defined as *currently available regulatory and/or HTA/payer pathways that have been designed to accelerate submissions, reviews and patient access to medicines. Pathways that fall into this category include and are not limited to Accelerated Assessment and Conditional Marketing Authorisation used by the European Medicines Agency (EMA), Accelerated Approval, Breakthrough Therapy and Fast Track used by the US Food and Drug Administration (FDA),.*

Survey responders were asked to rate the usefulness of currently available FRPs at the FDA, EMA and Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Whilst 62% of participants indicated that FDA pathways are fit for purpose, EMA pathways and PMDA pathways were regarded as useful by only 11% and 7% of respondents respectively (Figure 4).

Adaptive licensing

For purposes of the survey, AL was defined as *novel pathways transforming the medicines development process that are being designed and tested. These pathways go by a variety of names, most typically Adaptive Licensing, Staggered Approvals or Medicines Adaptive Pathways. Common elements include an early and controlled initial release following a shortened testing period in a limited number of patients; followed by intensive real-world monitoring with progressive data collection to more completely define the medicine's profile and manage the uncertainty about the products benefits and risks; leading to a follow-on full approval, an approval restricting use in a selected population, or a withdrawal. Active involvement of regulators, prescribers, patients and HTA/Payers is a hallmark of Adaptive Licensing pathways. Some Adaptive Licensing pathways could work within the context of current laws and regulations, while others will require a transformation of the legal environment, with a change in the risk-acceptance mind-set of all stakeholders, including regulators, payers, prescribers and patients.*

Most respondents (75%) indicated that it was important that EMA develop a transformative new pathway to accelerate medicine reviews and patient access; a somewhat smaller majority

(55%) of respondents felt it important that the FDA develop this type of pathway and 43% felt it important for the PDMA to do so. More than half (55%) of respondents indicated that over the next 5 years, a move to AL could play a role in accelerating access to medicines but only 34% believe that a move to AL could influence the improvement of cost-effective medicines development in that time period.

When asked for the two most important potential benefits of AL pathways, 83% of survey participants identified early approval and early access, leading to the ability to fulfil unmet need by providing earlier access to promising new therapies and ensuring that groups that will benefit the most from an innovation will have access to the new therapy. Other important potential benefits identified by respondents included faster and more efficient development and review, improved real-world data collection and post-approval tracking, as well as the opportunity to align stakeholders earlier in the process. Responders also felt that to more controlled environment offered by AL would result in fewer good products being withdrawn after marketing because of inappropriate widespread use in previously unstudied populations or in ways not previously studied.

Key characteristics of AL pathways identified by the responders included early approval and access; a process that is flexible, iterative and adaptive; initial approval based on limited data; the use of real-world data collection and risk management; stakeholder alignment; the existence of incentives, accelerated processes and 'adaptive' withdrawal; and the availability of scientific advice earlier in development.

There is currently no clear legal framework for AL and it was regarded by study participants as requiring a behavioural and cultural shift.

There is currently no clear legal framework for AL and it was regarded by study participants as requiring a behavioural and cultural shift. Participants additionally specified that AL should be transformational; that is, it should involve a different way of thinking. They also noted that AL may not be of equal importance across all disease areas but is certainly more highly applicable to areas of defined high unmet need such as oncology and rare disease.

When asked to identify the three most important elements in implementing an AL approach, 53% of respondents pointed to an enabling regulatory environment, including proper laws and regulations, containing intellectual property protections; 24% indicated well-defined product withdrawal and exit strategies to ensure that even if faced with a reduction in access, responding patients can continue to receive the medicine. Finally, an environment where there is true financial flexibility and risk-sharing between the sponsor and payer during the product's lifespan was identified by 19% of respondents.

Moving forward

Survey results showed a perception of that reluctance among regulators and HTA and payer organisations to make decisions based on novel clinical study designs or novel predictive endpoints might stand in the way of the implementation of ALs. However, responders felt that sponsors, regulators and HTA and payer organisations are collaborating effectively to define the value characteristics required of new products to be developed through AL. Globally, 53% of respondents indicated that the divergence of HTA and regulatory requirements in jurisdictions around the world might complicate the use of AL by sponsors and almost half (49%) of survey participants believed that regulatory and HTA evidentiary requirements need to be formally aligned by disease state. More than one third (37%) felt that there is insufficient infrastructure to monitor post-approval benefits and harms in the use of AL. The opinion of survey participants regarding the commitment of regulatory and HTA agencies

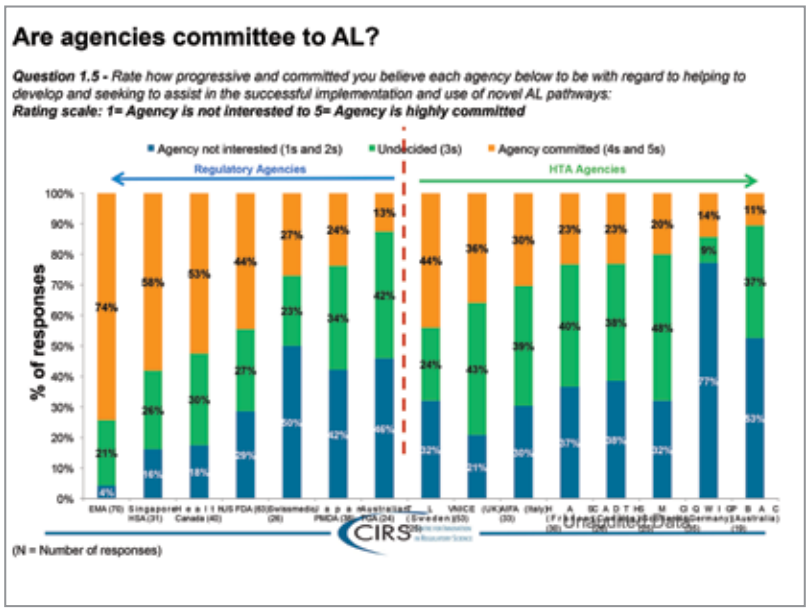


Figure 5. Difference between the perceived interest in HTA and regulatory agencies in implementing adaptive licensing.

to the development and implementation of AL pathways varied widely according to the agency's location and classification (Figure 5).. Ultimately, more than half of responders (53%) believed that it is unlikely that an AL approach will be fully implemented within the next 5 years, only 22% thought the full implementation in that time frame is likely and 25% were undecided

Mr Liberti concluded his presentation by outlining the principle barriers to implementation of AL pathways as identified by the survey including lack of definitions, little alignment and international standards; inconsistent evidentiary requirements and problems with exit strategies and disinvestment. Possible solutions to these barriers offered by survey participants included convergence of legislative requirements, early involvement of all important stakeholders in designing the process, collaboration on policy and process and beginning with the end in mind, all of which provided a direction for the presentations and discussions that would take place during this meeting.

EMA framework development and pilot study for adaptive licensing: What are the key considerations and aspirations?

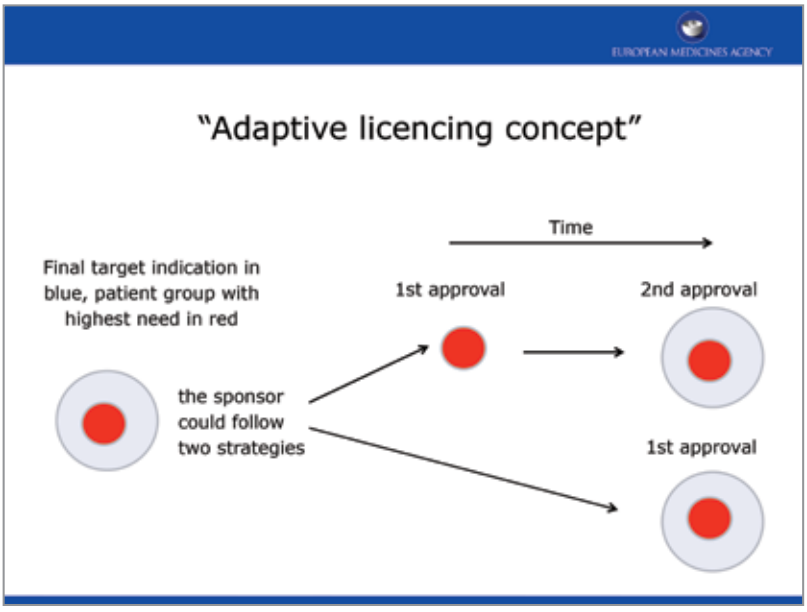
Prof Tomas Salmonson

Chair, Committee for Medical Products for Human Use, European Medicines Agency

Drivers enablers and barriers of adaptive licensing pathways

Four key factors are driving the development of adaptive licensing (AL) pathways. Patient expectations include the demand for timely access to new medicines and an emphasis on unmet medical need. Emerging scientific advances have targeted treatment populations and increased efforts for early disease intervention. At the same time, healthcare systems, payers and the pharmaceutical industry are under great pressure with respect to the sustainability of drug development. In fact, as the number of stakeholders in decisions about approval, reimbursement and use of medicines increases, drug research and development appear to have become more financially driven, with society itself under great fiscal pressure.

Figure 6. Adaptive licensing can provide expedited, staged approval.



A variety of factors are actual or potential enablers of AL pathways including improved understanding of disease processes and better knowledge management, innovative clinical trial designs and rapid healthcare learning systems. In addition, patient input assists in the understanding of acceptable uncertainty as regulators shift from prediction to real-time monitoring in order to characterise product profiles. In addition, clinicians are seeking ways to move toward more targeted prescribing.

The Adaptive Licensing Project

The European Medicines Agency (EMA) has explained AL as "a prospectively planned process that starts with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence-gathering and the adaptation of the marketing authorisation to allow broader patients to access medicine (Figure 6)." The process has evolved to include early dialogue among multiple stakeholders with the goal of shortening the time to initial approval of a product.

To address the trade-off between timely access and complete scientific evidence for benefits,

risks and relative effectiveness and to provide an environment that supports innovation, EMA launched the Adaptive Licensing Project (ALP) in March 2014. The project, which involves sponsors, health technology assessment (HTA) organisations, patient representatives and healthcare professionals, seeks to provide early access for patients, starting from approval in a niche indication with a high unmet medical need. Once an initial, limited approval is granted, collection of efficacy and safety data will continue in the niche indication and be extended to broader patient groups.

The ALP provides a framework for informal, confidential interactions, with discussion of 'live' assets. The project is attempting to refine the understanding of potential pathways and to discuss how best to address potential hurdles including those that are not yet apparent. Whilst the ALP offers advantages of early approval and access to patients with real need and includes the involvement of all stakeholders, uncertainties may be higher than with a standard approval at the time of initial licensing; whether this form of accelerated approval involves the risk of an increased number of unexpected safety issues or withdrawals will need to be determined through actual experience.

The project includes an iterative development pathway with expansion of the target population and/or progressive reduction of uncertainty around the initial decision; the potential for real-world data collection and use; engagement of HTA organisations and other stakeholders; unmet medical need that opens to more regulatory options and acceptance of uncertainties; the opportunity to influence the clinical development programme and the choice of 'large' and 'small' indications.

The Adaptive Licensing Discussion Group at EMA, which includes senior EMA staff, committee chairs and members as well as the Scientific Advice Working Party (SAWP) provides for safe-harbour discussions. The ALP does not represent a rescue path for developmental plans and the pharmaceutical industry has demonstrated great interest in this pilot; at the time of this Workshop, seven candidates were accepted for the EMA ALP from a total of 28 submissions. The number of candidates is expected to increase with time.

AL pathways are among the most likely ways to deal with the conflicting needs of timely access and complete evidence . . .

While a transition to use of AL pathways does not represent a 'magic-moment' decision to life-span pharmaceutical management or from regulatory prediction to monitoring, it does encompass the transition from the exclusive use of randomised clinical trials to a toolkit for evidence generation, from large to small patient populations, from a focus on licensing to a focus on patient access and from open to managed utilisation of new medicines.

European pharmaceutical regulation is already on a trajectory to the use of more adaptive pathways and the speed of change will depend on how fast pre-conditions can be met. AL pathways are among the most likely ways to deal with the conflicting needs of timely access and complete evidence and AL may ultimately be applied to all drug approvals, not just those involving high unmet need.

Reference

1. European Medicines Agency. Questions and answers following the initial experience of the Adaptive Licensing Pilot project Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/09/WC500172810.pdf Accessed August 6, 2015.

Building flexibility for regulatory approval in the US

Dr Amy G. Egan

US Food and Drug Administration Liaison to the European Medicines Agency

Drug development can be defined as the progressive reduction of uncertainty about human responses to a candidate medicine. Considerable uncertainty about these responses often exists at the time of drug approval. Adaptive licensing (AL) envisions a more explicit acknowledgement that evidence development is a continuum. In this continuum, regulatory approval comes in steps or stages and market access and use in practice is restricted in a manner commensurate with the current level of knowledge and evidence development continues in parallel with marketing.

Food and Drug Administration Safety and Innovation Act

The Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA) enhanced the authority of the FDA to consider appropriate scientific data, methods and tools and to expedite development of and access to novel treatments for patients with a broad range of serious or life-threatening diseases or conditions. FDASIA broadened the scope of accelerated approval and fast-track provisions, while maintaining safety and effectiveness standards. The act established a programme to encourage the development of surrogate and clinical endpoints, including biomarkers and other scientific methods and tools that can assist in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist. It additionally provided incentives for the development of antibacterial and antifungal drugs intended to treat serious and life-threatening infections.

Guidance for industry for expedited programs for serious conditions

In May 2014, the FDA issued guidance for industry, covering expedited programmes for drugs and biologics intended for the treatment of serious or life-threatening conditions. The guidance outlines four programmes that facilitate and expedite the development and review of new drugs, Fast Track, Breakthrough, Accelerated Approval and Priority Review.

The Fast Track designation for a drug application provides for more frequent meetings and communications with the FDA to discuss a drug development plan and ensure the collection of appropriate data needed to support approval, including the use of biomarkers. To qualify for Fast Track, a drug must be intended to treat a serious condition and have nonclinical or clinical data demonstrating its potential to address an unmet medical need. Alternatively, it must have been designated as a qualified infectious disease product (QIDP). In 2013, nine of 25 novel drugs (36%) that received approval had the Fast Track designation. In 2014, as of June 30, 64 drugs have been granted Fast Track designation.

The Breakthrough designation provides all the benefits of Fast Track, plus intensive guidance on an efficient early development programme (as early as phase 1) and the commitment from the FDA review staff to work closely together throughout drug development and review. A Breakthrough drug may be eligible for alternative clinical trial designs or the use of interim analysis by a data monitoring committee. A Breakthrough drug must have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement in one or more clinically significant endpoints over available therapies. As of 19 September 2014, the CDER had received 187 requests for Breakthrough designation. Of these, 57 were granted and 10 drugs had received approval. As of 31 August 2014, CBER had received 44 requests for Breakthrough designation, of which 6 were granted; none of these biologics has yet received approval.

FDASIA facilitates somewhat broader use of Accelerated Approval to expedite patients' access to important treatments for serious conditions. It provides additional flexibility concerning the implications of available therapy on eligibility for accelerated approval and clarifies the use of clinical endpoints. For Accelerated Approval, a drug must treat a serious condition and generally provide a meaningful advantage over available therapies and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is likely to predict an effect on IMM or other clinical benefit. Since 1992, more than 80 new products have been approved under Accelerated Approval.

The Priority Review designation can be granted

for a drug that treats a serious condition and if approved, would provide a significant improvement in safety or effectiveness; or, alternatively, for a supplemental application that proposes a labelling change pursuant to a report on a paediatric study under Section 505A, or an application for a drug that has been designated as a QIDP or an application or supplement for a drug submitted with priority review designation. In 2013, 9 of 25 novel drugs approved (36%) were approved under Priority Review. Of 47 new medical entities submitted during 2013, 17 (36%) were granted Priority Review.

The Generating Antibiotics Incentives Now Act (GAIN) pathway is open to QIDPs, defined as antibiotics or any drugs for treating, detecting, preventing or identifying a qualifying pathogen such as resistant gram-positive pathogens, multi-drug-resistant gram-negative bacteria, multi-drug-resistant tuberculosis and any other infectious pathogen identified by the Secretary as a significant threat to public health because of drug resistance or other factors. For appropriate products, GAIN extends data exclusivity by five years and provides six months of additional exclusivity for products with companion diagnostics. It also provides for priority review and makes products eligible for Fast Track designation. Use of this programme requires a review and possible revising of FDA guidelines regarding clinical trials and other requirements for approval of antibiotic drugs. As of 8 September 2014, the FDA has received 67 requests for QIDP designation, of which 55 have been granted and 6 are pending. Three drugs have been approved under the QIDP designation.

Lessons learned

Statutory criteria for the Breakthrough designation are subjective and require judgement by the FDA although all requests are reviewed by the Medical Policy Council to ensure consistency of standards and approach. In some cases, drugs have been designated breakthrough late in clinical development, including after a marketing application has already been submitted. However, the main focus of the programme is to identify drugs early in development and it is expected that a shift toward earlier designation will occur as the programme matures. It should also be recognised that the rate-limiting step to medicines' availability is often not clinical development and rather manufacturing development and scale-up.

. . . a "branding" mechanism is needed to convey to the healthcare community that drugs approved under the LPAD pathway carry a greater level of uncertainty and risk and to help prescribers determine whether such use is clinically justified . . .

The Breakthrough Therapy programme commitments have been resource intensive and the number of requests and designations has exceeded expectations. Work is currently underway to minimise any adverse impact the use of these resources may have on other programmes.

Breakthrough designations generally occur under an Investigative New Drug application and the FDA is prohibited from discussing details of its decisions. Additionally, sponsors may not make public announcements regarding these decisions and the resulting lack of transparency adds to the confusion regarding standards for the designation.

Common reasons for denial of requests for breakthrough status include a lack of clinical data in the evidence, the fact that the evidence is too preliminary to be considered reliable, a failure to demonstrate "substantial" improvement over available therapy, a reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient and post-hoc analyses of failed studies that identify a subset that may benefit.

FDASIA did not alter the standards of evidence in the governing legislation. That is, products reviewed through these pathways must meet regulatory requirements that an application demonstrate substantial evidence of effectiveness or clinical benefit. This evidence requires adequate and well-controlled clinical trials that are designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation." The usual approval standard requires two of these adequate and well-controlled trials.

FDA regulatory flexibility

Current regulations provide room for regulatory flexibility. As stated in Federal regulation 21 CFR 314.105(c) "The FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information…required

to provide for a particular drug to meet the statutory standards."

Indeed, between 1983 and 2010, use of the FDA Rare Disease Program led to the approval of 135 non-cancer new molecular entities. Two thirds of these submissions relied on only one adequate and well-controlled trial plus supportive evidence and nine of the approvals were based on surrogate measures of efficacy.[1] However, most of the recent new drug approvals for rare diseases—drugs that would qualify for the accelerated approval program based on the seriousness of the disease and the lack of available therapies and that have shown effects on surrogate or intermediate endpoints— did not involve accelerated approval but were granted regular or traditional approval.

FDA's current approach to adaptive licensing

Accelerated approval allows for initial approval based on a surrogate that has not yet been fully validated or on an intermediate clinical endpoint, although the limitations of this approach were demonstrated by the approval and subsequent revocation of that approval for bevacizumab (Avastin) for metastatic breast cancer based on the results of a single trial.

FDA's adaptive approach includes the staged approval approach for drugs intended to treat type 2 diabetes, where a certain degree of cardiovascular risk must be excluded pre-approval, followed by exclusion of a lower degree of CV risk post-approval. FDA's adaptive approach has allowed for the approval of products for more limited patient populations through the use of risk evaluation and mitigation strategies (REMS), while trials are conducted for broader target populations. This is evidenced in the approvals of lomitapide (Juxtapid) for homozygous familial hypercholesterolemia (HoFH) and metreleptin (Myalept) for complications of leptin deficiency in patients with congenital or acquired generalised lipodystrophy .

FDA's adaptive approach includes its use of regulatory flexibility, as evidenced by allowing the use of statistical criteria that are somewhat less rigorous than usual for evaluation of products for rare diseases; by allowing the use of single-arm studies to demonstrate efficacy, e.g., for the previously mentioned lomitapide and for eltrombopag (Promacta) for severe aplastic anaemia; by allowing the use of a single-arm study plus confirmatory evidence for rare diseases; and by allowing approval in narrow populations with restrictions on use, followed by further study and post-marketing reassessment, e.g., for lomitapride and mipomersen (Kynamro), for the treatment of HoFH.

FDA commitment

The FDA recognises its role in fostering the application of scientific advances to the treatment of disease through drug development, including the use of novel approaches that can facilitate development of treatments for unmet need. Current collaborative efforts include those with the Biomarkers Consortium, the Clinical Trials Transformation Initiative and the Critical Path Institute. The agency is also developing guidance for innovative clinical trial designs including adaptive non-inferiority and enrichment trial designs as well as a qualification process for drug development tools. Public-private partnerships have been established in the development of gastroenterology regulatory endpoints and the advancement of therapeutics for inflammatory bowel disease.

Future initiatives

The FDA believes it necessary to consider new mechanisms for encouraging the development of new antibacterial drugs to address unmet medical needs in the treatment of serious and life-threatening bacterial infections, including the establishment of a new Limited Population Antibacterial Drug (LPAD) program. LPAD would be based on more streamlined development programmes that establish drug safety and effectiveness in a limited patient population with serious or life-threatening infections and unmet medical needs. Because the benefit-risk would be assessed in a limited population, a "branding" mechanism is needed to convey to the healthcare community that drugs approved under the LPAD pathway carry a greater level of uncertainty and risk and to help prescribers determine whether such use is clinically justified in patients outside the indicated population for whom a drug's benefits would not have been shown to outweigh its risks. This labelling is especially important in the context of antibiotic drugs, where historical overuse has led to increased antimicrobial resistance.

Finally, it's important to recognise that although these accelerated pathways address uncertainties about efficacy and safety they do not address scientific uncertainties that lead to most clinical development failures, that is, a failure to predict the lack of efficacy.

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Medicines adaptive pathways: A practical strategy to improve patient access to medicines?

Dr Brian O'Rourke

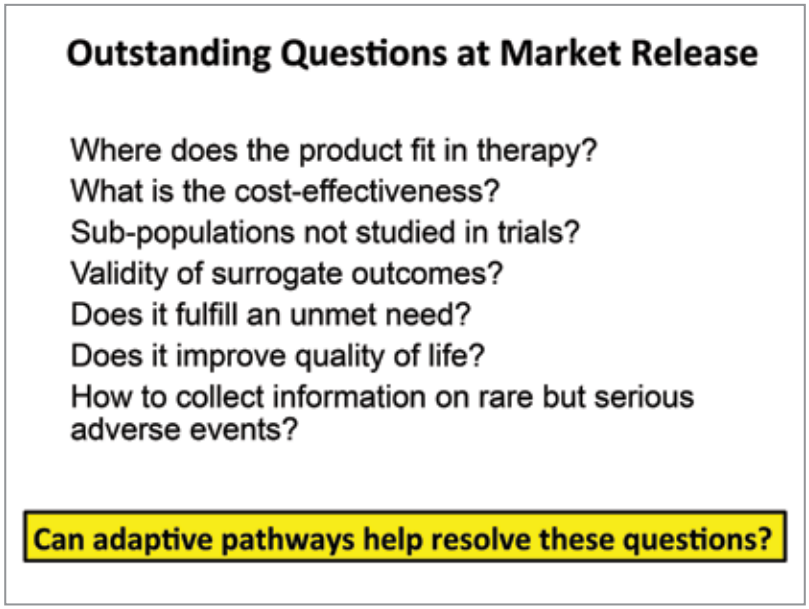
President and CEO, Canadian Agency for Drugs and Technologies in Health

The promise of AL

Adaptive licensing (AL) promises a number of benefits that include earlier access to promising therapies and a movement from a binary to a more flexible and iterative process in decision making about medicines. The AL model may also improve understanding of disease, introduce innovative clinical trial designs and usher in a transition from prediction to real-time monitoring of the effects of medicines. In addition, AL has the potential to maximise the positive impact of new drugs through more targeted prescriptions and enhanced patient care decisions. Furthermore, patients may be increasingly involved in the regulatory and reimbursement processes.

AL pathways may also help resolve issues that are unknown at the time of a medicine's initial approval such as its cost effectiveness, its place among available therapies and its ability to fulfil unmet needs and have an impact on patient quality of life (Figure 7).

Figure 7. The role of adaptive licensing in resolving unanswered questions at market release.



. . . real-world evidence will become the norm in decision making about new drugs but appropriate contextualisation will be critical to effective decisions.

Key challenges and opportunities from a payer perspective

Despite the advantages that may accrue from the use of AL, payers need to know if stakeholders are demanding these pathways as a response to a perception that the current regulatory and reimbursement models need improving, particularly with regard to the speed or efficiency with which they provide access to medicines.

Recently, the Vancouver Group, an informal group of payers from around the world, met to consider AL and the consensus was that although AL began as a regulatory initiative, implementation without payer involvement will increase the regulatory-reimbursement divide. In fact, some meeting participants questioned whether AL might be a method to get more drugs listed at a faster rate, presenting an additional cost burden to payers. Other concerns regarding the use of AL include its potential to increase the off-label use of drugs unless rigid safeguards are put into place. Additionally, implementation and monitoring the effects of medicines approved through AL may present numerous challenges such as ensuring the adequacy of systems for gathering and analysing real-world data. Managing multiple agreements for risk sharing, access and coverage as new evidence develops will also pose a challenge. Methods for delisting medicines that do not perform as expected present additional concerns as do the need for adaptive pricing models and potentially, for pricing by indication.

However, the move to AL pathways also presents a number of significant opportunities. It allows early engagement between the various stakeholders including the sponsor, patients and clinicians and may also improve engagement between regulators and payers. AL may be especially beneficial for particular types of medicines that might include expensive drugs, biologics and antivirals and orphan therapies. The use of AL pathways could result in the establishment of new international registries for the collection of real-world evidence but efforts are required to improve methodologies

to capture this evidence. New flexible pricing models might also be introduced with AL, including new rebate and reimbursement contracts, price increases that are commensurate with accumulation of effectiveness evidence and pricing by indication; however, payers have expressed scepticism regarding some of these models and effective industry-payer dialogue would be required.

The development of AL pathways also presents opportunities for enhancing HTA and regulatory connections including the alignment of advice, through joint pipeline and scientific advice meetings, the alignment of timelines with parallel or near parallel review processes and the potential alignment of regulatory and HTA decisions.

Conclusions

It is likely that AL will be well accepted by clinicians and patients; however, industry will need to implement AL advantages, payers are likely to remain sceptical and it is not certain that there will be international regulatory consensus on the concept. Given current developments, real-world evidence will become the norm in decision making about new drugs but appropriate contextualisation will be critical to support effective decisions.

Lessons learned from four years of multi-stakeholder progress in MIT NEWDIGS

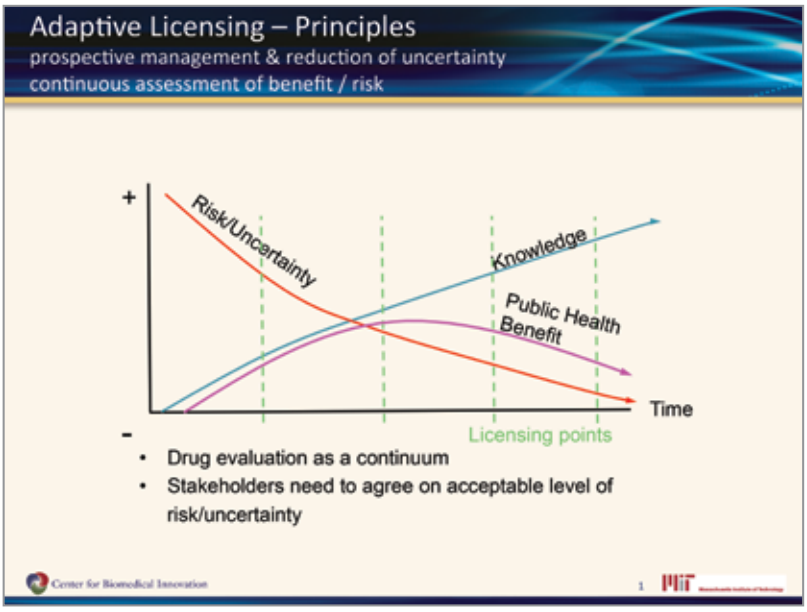
Dr Tony Hoos

Core Member of NEWDIGS & President M4P Consulting, UK

NEWDIGS

The Massachusetts Institute of Technology New Drug Development Paradigms (NEWDIGS) team consists of members from academia, regulatory, payer and health technology assessment organisations, patient and provider groups and pharmaceutical companies with a mission to reliably and sustainably deliver new, better and affordable therapeutics to the right patient faster.

Figure 8. Evaluating a drug at multiple time points across the development continuum may maximise public health



In fulfilment of that mission, NEWDIGS seeks to find systems solutions. The need for such a solution in the biopharmaceutical industry becomes evident when considering the tremendous and ever-growing investment required for the growth of knowledge in this field compared with the investment required in other industries. For example, in 2007, the R&D investment in the highly regulated aerospace industry was approximately $22,000 per employee compared with $105,000 spent per employee to develop medicines. Phase 3 trials, which are becoming larger, more complex and longer, can absorb as much as 90% of the entire development budget. QTc studies in trials cost €2.4 million for every one sudden cardiac death prevented, or €187,000 per quality-adjusted life year.[2] It has been reported that in the period 1995 to 2009, periodic safety update reports (PSURs) for biologicals in Europe cost €342,110 for every QALY gained.[3] Such expenditures point to the need to determine how much risk is acceptable for how much benefit and how to assess acceptable risks and benefits – a task that will require efforts from multiple stakeholders.

The move to adaptive licensing

Because public health benefit may be reduced when an extended time span is required to increase knowledge and reduce uncertainty, it may be desirable to employ a programme

of adaptive licensing, thereby establishing several licensing points, rather than just one, understanding uncertainty and managing risk in a continuum (Figure 8). In a key publication in which Eichler and colleagues from NEWDIGS established a framework for a discussion of individual AL pilot studies, AL was discussed as a

"prospectively planned, adaptive approach to regulation of drugs. Through iterative phases of evidence gathering followed by regulatory evaluation and license adaptation, AL seeks to balance timely access for patients with the need to provide adequate evolving information on benefits and harms."[4]

There are multiple important differences between AL and traditional licensing paradigms (Figure 9) and AL is not another new regulatory or reimbursement pathway but rather a process to facilitate broader and more coordinated application of existing flexibilities. After Oye and associates emphasised that fact and established that AL could occur using existing legislation,[5] the European Medicines Agency (EMA) initiated a pilot programme, inviting companies to submit development plans for new medicines for consideration for a prospective AL study.

Eleven medicines were selected for the pilot through a process of nomination and evaluation, representing a wide range of drugs from antibiotics, monoclonal antibodies and vaccines to drugs for tuberculosis and dyslipidemia. Medicines that were selected were not necessarily orphan drugs or treatments for rare diseases and because AL should be prospectively planned, an attempt was made to choose drugs in earlier phases of development.

Figure 9. Differences between standard and adaptive licensing.

Comparison of Traditional and Adaptive Licensing Paradigms

Traditional	Adaptive Licensing
"Opportunistic" development plan	Prospectively planned and coordinated development
Phase 1, 2, and 3 studies, ≈ 8-12 yrs and many highly selected patients	Phase 1, 2 and registration study(s), ≈ 4-8 years with fewer less selected patients
Trial patients may differ significantly from treated population after approval	"Real world" safety and effectiveness data collected early in lifecycle
Ad hoc process for review of post-marketing data and regulatory action	Planned cycles of data gathering and review and regulatory action to relax or tighten access
Off-label use common	Monitoring and controls restrict off-label use
Uncertainties around risks and benefits may not be well understood by patients and providers	Risks and benefits actively communicated to patients and providers
Payer data may not support reimbursement at time of licensure	Generation of payer data assured and controlled

AL is not another new regulatory or reimbursement pathway, but rather a process to facilitate broader and more coordinated application of existing flexibilities

Development scenarios for each of the selected medicines were then constructed through a series of sessions with the sponsors. Scenarios might include any of thirteen features such as continuous learning due to multiple collections and analyses of data, registry or observational study to collect real world data or initial authorization based on surrogate endpoints followed by clinical confirmation (Figure 10).

Generalisable learnings

Some general learnings can be derived through the NEWDIGS AL work to date.

- The success of adaptive proposals depends on an acceptable benefit-risk balance, which may be easier to achieve with products developed to fulfil a highly unmet medical need.
- The confidence of regulators and payers in post-authorisation control can be facilitated by identification of a well-defined patient population.
- Plans are needed for the early collection and analysis of real-world data.
- It is expected that the results of early trials, whether surrogate or clinical outcomes, will be replicated with time in expanding or new populations.
- Earlier development candidates (preclinical to phase 2a) will benefit most from an AL approach.
- If a surrogate endpoint is used, its validation is not required and there should be evidence that it has the potential to predict clinical benefit.
- Importantly, AL is not a rescue path for failed development candidates and it is not a method for 'cutting corners'.
- Manufacturing and toxicology activities will need a parallel staged plan that extends across the lifespan of the medicine.
- Although initial development activities may be abbreviated and accelerated, the post-

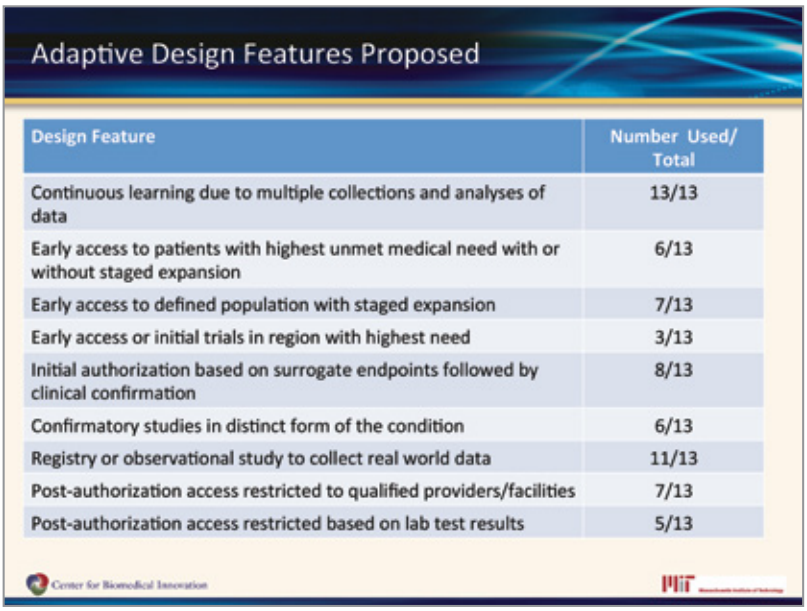


Figure 10. The development scenarios for medicines in the EMA AL pilot could contain any of thirteen features.

authorisation activities will require additional resources from all stakeholders.

The NEWDIGS adaptive licensing initiative concluded its design phase with the initiation of the EMA pilot programme in March 2014. Focus is now on enabling successful implementation and fostering global adoption. NEWDIGS is undertaking two new activities in order to support these goals —the Janus and Data initiatives. The Janus Initiative will employ modelling and simulation in an adaptive process to analyse uncertainty and the benefit-risk balance and their effects on timelines and other factors. The Data Initiative will assess the readiness of the framework to support the EMA pilot programme.

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Longitudinal modelling and adaptive trials

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. . . surrogacy is not necessary to establish confidence in a predictive endpoint. Rather, modelling should be used during a trial to learn how well an endpoint predicts a desired outcome, with uncertainty incorporated into predictions . . .

Longitudinal modelling

In 2006, the US Food and Drug Administration (FDA) Critical Path Opportunities Report identified the two areas that were considered key to enhancing the development of new medicines: biomarker development and streamlining clinical trials.[1] As part of the Critical Path Initiative, Eli Lilly worked closely with the FDA to design a seamless phase 2/ phase 3 adaptive clinical trial in type 2 diabetes, including an active comparator and a placebo. Unlike traditional clinical trials in which researchers report the effects of a medicine against clinical endpoints and do not model results for individual patients over time, adaptive trials do try to streamline research and expedite the availability of medicines by using early trial data to develop models of expected later results. The phase 2 portion of the design used the adaptive randomisation of patients to one of seven dosages of the study drug to identify the dosages that proved most informative about both safety and efficacy. The trial would then switch seamlessly to the phase 3 portion, which examined one or two of those informative dosages. The sample size for phase 3 was determined via predictive power, considering the available phase 2 data and the adaptive transition to phase 3 was based on Bayesian predictive probabilities. Both phases of the study were to be driven by the primary endpoint of Clinical Utility Index (CUI) at twelve months, a combined score based on haemoglobin HbA1c levels plus weight loss for efficacy and diastolic blood pressure plus heart rate for safety. When the CUI score for any of the experimental dosages reached zero, that dosage was dropped from the study (Figure 11).The dose-response was to be longitudinally modelled, which was considered critical, since it was expected that doses for study might be chosen before any patients had reached 12 months of treatment.

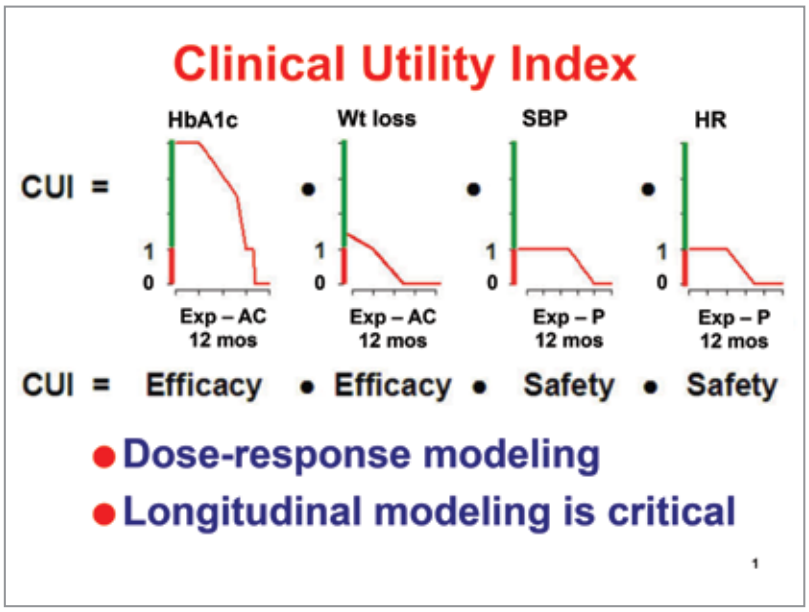

Figure 11. The Clinical Utility Index in type 2 diabetes

The use of this adaptive design in the phase 2 portion of trial of the experimental drug dulaglutide for type 2 diabetes mellitus resulted in the choice of two dosages for use in phase 3 trials. Using those dosages, dulaglutide was found to be associated with statistically superior reduction in HbA1c from baseline compared with the diabetes medications, exenatide, metformin and sitagliptin in three separate phase 3 trials and in September 2014, the US FDA approved the its use. Eli Lilly now uses modelling simulations as a regular part of its drug development programme.

Platform trials

In the ISPY-2 trial, six pharmaceutical companies pooled resources through their participation in a phase 2 platform trial coordinated with the FDA, in which 680 participants were randomly assigned to one of eight different therapies (matched to ten biomarker signatures) for neoadjuvant breast cancer at twenty treatment centres, with a primary endpoint of pathologic complete response (pCR). In the continuous screening process for the trial, treatment arms are continually evaluated and either discontinued for futility, graduated to a phase 3 trial or continued in another disease subtype, permitting the potential additions of new

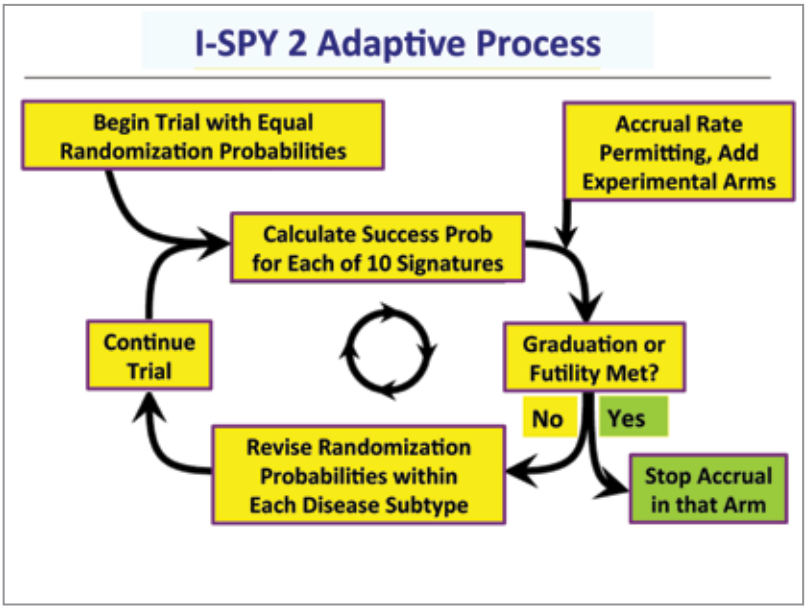

Figure 12. The I-SPY 2 adaptive process.

treatment arms without the need for regulatory protocol approval (Figure 12). At the time of this Workshop, two therapies, neratinib and veliparib, had progressed to phase 3 trials and in May 2012, the US FDA Center for Drug Evaluation and Research (CDER) issued a guidance for industry specifying the approved use of pCR as an endpoint to support accelerated approval for treatments for neoadjuvant breast cancer.

In ISPY-3, pCR and event-free survival (EFS) will be addressed in a single trial. A pCR analysis will be conducted on specimens of patients who have completed surgery and accelerated approval will be granted if compounds demonstrate superiority in pCR and full approval if superiority in EFS is observed. The relationship between pCR and EFS has been previously modelled by Cortazar and colleagues[2] and will be updated to reflect the results in ISPY-3.

The Lung-MAP study is another multi-centre, multi-sponsor platform trial that employs seamless transition from phase 2 to phase 3 but does not use longitudinal modelling. Patients in this study are matched to sub-studies based on their genomic profiles. Based on the success of these trials, other oncology platform studies have been initiated. Figure 13 shows the characteristics of those trials. Additionally, Europe's Innovative Medicines Initiative has issued a call for proposals for a platform trial for Alzheimer's disease therapies.

The advantages of platform trials include the fact that experimental drugs are matched with biomarker signatures and a common control is used, resulting in significant cost and time savings. Better therapies are approved more quickly and successful drug-biomarker pairs graduate to small, focused, more successful phase 3 trials that are based on Bayesian predictive probabilities.

The success of these trials points to the fact that surrogacy is not necessary to establish confidence in a predictive endpoint. Rather, modelling should be used during a trial to learn how well an endpoint predicts a desired outcome, with uncertainty incorporated into predictions through techniques such as the use of multiple imputations and the model updated to reflect actual trial data.

Figure 13. Common features of platform trials.

Characteristics of Modern Platform Trials	I-SPY 2	MICAT	BATTLE	LUNG MAP	UK Matrix
Screen markers for all patients	✔	✔	✔	✔	✔
Master protocol	✔	✔	✔	✔	✔
Drugs from many companies	✔	✔	✔	✔	✔
Combination therapies	✔	✔			
Sequential therapies		✔			
Regimens enter & leave trial	✔	✔		✔	✔
Learn off-target effects	✔	✔	✔		
Pair regimens with biomarkers	✔	✔	✔		
Common control arm	✔	✔			
Adaptive randomization	✔	✔	✔		
Adaptive sample size	✔	✔			
Early "curable" disease	✔				
Registration endpoint	✔			✔	
Seamless phases				✔	
Longitudinal modeling	✔	✔			

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Medicines adaptive pathways (facilitated regulatory pathways):

A practical strategy to improve patient access to medicines

Mark Higgins

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The current process for parallel scientific advice is lengthy and formal and adaptive licensing and more flexible regulatory interactions should be supported.

Cystic fibrosis

Cystic fibrosis (CF) is a life-shortening orphan disease caused by a defective CF transmembrane conductance regulator (CFTR) protein due to mutations in the gene which encode for CFTR. The CFTR gene mutation produces reduced quantity or function of the CFTR protein, resulting in defective chloride ion transport, leading to depletion of airway surface liquid and defective mucociliary clearance. The pathophysiologic cascade continues with a cycle of infection, inflammation and mucus obstruction, which over time produce scarring and ultimately end-stage lung disease. Cystic fibrosis is a multi-organ disease and although pulmonary disease is the most common cause of morbidity and mortality, CF can also affect the pancreas, sinuses, liver, gastrointestinal tract and reproductive system as well as salt balance. In Europe, the prevalence of CF is 1.26 cases per 10,000 individuals, corresponding to 44,245 cases.1,2 The median age at death is 29 in the United Kingdom2 and 25 years in the European Union (EU).3 Among persons with CF, respiratory disease and lung transplantation-related factors are the leading causes of mortality in the EU.3

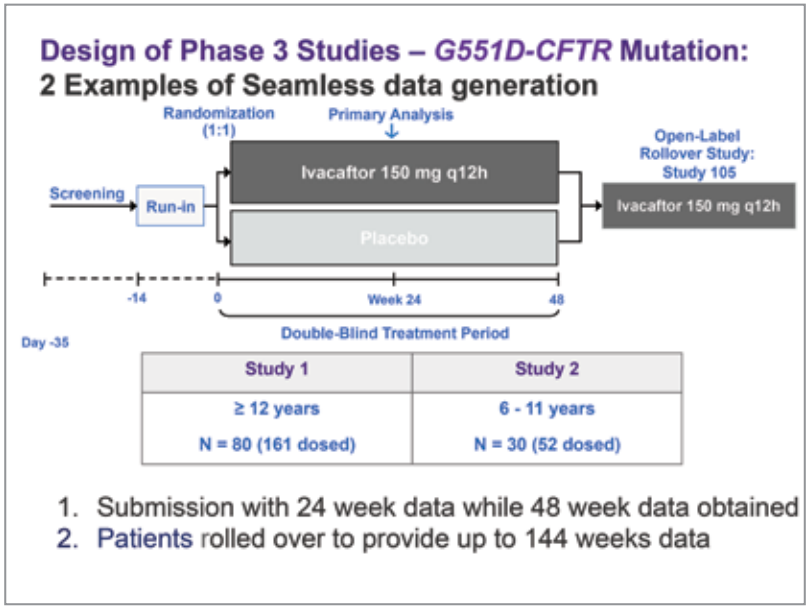

Figure 14. Data submitted with marketing approval application after first 24 weeks in ivacaftor studies.

The gene defects in CF fall into five main classes and could be addressed either by affecting the quantity of CFTR at the cell surface or by increasing the function of the CFTR protein; the latter approach resulting in increasing the probability of open chloride channels and thus channel conductance. Vertex seeks to develop orally bioavailable small-molecule CFTR modulators to be used alone or in combination for the treatment of CF. This strategy has the potential to eventually allow treatment of up to 90% of CF patients.

The CFTR modulator Kalydeco (ivacaftor) is a selective potentiator of the CFTR protein and restores CFTR channel gating to enhance chloride transport. Ivacaftor was granted an EU orphan designation in 2008 for treatment of CF due to unmet medical need and its novel mechanism of action. A paediatric investigation plan for ivacaftor was developed in 2009, which underwent four modifications based on scientific advice prior to submission of a marketing approval application.

The first target of ivacaftor research was treatment for patients with a specific genetic mutation designated G551D, who had the greatest expectation of clinical benefit. Ivacaftor was initially approved for treatment of patients with this mutation and then studied in patients with other defects of gating mechanisms and residual function. The ivacaftor approval was eventually extended to eight further gating mutations and its development programme illustrates the potential to gain approval for a very small population and subsequently expanding to progressively to additional populations.

Seamless data generation examples

Seamless data generation was achieved in the design of phase 3 studies involving the G551D mutation. Two studies were conducted: one with patients over age 12 and one with patients 6 to 11 years old. These studies benefitted from the

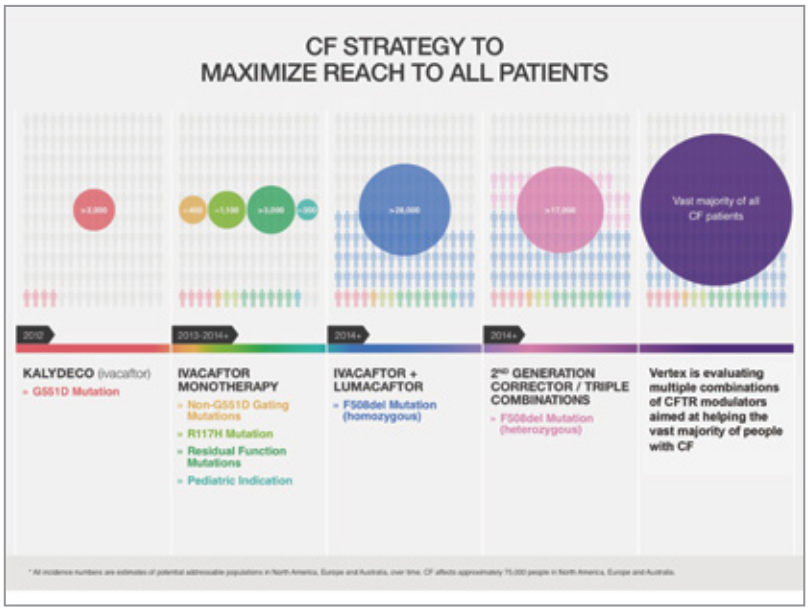

Figure 15. The ivacaftor development programme illustrates the potential to gain approval for a very small population, subsequently expanding to progressively larger populations,

existence of excellent patient registries in the US (capturing 90% of CF patients) and Europe (capturing 87% of CF patients in the UK). The primary analysis encompassed data from 24 weeks of therapy with ivacaftor 150 mg every 12 hours, with a placebo control. At the end of 24 weeks, data were submitted with the marketing approval application and treatment, followed by data from 48 weeks (Figure 14). The patients continued in an open-label rollover study that collected data for up to a total of 144 weeks. The marketing approval application was submitted in Europe in October 2011 and approved nine months later on the basis of compelling efficacy and safety findings. An application to the US FDA was submitted in October 2011 and approval was granted 105 days later, in January 2012.

Vertex also conducted the KONNECTION Study (N = 39), which compared ivacaftor with placebo in an extremely small patient population)~1% of CF patients) who had other defects of the gating mechanism. This study employed a crossover design in which patients received ivacaftor or placebo for 8 weeks. These data were then submitted for application to extend the indication. Following a 4-week washout, patients received open-label treatment with ivacaftor for another 16 weeks. Approval for the indication extension was received within nine months of submission in Europe and within five months of submission in the US.

Options used and not used for accelerated approval and access

Important learnings acquired through the ivacaftor programme included the use of system flexibilities, such as an orphan designation, the protocol assistance process to gain access for advice and accelerated review to reduce review time. The company chose not to use other flexibilities such as a surrogate marker that is not accepted by all health authorities; nor did it pursue conditional approval or early interactions with health technology assessment organisations.

Conclusions

Cystic fibrosis is a complex disease but it is expected that CFTR modulators could benefit up to 90% of CF patients (Figure 15). Experience indicates that a mutation-by-mutation research approach delays access to potentially beneficial therapy. The current process for parallel scientific advice is lengthy and formal and adaptive licensing and more flexible regulatory interactions should be supported.

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Managing uncertainty in drug approvals

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Health Canada policies and regulations

The mandate of Health Canada's Health Products and Food Branch is to take an integrated approach to managing the health-related risks and benefits of health products and food by

- minimising health risk factors to Canadians while maximising the safety provided by the regulatory system for health products and food and by
- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Federal legislation and guidance governing drug regulation include the Food and Drugs Act and associated regulations and Patented Medicines (NOC) Regulations. Policies and guidelines include international guidelines such as those of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and are intended to support the interpretation of the laws and regulations.

Health Canada can reach several types of decisions for dossier submissions. A Notice of Deficiency may be issued if deficiencies or significant omissions are identified during the review of a submission that preclude its continuance. A Notice of Non-Compliance is issued after the comprehensive review of a submission is complete, if safety, efficacy or quality have not been established to the satisfaction of the regulations. A Notice of Compliance is issued as a positive decision after the comprehensive review of a submission is complete. Under these circumstances, the manufacturer receives a Notice of Compliance, a Drug Identification Number (DIN) and an approved Product Monograph. A Prescription Status Assessment will also be performed in which criteria for prescription are assessed, such supervision by a practitioner are assessed. A final negative decision is issued as a Notice of Withdrawal.

Notice of Compliance With Conditions

In addition to these decisions, policies and guidelines that support Health Canada Food and Drug Act and Regulation include a policy for the issuance of a Notice of Compliance with Conditions (NOCc). An NOCc is granted to facilitate earlier access by physicians and patients to a drug for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating disease or condition for which there is no alternative therapy available on the Canadian market or where the new product represents a significant improvement in the benefit-risk profile over existing products. In addition the drug must be of high quality and demonstrate an acceptable benefit-risk profile and promising evidence of clinical effectiveness in clinical trials.

Health Canada's process entails significant involvement with industry and typically includes a pre-submission meeting to request NOCc advance consideration. In addition, the agency may seek external advice on endpoints, clinical relevance or other factors related to the submission. The increased level of uncertainty associated with medicines for which data are still being accrued may lead to greater time spent in review and in interactions with the sponsor. However, like a priority review, submissions granted advanced consideration for NOCc status are subject to a shortened review period of 200 days compared with 300 days for a normal review.

A variety of conditions are associated with an NOCc. These include restrictions on advertising and labeling, an agreement to carry out additional clinical trials to verify the clinical benefit of the drug and a requirement to undertake increased monitoring of the drug and reporting to Health Canada. The sponsor is also required to provide educational material, including the nature of the conditions for use, for health practitioners and patients.

Because clinical benefit for drugs authorised under the NOCc Policy has not yet been confirmed, public and private drug plans may or may not cover the costs. However, once a sponsor has provided Health Canada with satisfactory evidence of a drug's clinical effectiveness and Health Canada is satisfied that all agreed stipulations have been met, the conditions associated with market authorisation will be removed in accordance with policy.

Transparency, confirmatory trials and interactions

NOCc are generally very detailed, with the granted indications and patient populations specifically described. Tools for ensuring transparency include the Product Monograph, which details labelling requirements, Healthcare Professional communication and Letter of Undertaking.

Before NOCc authorisation, sponsors are required to submit a draft Letter of Undertaking to Health Canada for comment and authorisation. It includes a listing of the confirmatory trials to be conducted; post-market surveillance commitments, including a risk management plan; advertising, labelling or distribution requirements; a complete listing of ongoing additional clinical trials related to the product and market authorisations that have been received from other regulatory authorities

Sponsors must undertake to design and carry out confirmatory trials to verify the clinical benefit of NOCc-authorised drugs. An outline of these trials, including timeframes for initiation and completion, must be submitted and case-by-case agreement on the proposed trials obtained from Health Canada. Fulfilling these commitments, however, can be challenging because of changes in the clinical landscape and resulting difficulty in recruitment.

The Summary Basis of Decision and Post-Authorisation Activity Table, which detail the rationale for approval and all activity updates for the product are publicly available on the Health Canada website.

Moving forward

Health Canada is experiencing significant increases in the use of the NOCc pathway, with corresponding increases in demands for time and resources but greater opportunities for dialogue among all stakeholders. How the agency responds to this will be affected by the changing regulatory landscape in Canada.

Medicines Adaptive Pathways to Patients (MAPPs) from an HTA perspective

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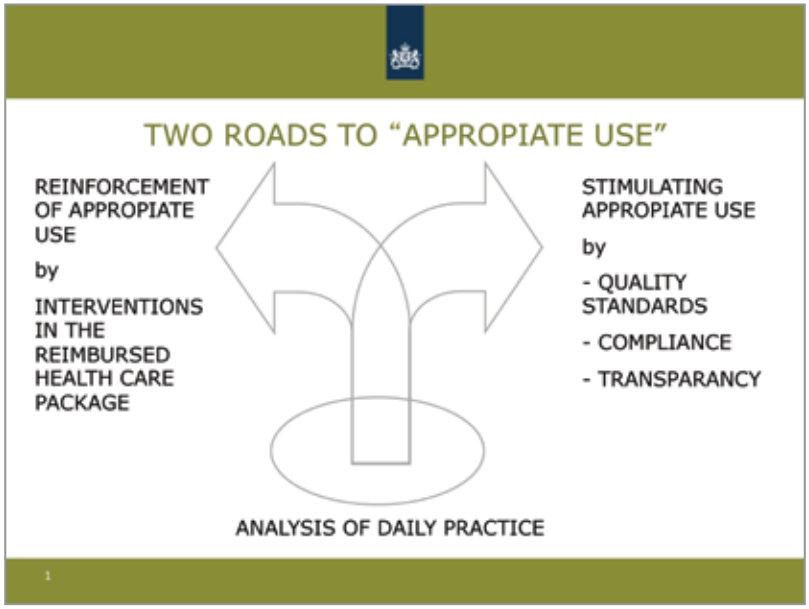
CVZ to ZIN

As of 1 April 2014, the Health Care Insurance Board (College van Zorgverzekeringen, CVZ) became the National Health Care Institute (Zorginstituut Nederland, or ZIN). It is anticipated that the new organisation will be better positioned to influence permanent improvements in healthcare, including client orientation, quality, safety and efficiency. As part of the broader ZIN commitment, the new Institute for Health Care Quality will work toward permanent improvements in the quality of care and the Institute of Health Care Professions will focus on innovation and improvements in health care professions and training courses. These new functions join existing CVZ organisations that include the Institute for Health Care Coverage, which provides advice on the basic insurance package for healthcare and the Institute for Health Care Insurance, which implements civilian arrangements within the framework of the Health Insurance Act and conducts risk adjustments.

When considering the two general roads to achieve appropriate use of medicines, it could be said that CVZ focused on the path that reinforced appropriate use by interventions in the reimbursed healthcare package whilst ZIN additionally focuses on stimulating appropriate use by ensuring quality standards, compliance and transparency (Figure 16).

Figure 16. Moving toward appropriate use of medicines.



Medicine's Adaptive Pathways to Patients

As a reflection of that more proactive pathway, health technology assessors may wish to use the term Medicine's Adaptive Pathways to Patients (MAPPs), rather than adaptive licensing (AL). The primary differences between these two terms may lie in the MAPPs focus on life cycle approach for new technologies and the essential collaboration between regulators and health technology assessors and payers.

As part of this life cycle approach, HTA organisations should be involved in the development of early scientific advice and the relative effectiveness assessment (REA) of medicines along with regulators to maximise efficiency as well as safety and efficacy assessment and additional data collection in the post-market period (Figure 17).

In fact, MAPPs may be useful for managing uncertainty after market registration, including uncertainties about effectiveness and cost-effectiveness, off-label use and budget impact. However, use of MAPPs will depend on the organisation of the healthcare system. For instance health care systems may use closed and open system for reimbursement. In a closed system, an assessment of a product is required before reimbursement can be given, whereas in an open system, reimbursement is provided unless there has been a negative assessment. In the Netherlands mostly an open system is used; only for extramural medicines a closed system is used. Additionally, in the Netherlands a risk-based approach is used for the open system, in which a health technology assessment of a new product is conducted only if has been determined that there are safety risks, budget-impact issues or uncertainties.

Health technology assessors can also recommend conditional reimbursement or coverage with evidence development in which the value of an intervention is monitored in real life and then reassessed, typically, within four years.

Some health technology agencies may be sceptical about MAPPs because of the challenges that are involved in the continuing assessment of medicines. Comparative effectiveness research studies can create extra tasks for healthcare professionals; also these

studies quite often have typically have small sample sizes and may lack consistency in data collection methods. In addition, there are differences in patient characteristics between treatment groups studied and quality of life is often measured for a given health state rather than for those different treatment groups. Finally, after new drugs are introduced to the market existing treatment paradigms may change over time and subsequently comparisons with older medicines become more difficult.

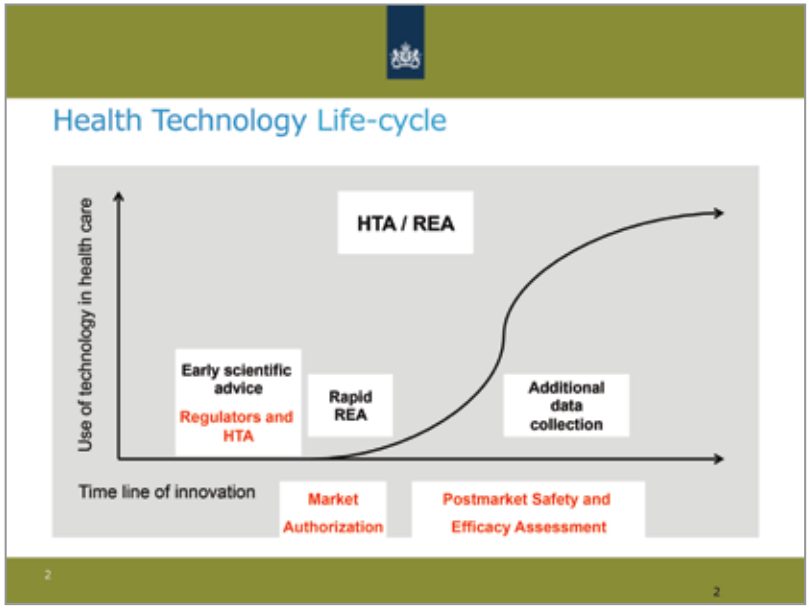
Although results of CER studies have resulted in recommendations to stop reimbursement in the Netherlands, implementing these recommendations can prove to be politically difficult such as was the case for infliximab, which was being used in the treatment of ulcerative colitis and plaque psoriasis even though the manufacturer collected insufficient research data on these indications and for alfa-glucosidase in Pompe and alfa-galactosidase in Fabry, for which reimbursement was recommended to be discontinued except in certain circumstances. In the case of omalizumab in persistent severe allergic asthma, however, a "no-cure no-pay" agreement was arranged between manufacturers, prescribers, patients, ZIN and the Ministry of Health for a two-year trial period, which may prove to be a successful innovative model.

MAPPs may provide for stricter definition of the exact population that will be treated with a drug and thus may avoid "indication-creep": MAPPs may also make it possible to better organise patient registries, with collaboration between regulators and HTA organisations, as well as between countries. In addition, MAPPs may provide more influence for HTA organisations in priority setting and selection of new pharmaceuticals. However, there are challenges associated with the use of MAPPs in different member states in the European Union, including non-participation, variable price setting in different states and political pressures that may result in enlargement of initial, narrow indications.

MAPPs may provide more influence for HTA organisations in priority setting and selection of new pharmaceuticals.

Possible solutions to these potential problems include the early involvement of HTA organisations and payers in the MAPP process, especially early international collaboration. Probably in the beginning of the experimenting with MAPPs this will most likely involve a small number of member states. In addition, work should begin on organising patient registries, with a definition of the minimum datasets and infrastructure for each member state and alignment of the research requirements of regulators and HTA organisations and payers.

Figure 17. The health technology life-cycle.



Medicines adaptive pathways – Building blocks and necessary strategies:

A regulatory perspective

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Vice Chair European Medicines Agency Pharmacovigilance Risk Assessment Committee

Adaptive pathways and regulatory evolution

There are multiple positive aspects to the use of adaptive pathways for the review of new medicines such as their potential to provide a well-defined target population and to manage and monitor risks. These pathways also aim for a progressive reduction of uncertainty by means of prospectively planned data collection, periodic re-evaluation of the benefit-risk balance and monitoring the effectiveness of risk minimisation. In addition, adaptive pathways entail early and sustained engagement of stakeholders and through use of a systems approach can make the best use of available data and existing infrastructure.

Elements of an adaptive pathway fit well into current regulatory approaches, which have undergone a significant evolution since the earlier time of binary decision making. This regulatory evolution has encompassed more proactive pharmacovigilance since the introduction of risk management plans, with strengthened methodologies for investigating drug safety and monitoring the benefit-risk balance in real-world populations. It is now recognised that pharmacovigilance requires a variety of data streams and the current regulatory ambition is for benefit-risk monitoring to be integrated throughout the lifecycle of a product. International Conference for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) E2E guidelines now specify regulatory determinations of what is known and important, as well as what is unknown and the collection of data for new medicines is planned in advance to reduce uncertainties and manage risk. In addition, as discussed by Professor Salmonson, in March 2014, the European Medicines Agency

Elements of an adaptive pathway fit well into current regulatory approaches, which have undergone a significant evolution since the earlier time of binary decision making.

(EMA) launched a pilot project to test adaptive licensing (AL). This pilot project builds on the properties described above and on experience with real-world monitoring. It will employ tools to collect and analyse data in real time, not just through formal studies and includes measures to address concerns about off-label drug use.

Addressing uncertainty

Duijnhoven and colleagues showed the average number of patients studied prior to approval of new medicines ranged from 438 for an orphan drug to 2,338 for drugs for chronic conditions. These numbers were sufficient to establish the efficacy of these products and uncertainty regarding safety remained at the time of approval.[1] However, there are three key existing regulatory strategies for uncertainty and benefit-risk management: First, regulators can employ the lifecycle approach, which builds on the concept of the risk management plan and documents how important risks will be managed, data collected and studies undertaken to investigate important risks, uncertainties and missing information. Second, regulators can require post-authorisation safety studies and post-authorisation efficacy studies, signal management, periodic re-evaluation of benefit-risk balance and monitoring of the effectiveness of risk minimisation. Third, regulators can build partnerships, engaging stakeholders and building trust.

Risk management plans consist of a building phase, in which prior knowledge such as disease understanding, patient variability and drug variability is enlarged, important risks and uncertainties are identified and plans for post-marketing data collection are developed; an implementation phase, in which studies and monitoring take place and a delivery phase in which the risk management plan is evaluated to determine if it has reduced important uncertainties, contributed to patient safety and sustained the benefit-risk ratio of the product.

A Post-authorisation Safety Study (PASS) to further investigate a new medicine's safety or efficacy can be a clinical trial or

non-interventional study that is voluntarily developed by industry or required by regulators. Observational PASSs have an established role in studying post-marketing safety; however, they are associated with multiple challenges in design, execution and interpretation. Furthermore, it can be difficult to develop guidelines for these studies, as many challenges are related to the specific drug being studied.

Many registries exist that can provide post-marketing data for analysis such as the British Association of Dermatology Biologic Interventions Register and the British Society of Rheumatology Biologics Register. These registries represent potentially important data sources with the power to deliver high-quality comparative data, appropriately sized cohorts to meet objectives and the potential to raise new issues and inform ongoing reviews. Optimal use; however, requires clear plans for analyses and publication

In addition, early engagement may be key to the successful use of registries to share knowledge of identified and potential risks, help define data capture, timescales for delivery of key results and to build productive relationships.

In database analyses, questions may arise about the possibility for randomisation, the existence of confounders and the adequacy of information. Networks of registries may offer potential solutions to these hurdles and there are a number of opportunities for partnership approaches. New pharmacovigilance legislation provides a legal mandate for EMA and national regulatory agencies to impose or support registries and encourage joint studies. The Joint Action on Cross-Border Patient Registries iNiTiative provides draft methodological guidance and core data elements for registries. Other EU projects include European Reference Networks; RD CONECT, which is an integrated platform for registries and a biobank; the European Research and Infrastructure Consortium, which is a platform for registries, the European platform of rare disease registries and other disease registries such as the network of European cancer registries.

Proactive Monitoring of Safety Signals may lead to the update of risk management plans, evaluation for EMA referral, updated prescriber information, continued ongoing assessment or no recommended action (Figure 18).

The EMA Additional Monitoring Scheme provides for the public listing of new medicines that are subject to supplementary observation for which patients are encouraged to provide additional information regarding any associated side effects.

Periodic Safety Update Reports (PSURs) are a major tool for updating benefit-risk information about new medicines. They represent an opportunity to update a product label and further optimise a benefit-risk profile based on accumulated evidence and emerging information. PSURs are most frequently used for maintenance of labelling information with through variations such as enhanced risk minimisation (e.g. new warnings, monitoring requirements). In some, more exceptional instances, PSURs may be used for new information such as contraindications or refinement of indications.

A Referral is a procedure in which the European Commission, EU member states or industry requests that the EMA determine a course of action regarding concerns over the safety or benefit-risk balance of a medicine or a class of medicines. Safety-related referrals are assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) and then either by the Committee for Medicinal Products for Human Use (CHMP) or, for nationally authorised medicines, by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and all other referrals on human medicines are assessed by the CHMP only. A decision regarding a range of regulatory options

Figure 18. The EMA monitors safety signals for new medicines.

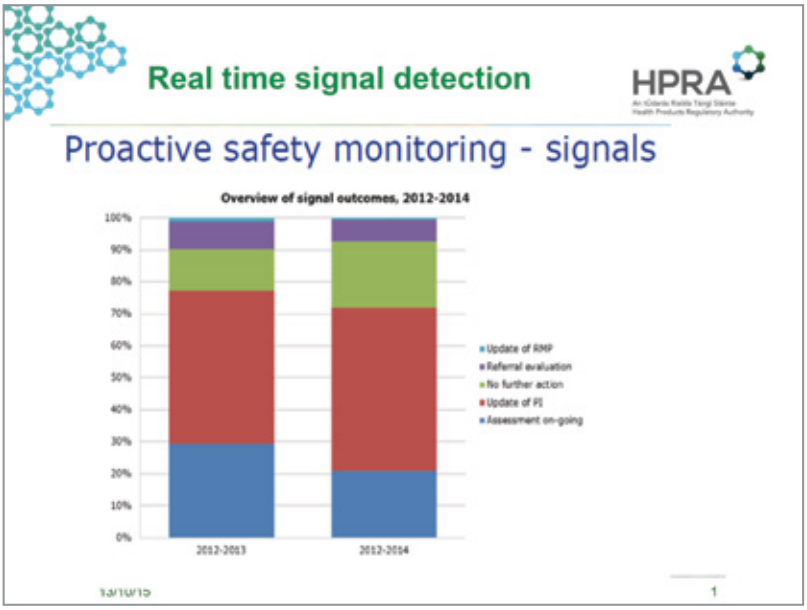

Figure 19. The positive effects of regulatory-stakeholder interactions.

– maintenance, variation, suspension or RMP updates such as further studies is reached within an average of seven months.

Post Authorisation Efficacy Studies (PAES) are an additional regulatory tool to address well-reasoned uncertainties concerning efficacy in justified circumstances. Prior to Delegated Regulation (EU) 357/2014, legal frameworks existed for PAES in the context of Conditional Marketing Authorisation, Marketing Authorisation in Exceptional Circumstance, Marketing Authorisation for Advanced Therapy Medicinal Products, Paediatric Use of a Medicinal Product and Referral procedures. The PAES Delegated Regulation may be required for centrally or nationally authorised products at the time of marketing authorisation when concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed.

PAES may also be required after granting a marketing authorisation if the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly. However, the regulation specifically states that "PAES must not be used as a justification for premature granting of MA or to cure absence of any data required to establish the efficacy of the medicinal product."

Conclusions

Spurred by changes in science, medicine and society, the regulatory toolbox has expanded and EU regulators are incorporating new methodologies, building on best practices and increasing the level of engagement with stakeholders (Figure 19). Risk management plans have become established as a mechanism for planning data collection to reduce uncertainties and manage post-marketing risk and with the use of tools such as post-authorisation efficacy studies have the potential to become benefit-risk management plans. The lifecycle approach is already in operation, with the use of signal management and periodic benefit-risk reviews, leading to better product information. Finally, there is evidence of increasing regulatory and industry experience in responding to emerging information on safety and efficacy throughout the product lifecycle and in communicating updated recommendations promptly.

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What sort of decision is required when the post-approval evidence does not support the initial potential? HTA perspective

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Adaptive pathways and risk management

Health technology assessment (HTA) organisations recommend early access to innovative medicines approved through adaptive pathways when these products promise efficacy and safety. However, when medicines do not live up to that promise, HTA agencies must also develop strategies for their withdrawal, variously termed "managed exit" or "planning for failure." Managed exits can be particularly challenging though, because of the perception by many that the withdrawal of approval is worse than not granting approval at all.

Coverage with evidence development within a managed entry scheme for reimbursement extends beyond risk management plans (RMPs) for regulatory purposes. It is designed to anticipate the sources of potential problems for medicines approved through adaptive licensing and to take preventive or mitigating actions. These problems include the occurrence of unexpected harms such as rare, delayed and severe adverse events or the results of post-marketing analyses that show that health gains produced by a product are inadequate. The managed entry scheme also provides for management of stakeholders and ensures the carry-through of planned processes. Implementation of coverage with evidence development can be complicated; however, by issues such as the addition of alternative therapies to the market, which can make it difficult or impossible to complete planned post-marketing studies.

Regulators and health technology assessors have different expectations for the evidence underpinning market authorisation for new medicines. In granting marketing approval, regulators require evidence that the extent of benefits, otherwise known as the extent of health gains, outweighs the extent of harms whilst HTA agencies and payers require evidence that the extent of benefits outweighs both the extent of harms and the extent of costs. When a product receives market authorisation, including via adaptive pathways, HTA agencies make decisions on the basis of the degree of confidence they have in the potential benefits of the product and they expect that these decisions will be confirmed by analysis of data collected in the post-marketing period. It is important to note that from the HTA perspective, adaptive pathways should be used only if there is confidence that later evidence will be more convincing than the evidence available at the time of market authorisation and these pathways should be used only as a last resort.

Post-authorisation evidence

The Health Technology Assessment International Policy Forum has specified that evidence obtained after market authorisation must be more convincing than the evidence in the original application. Specifically, the research should be focused and based on limited research questions and answers to these questions should be obtained in a reasonable, defined time. In addition, the funding source for the research should be agreed in advance and the collection, analysis and reporting of data should be independent and transparent.[1] It is also important that the findings of the research be unequivocal for all stakeholders and that they be obtained by scientific methods that are fit for purpose. Fit-for-purpose scientific methods often need to detect smaller or later comparative treatment effects that are more meaningful to patients. Such studies usually require randomised designs to minimise selection bias; however, because the product may no longer be at clinical equipoise, such studies should already be ongoing, with recruitment completed and few later treatment departures.

In post-authorisation evidence development, established clinical endpoints should replace surrogate markers, changing in oncology trials for example, from the measurement of progression-free survival to overall survival. However, this research can be by inadequate follow-up or treatment departures such as the use of alternative therapies in the comparator arm after progression, resulting in a lack of evidence for incremental gain over a comparator. In fact, a significant risk with adaptive pathway trials is that a core research question is identified, especially in relation to comparative effectiveness for patients and is never answered. This tells current patients and prescribers that

assessors were not confident in the potential of a drug and perpetuates the lack of confidence for all future patients and prescribers.

The Green Park Collaborative is a multi-stakeholder forum to support dialogue and consensus on methodological standards for clinical research, emphasising the evidence needs of payers and informed by views of patients and clinicians. The group has sought to develop condition-specific effectiveness guidance documents, starting with Alzheimer's disease and a two-part clinical trial design for an Alzheimer's therapy was proposed for consideration by this group. In the first, short-term part of this design, which would be used to inform market authorisation and reimbursement decisions, the ability of a new treatment to achieve a surrogate outcome such as improvement in cognitive scores versus placebo would be assessed at different stages of disease development to determine the stage of optimal use. In the second, long-term portion of the design, individual patient data could be accrued for the treatment's effect on clinical outcomes such as institutionalisation or death (Figure 20).

Adaptive pathways and cost

The confidence discount was established in 2011 through a Memorandum of Understanding between the Commonwealth of Australia and the industry group Medicines Australia:

"The Commonwealth undertakes to introduce a mechanism whereby the Pharmaceutical Benefits Advisory Committee may recommend Pharmaceutical Benefits Scheme coverage at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price. The PBAC will provide advice in relation to sources of uncertainty and specific evidence required to support a subsequent application."

Clause 26 – Managed Entry Scheme

The confidence discount is established with the agreement that there is a clinical need for a medicine but insufficient evidence to justify a preferred price; there is, however, an expectation that later evidence will be more convincing. Thus, a lower price for the medicine is established with the understanding that if later evidence confirms that health gains are associated with the product, the supplier can request a higher price. If the later evidence does not support the expected potential of a product, its use can be continued if the price is still justified as being acceptably cost effective but if the lower price is no longer justified, mitigation is needed. Whilst this agreement places an explicit value on the lack of confidence and avoids perverse incentive signals, it is difficult to reconcile with existing industry incentive models. This agreement has not yet been taken up by industry and is currently being re-evaluated by the Australian Access to Medicines Working Group.

Mitigation strategies

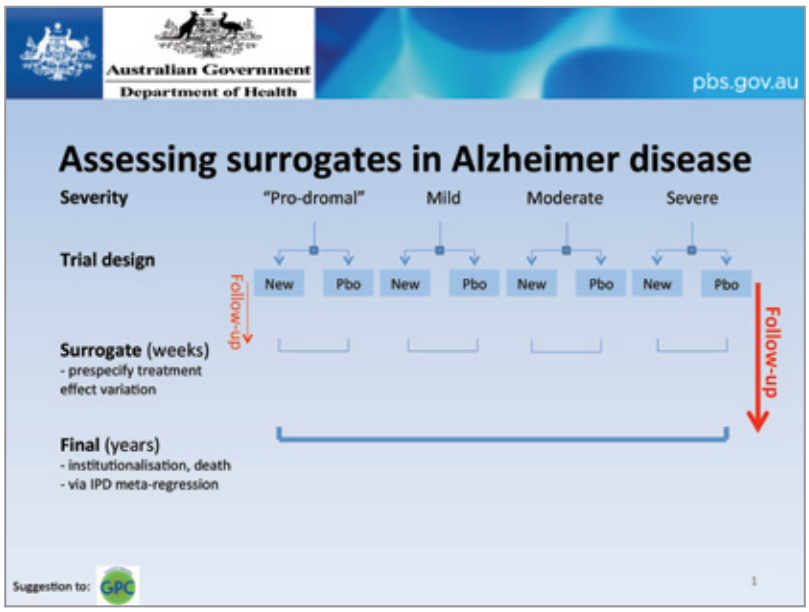
Mitigation can involve partial disinvestment, which may take the form of

- a decrease in price as occurred with cinacalcet, a treatment for secondary parahyperthyroidism that demonstrated effects against surrogate outcomes but did not provide clinical benefits or
- a decrease in the eligible population by removing patients with lesser benefit or increased harm, as occurred with anti-epidermal growth factor receptor (EGFR) antibody treatment for colorectal tumours, which was not effective for patients with a KRAS mutation

Full disinvestment is a more drastic mitigation, in which the product is removed entirely from reimbursement.

Managing stakeholders of adaptive pathways requires full transparency from the outset, including facts, details and results of the arrangement. Because the payer is invested in

Figure 20. A two-part trial design for answering short- and long-term questions about an Alzheimer's treatment.



data collection, partial transparency because of commercial interests is not an option. The goal of adaptive pathway arrangements should be the full involvement of all stakeholders.[2]

Post-authorisation research can produce evidence against which regulators and HTA agencies must develop strategies for action, including

- Evidence that a product is considered harmful; that is, its harms are shown to exceed its benefits and it must be withdrawn.
- Evidence that a product is considered wasteful; that is, its comparative benefits balance comparative harms, so a price advantage is unjustified. In this case, disinvestment exposes inter-individual variation against the population-based assessment of balance.
- Evidence that a product is beneficial and not cost-effective. In this case disinvestment presents challenges for all stakeholders and few if any examples of this exist.
- Evidence that has consequences for other study drugs in the same category. In this case whether regulatory or HTA action is applicable to all products within a category is yet to be determined.

An understanding of the challenges of disinvestment should guide the development of adaptive pathway agreements.

Conclusions

An understanding of the challenges of disinvestment should guide the development of adaptive pathways. The methods used to generate post-authorisation evidence should give greater confidence to evaluators rather than the results. Finally, evaluators should beware of agreeing to research questions that may never be answered and should consider establishing "confidence discounts" to avoid establishing perverse incentives for industry to use adaptive pathways.

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Post-approval evidence: contingency planning – An industry perspective

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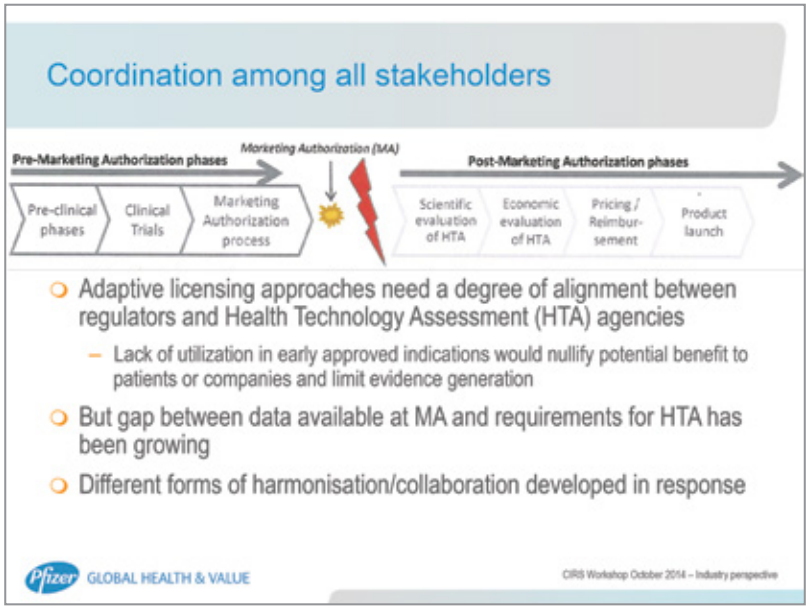
Adaptive approaches to approval by regulatory and health technology assessment agencies expedite the availability of innovative medicines based on less evidence than is typically available with the use of traditional review pathways. This evidence is subsequently significantly supplemented with data in the real-world setting, effectively bridging the gap between efficacy and effectiveness. As Eichler and colleagues have noted, "Adaptive licensing approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions."[1]

Stakeholder coordination is key to implementing adaptive licensing, in particular, alignment of the regulatory and health technology assessment perspective. Discussion should identify common threads, as well as divergences, between these perspectives and seek ways address the differences. Especially important are the questions of what to do if post-marketing evidence does not meet expectations as well as what to do if this evidence exceeds expectations.

Figure 21. Coordinating stakeholder perspectives.



Before an adaptive licensing agreement is made and data collection starts, the criteria for making later decisions need to be established. These criteria will be used to determine the course of action if the post-authorisation evidence for the medicine does not show the expected benefit. Possible decisions in this case include removing the medicine from the market, adjusting access restrictions to better target use to the patients most likely to benefit, changing the price of the medicine and establishing new safeguards to ensure that an extreme remedy like removing the medicine from the market is not necessary. The adaptive licensing agreement should also include a plan of action if the post-market evidence shows a benefit of the expected type but of a lesser magnitude and if the evidence shows that the benefit is greater than expected.

Challenges of stakeholder coordination

Coordinating the perspectives of regulators and HTA agencies can present significant but important challenges, because if HTA agencies do not accept a new drug at the time of initial market authorisation, lack of utilisation would nullify the potential benefit to patients or companies and limit the potential for generating evidence (Figure 21). Unfortunately, however, the gap between the data available at market authorisation and the requirements for HTA acceptance has been growing. Different forms of harmonisation among stakeholders have been developed in response.

A coverage with evidence development (CED) approach may be appropriate for some medicines for which the evidence of clinical benefit that is critical for the reimbursement decision remains incomplete. A CED approach may be applicable when a new technology has demonstrated significant clinical benefit in phase 1, 2 or intermediate phase 3 trials for which pivotal studies have not been completed or in cases in which performing additional randomised clinical trials may be ethically unacceptable. Areas for inclusion or exclusion need to be characterised, including for example, rare diseases, chronic care, oncology, end-of-live diseases and vaccines. Also of interest are drugs with a demonstrable potential to expand their indications.

Evidence requirements

Regulators currently may accept a mix of

randomised controlled trials and real-world data for adaptive licensing review but it remains unknown if reimbursement authorities are willing to accept this level of evidence. In addition, the use of real-world data raises a number of questions including whether the data will be accrued quickly enough, will be available to all stakeholders and are of the appropriate type with the necessary measures in place to track the answers to stakeholder questions. In addition, the development of enough data to meet study requirements for medicines for rarer diseases may present challenges if the number of available patients is not sufficient to add appreciably to the evidence base. Other questions include how firmly stakeholders can commit to specified analyses that may not be state of the art at the time of data collection and how data on healthcare interventions can be used effectively.

An ideal post-approval evidence scenario

In an appropriate scenario for the development of post-approval evidence, reimbursement coverage should be provided at mutually agreed terms while additional evidence is generated over a mutually agreed timeline. Coverage should be agreed at a price reflecting the value of innovation, as if the data had been available at the time of product approval and launch. At the end of the evidence generation period, reimbursement terms may be altered pending an analysis of the expected value at the time of agreement versus the determined value following the analysis of the additional clinical evidence. The schedule of such a review, the analyses to be conducted and the implications should be established a priori by agreement. If the evidence supports the expected value, there should be no price reduction or imposition of additional restrictions to reimbursement. If the target population was initially restricted by agreement for evidence development, reimbursement should be expanded to the full target population. If the evidence is negative, there may be conditions for re-examination or further development of evidence. If the extreme action of drug withdrawal is required, it may be implemented immediately or phased in over time. Less extreme measures would include increased restrictions on the reimbursed patient population, start-stop rules, dosage caps, pricing adjustments going forward and rebates on past sales.

The adaptive licensing agreement should also include a plan of action if the post-market evidence shows a benefit of the expected type but of a lesser magnitude and if the evidence shows that the benefit is greater than expected.

Variability in the terms of the agreement should be based on all the relevant facts and circumstances, such as unmet medical need, the size of the patient population, national and payer priorities and interests, potential use in other populations and data requirements. If withdrawal of a medicine is required, it will be important to consider public viewpoints on the withdrawal. If the product results are good but not as good as originally anticipated, decisions should include consideration of the implications for trust in the healthcare system as a whole and for the stakeholders.

The consequences of withdrawal

If a medicine has to be withdrawn, key considerations must be addressed. Decision makers should consider the interests of patients who are already getting results from a medicine, even if the average result is weaker than expected. To ensure consistency, stakeholders must agree that the evidence for withdrawal is clear and that it supports the desired action under the circumstances. Finally, efforts should be made to protect the reputation of the healthcare system and stakeholders to maintain the public trust, as a withdrawal may reflect badly on the healthcare system.

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How should a company address opportunities to use facilitated regulatory approaches?

Merete Schmiegelow

*Senior Director, Regulatory Policy, Novo Nordisk, Denmark**

*This presentation reflects the 2014 views of the presenter and not necessarily those of Novo Nordisk.

The definition of a positive benefit-risk balance should also be revised to accommodate both a reduction in risk aversion in regulators and health technology assessors and the incorporation of the patient perspective for new medicines having a substantial advantages over current alternatives within unmet medical needs.

A review of license applications for new molecular (chemical) entities and biologics between 1996 and 2010 shows that R&D productivity declined over that interval, while R&D costs rose steadily.[1] In addition, although advances in science have increased the effectiveness of medicines by enabling the identification of active substance(s) having significant advantage(s) in the treatment of appropriate target population(s) with unmet medical needs, current regulatory pathways for marketing authorisation of those medicines have not facilitated more efficient development and/or faster approval times and access to the patients in praxis (Figure 22). Facilitated regulatory pathways for marketing authorisation may help to address these issues and speed up the availability of new medicines offering a substantial advantage in fulfilling unmet medical needs.

The goal of facilitated regulatory pathways is to speed up efficient product development, marketing authorisation and patient access to new medicines with a positive benefit-risk balance and with substantial advantage to any current alternatives serving unmet medical needs and improving public health. The use of these pathways requires iterative phases of evidence gathering to reduce uncertainty. The terminology for proposed alternative pathways has not been aligned and includes Adaptive Licensing, Staggered Approval, Progressive Licensing and the European Federation of Pharmaceutical Industries and Associations' (EFPIA's) Medicines Adaptive Pathways to Patients (MAPPs). Today (2015), the EMA uses the term Adaptive Pathways.

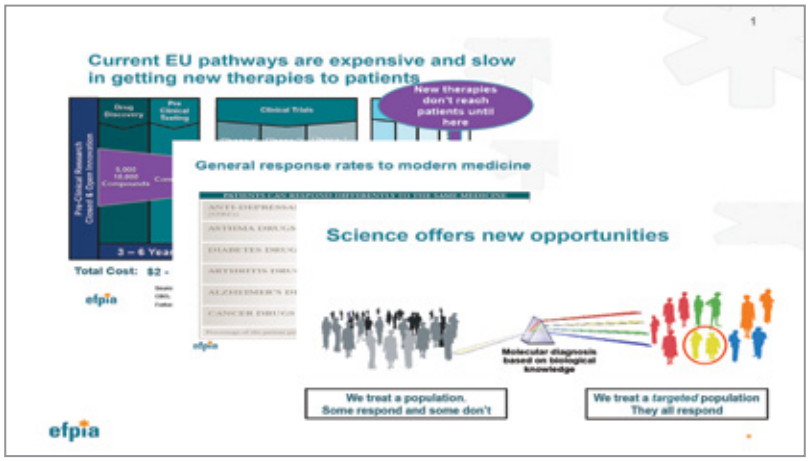

Figure 22. Patient access to innovative therapies can be slowed by regulatory approval processes.

The regulatory pathways for expedited development and approval processes for medicines with substantial advantage within unmet medical needs in the EU are 1) Conditional Approval and 2) Accelerated Assessment. In the US there are four pathways used for this purpose: 1) Accelerated Approval is similar to the EU Conditional Approval and 2) Priority Review is similar to the EU Accelerated Assessment; 3) Fast Track Designation and 4) Breakthrough Therapy; however, do not have similar pathways in the EU.

Key challenges and recommendations for facilitated regulatory pathways for medicines with substantial advantages to current alternatives on the market within unmet medical needs*

A number of key challenges face expedited regulatory pathways and adjustments to meet these challenges are proposed. Among these recommendations are:

- Industry should have the option to use non-standard EU regulatory pathways, rather than making these mandatory in case assumptions are fulfilled.
- Unmet medical needs should be more precisely defined and should take patient perspectives into account.
- A new medical Marketing Authorisation Application (MAA) should be developed to include provisions for Type 2 variations of

new indications and extensions for medicines with substantial advantages compared with current alternatives on the market and within unmet medical needs.

- Currently, EU Conditional Approvals are restricted to therapies for serious, life-threatening, emergency situations and orphan drugs. Other conditions should be added for medicines that appear to demonstrate a substantial clinical advantage relative to current alternatives on the market.
- The definition of a positive benefit-risk balance should be revised to accommodate both a reduction in risk aversion in regulators and health technology assessors and the incorporation of the patient perspective for new medicines having a substantial advantage over current alternatives within unmet medical needs.
- Although conditional approvals covering medicines with substantial advantages within unmet medical needs allow for a less complete data package, the standards for these data are unchanged. Steps should be taken to ensure that requirements for the entire data package including pre- and post-approval are not greater or of longer duration than those required for a normal MAA and that flexibility for clinical trial design is enhanced.
- More transparent criteria are needed both for justifying accelerated assessment and for decisions by the Committee for Medicinal products for Human Use (CHMP) to withdraw a conditional approval.
- The clock for patent expiration could be reset once a full data package for a product is approved to accommodate industry concerns about intellectual property rights and patent expiration.
- Health Technology Assessment (HTA) bodies and payers should be ready to acknowledge appropriate price and reimbursement levels from the time of first market authorisation and should consider increases in prices and reimbursement as more data for conditionally approved medicines accumulate.
- There has been considerable discussion of how products approved under Adaptive Pathways should be prescribed. Experts should always supervise the use of these products. Although, it may be impossible to prevent off-label use of products, it may be easier to monitor with Adaptive Pathways.

Conclusion

It is recommended that for new medicines with a substantial advantage compared with current alternatives within unmet medical needs, the criteria for using the Conditional Marketing Authorisation and Accelerated Assessment in the EU should be adapted or deleted and replaced with Adaptive Pathways, taking into account the perspectives of HTA bodies, organisations that issue clinical treatment guidelines and patients.

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How do HTA use models and simulation to extrapolate efficacy data and how these could be used effectively in a facilitated or adaptive pathway?

Dr Sarah Garner

Associate Director, R&D, National Institute for Health and Care Excellence, UK

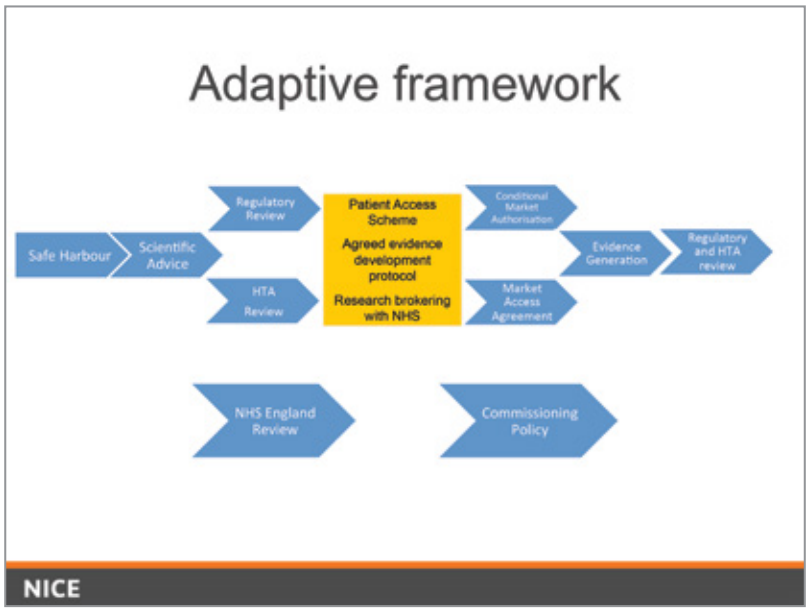
NICE and non-RCT evidence

The long-established pathway for drug development proceeds from pre-clinical research through phase 2a, 2b and 3 studies, followed by regulatory review and a decision on marketing authorisation. The addition of health technology assessment agency and reimbursement organisation review has added additional, different requirements and perspectives to medical decision making, after which real-world data are gathered in phase 4.

The National Institute for Health and Care Excellence (NICE) has specified HTA analyses may require evidence from experimental and observational sources other than randomised clinical trials (RCTs), for situations in which RCTs are unavailable and to supplement information from RCTs when they are available. Despite problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and endpoint in some non-RCT research, data from non-RCT sources are needed, in particular to estimate relative treatment effects over longer time horizons or to measure particular outcomes that have not been included in RCTs. Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn. Whatever the sources of the evidence available on a particular technology and patient group, they will be integrated into a systematic review with explicit, valid and replicable methods.

NICE experience with non-RCT evidence includes it use for the appraisal of retigabine for adjunctive treatment of partial onset seizures in epilepsy, because clinical trials mandated forced titration, rather than titration tailored to the individual patient as is seen in practice. Non-RCT data were also used for estimating clinical efficacy through modelling such as occurred in the appraisal of insulin pumps for diabetes in which an estimate of clinical efficacy was derived from the Insulin Pumps Clinical database, which was much larger, of longer duration and more representative of people likely to be considered for therapy in routine clinical practice than the populations in the RCTs available. Appraisals have also been conducted through the use of non-RCT data for long-term use as was done for alitretinoin for eczema and observational data as was done for omalizumab for severe persistent allergic asthma, when these data were used for extrapolation of treatment effect and for health-related quality of life in children.

Figure 23. The proposed adaptive framework



Frameworks for assessment

In the current framework for pharmaceutical decision making, there is very little communication between regulatory authorities and HTA agencies. The regulators make their decision first, after which an HTA decision is reached. Only then is a final determination made as to whether and under what circumstances reimbursement agencies such as the National Health Service will pay for the product. Adaptive licensing (AL) presents an opportunity to re-arrange the framework for review and decision making to improve the process (Figure 23).

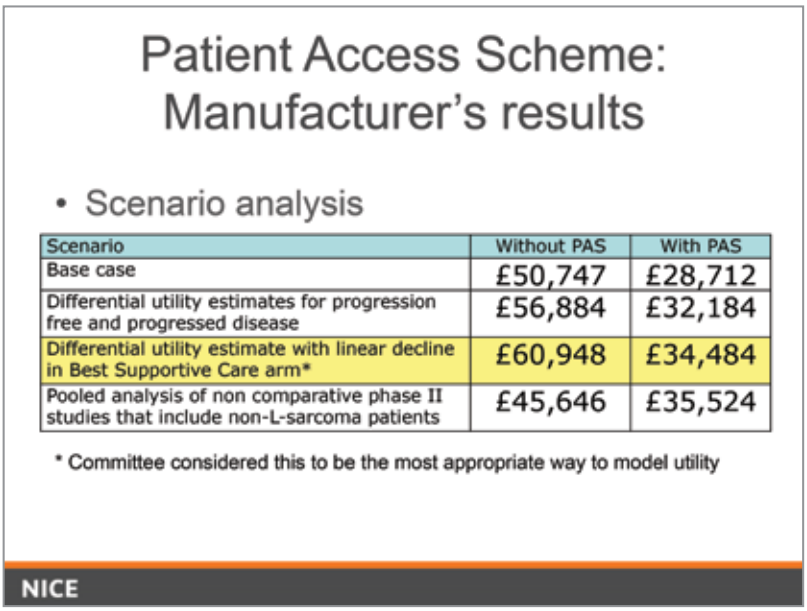
The Adaptive License process could begin with a safe harbour for discussions amongst stakeholders, followed by the development of scientific advice. Regulatory and HTA review

then occur simultaneously, leading to a Patient Access Scheme, a protocol for agreed evidence development and research brokering with the payer. Once these processes are complete, a Conditional Market Authorisation and Market Access Agreement are issued and post-marketing evidence generation begins. At appropriate times, regulators and HTA agencies conduct follow-up reviews.

Highly specialised technologies

Highly specialised technology (HST) evaluations are recommendations on the use of new and existing highly specialised medicines and treatments for very rare conditions. The manufacturer or sponsor of the technology and consultants are invited to provide an evidence submission on the potential clinical effectiveness and value for money of a treatment. NICE commissions an independent academic centre to technically review the evidence submission and prepare a report. An independent advisory committee considers the evaluation report and hears evidence from nominated clinical experts, patients and carers. The Evaluation Committee makes its provisional recommendations in the Evaluation Committee Document. Consultants and commentators have four weeks to comment on the ECD a, final evaluation is determined and guidances is produced. The criteria for decision-making include the nature of the condition, the impact of the new technology, the cost to the NHS and Personal Social Services and the value for the money. Also important are the impact of the technology beyond direct health benefits

Figure 24. Modelling for utility in a Patient Access Scheme for trabectedin.



. . . data from non-RCT sources are needed to estimate relative treatment effects over longer time horizons or to measure particular outcomes that have not been included in RCTs.

and the impact of the technology on the delivery of the specialised service.

Early Access to Medicines Scheme

The Early Access to Medicines Scheme (EAMS) was initiated in the UK in September 2014 for medicines for life-threatening or seriously debilitating conditions, without adequate treatment options, representing a high unmet need. The medicinal product must offer promise that it is likely to offer benefit or significant advantage over and above existing treatment options and its potential adverse effects are likely to be outweighed by benefit. EAMS is primarily aimed at medicines that have completed phase III trials and may be applied to completed phase II trials in exceptional circumstances. EAMS has elicited a number of questions including those that centre on opportunities for data collection and excess treatment costs and who should pay for them, how much time there will be between market authorisation and market access and the exit strategy if needed after accrual of post-authorisation evidence. EAMS will require considerable upscaling by the NICE Appraisal Committee and it may be necessary to develop new skills to deal with the volume and types of data that will be gathered.

Patient Access to Medicine Scheme

The National Health Service Patient Access to Medicine Scheme (PAS) is designed to ensure that patients can gain access to medicines that are likely to have a high cost and that are not likely to be considered cost effective by payers. In this two-part model, a discount of 12.5% on the list price of the product reduces financial uncertainty at the time of approval and possible future rebates are linked to the performance of the product in a future head-head comparison against the gold standard competitor, providing the payer with a long-term assurance of effectiveness.

Dr Garner concluded by providing two examples of NICE use of modelling and Patient Access Scheme discounts in the appraisal of promising medicines. For trabectedin in soft-tissue sarcoma, one RCT was carried out in patients

after failure of previous chemotherapy including anthracyclines and ifosfamide using two different dosage regimens with no placebo or comparator. Pooled results from three previous non-randomised phase II studies suggested more trabectedin activity and data were for a small number of patients, so comparator data (best supportive care) were derived from studies in EORTC STBSG database. The NICE committee attempted three different types of scenario analysis before deciding on the most appropriate way to model utility for the product, resulting in positive NICE guidance (Figure 24).

Pazopanib received conditional marketing authorisation for the first-line treatment of advanced renal cell carcinoma and for patients who have received prior cytokine therapy for advanced disease. The conditional licence was linked to the provision of further data supporting the efficacy and safety of pazopanib compared with sunitinib and a pooled analysis of data two other studies. An indirect comparison of these trials produced a survival curve that resulted in positive NICE guidance.

How do patients perceive early access schemes and adaptive licensing measures – with hope or concern?

Alastair Kent

Chair of Rare Disease UK and Director of Genetic Alliance UK

Genetic Alliance UK citizen jury and quantitative survey

Genetic Alliance UK is an alliance of approximately 180 patient organisations ranging from the large British Heart Foundation to small organisations supporting families with very rare conditions. These organisations represent people with conditions that are intractable, often incurable, life-limiting and sometimes progressive and quickly lethal. The patients with these diseases are the only involuntary partners in the process under discussion and the only way they can expect to achieve any improvement in the quality or quantity of life is through high-quality biomedical research. This research must be accompanied, however, by a framework that translates research outcomes into interventions that can be applied to the patients systematically, sustainably, effectively and affordably, including a regulatory system that is fit for purpose.

The Genetic Alliance UK recently completed a benefit-risk project involving a citizens' jury of patients with life-limiting diseases and their caregivers and a quantitative survey to obtain the views of more than 600 individuals in five countries. The results of this project indicated that patients did want to have their voices heard, that their views on the benefits and risks of new medicines may differ significantly from regulators and that they wanted those views to exert a greater influence in determining the benefit-risk balance.

Although patients have no interest in measures that do not work, it is important to recognise that a medicine that only offers a 10% chance of success may represent a valuable improvement if the probability of failure otherwise is 100%. Patients would also like to see a greater emphasis on the psychological and social aspects of their disease, including the quality and quantity of life.

The study also revealed that patients do want to support and participate in research but they want trial designs that fit their lives and help managing the impact of an investigative regimen such as planning study visits outside of rush hours in public transportation, help paying for transportation and assistance in child care arrangements. Respondents indicated that research should focus on what is important, rather than on what can be counted, for example, determining how to preserve the dignity and independence in daily activities of a patient with Alzheimer's disease rather than only trying to maintain that person's intellectual capacity.

The small patient populations which are implicit in rare diseases and which often make it difficult or impossible to conduct a gold-standard, double-blind, multicentre, randomised, placebo-controlled clinical trial may change the paradigm of clinical research. Since the European Medicines Agency Orphan Medicinal Products designation took effect in 2000, eight to ten orphan drug approvals are granted each year,

a rate that needs to be increased to meet the needs of 6000 orphan diseases. Increasing the rate with the current approval system may not be achievable, however, because it will not be possible to get the evidence to demonstrate quality safety and efficacy in a way that is affordable and sustainable.

Adaptive licenses strengths and challenges

The current regulatory system, therefore, may be considered to be "broken" for these types of diseases and adaptive licensing (AL) may present an alternative. An AL approach has a number of strengths including the fact that it allows people with unmet health needs and life-limiting conditions to participate in the development of medicines at an earlier stage, permitting a focus on what matters to patients. Furthermore, AL allows for the development of unexpected insights, both good and bad and creates an opportunity for a genuine partnership across healthcare stakeholders. Potential deal-breakers for these pathways, however, include a lack of willingness on the part of regulators and HTAs to participate in the system, industry to expose assets and clinicians to accept the additional burden of new trials. In addition, Rumsfeld's "unknown unknowns" arises at an earlier stage of development and stakeholders must face the prospect of negative public media attention if products marketed under AL have undesirable effects.

The AL approach will also create effects on health technology assessment, pricing and reimbursement, including the fact that less data will be available when agreements and decisions are made. In addition, because drugs approved through AL will already be on the market in an evolving situation, valuing and pricing a drug will become more complex. Finally, political sensitivities will be an important consideration

Adaptive licensing . . . allows for the development of unexpected insights, both good and bad and creates an opportunity for a genuine partnership across healthcare stakeholders

and patient engagement and advocacy will be at the forefront along with the necessary transparency regarding costs and the rationale for reimbursement decisions.

Early Access Schemes strengths and challenges

Early Access Schemes (EASs) also have strengths including possible health gains, the potential for industry to rescue assets, the capacity to produce breakthroughs in intractable conditions and the enhancement of patient participation in decision making. Potential deal-breakers with an EAS include the questions of who pays for a drug and how to monitor and evaluate it, the later channelling of EAS-approved medicines into the standard regulatory system and the continuity of these medicines in a clinical development context. In addition the use of EAS may be complicated by the vulnerability of desperate patients and the damage to proper clinical development, particularly in small populations with rare diseases.

The use of both AL and EAS requires transparency, early stakeholder engagement, the consent of patients, robustness in modelling and challengeable findings. There must also be clear, coherent media and public communication to avoid unjustified attacks on either the pharmaceutical industry or regulators and strong political support.

What do HTA bodies need to see in order to provide a decent added benefit rating so that industry can achieve appropriate prices and be incentivised to use an adaptive approach?

Professor Adrian Towse

Director, Office of Health Economics, UK

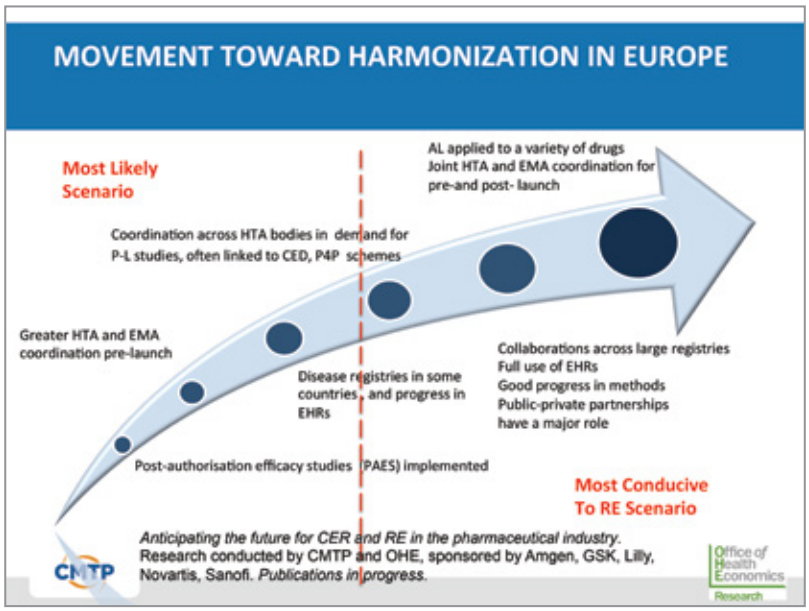
Expected net product value and adaptive licensing

For the pharmaceutical company, the expected net product value (eNPV) of a drug depends on revenues, costs, success and discount rates and the opportunity cost of capital including the timing of when the costs are incurred. The potential for adaptive licensing (AL) pathways to improve eNPV depends on prices, volumes, costs, timing and success rates. However alternatively, with the use of current regulatory pathways the economics of drug development are becoming increasingly unsustainable.

Modelling suggests adaptive licensing can improve eNPV and increase the overall numbers of patients treated compared with traditional licensing and it may also have the opposite effect. Baird and colleagues compared actual and modelled clinical development and licensing programmes for three case studies with metrics that were incentives to industry, regulators, patients and prescribers including, changes in patient access, numbers of inappropriately treated patients and eNPV.

- In the case of Zelboraf for skin cancer, the traditional route to marketing would have yielded an eNPV of US$23 million, whereas the eNPV for an adaptive pathway would have been US$30 million and the eNPV for fast track, which was the actual pathway taken, was US$34 million. Although the product launch date would have been the same for both the fast-track and adaptive approaches, the decreased eNPV for the adaptive pathway was due to the associated requirement for continuous planned data collection.
- For Gilenya for relapsing multiple sclerosis the actual development pathway realized an eNPV of US$127 million, which was not as great as the US$169 million a more adaptive pathway would have yielded from smaller, quicker trials and a narrower authorisation with later expansion of the label.
- Acomplia for obesity produced negative eNPVs for both the actual pathway taken (- US$73 million), which resulted in a lack of approval in the US and withdrawal after two years in the EU and the modelled adaptive pathways (-US43 million and -US$16 million). Differing degrees of adaptivity, post-market surveillance and controlled off-label adherence maintained over the product lifecycle would have kept the product on the market with costs accrued for monitoring.[1]

Figure 25. Future scenarios for generating relative effectiveness evidence in Europe.



Conditional market authorisation and post-authorisation safety studies

In addition, conditional market authorisation does not seem to be working in the way that was intended and some post-authorisation safety studies may not be a good use of resources. The 2014 Escher report, which cites survey results of members of the European pharmaceutical industry, states that conditional market authorisation is perceived as a rescue option for regulators and companies, rather than as a prospectively planned pathway to provide early access. Furthermore, it is not clear that post-authorisation safety studies represent good value. Of the cohort of 47 new active substances approved in the EU in 2007, at least one post-authorisation safety study was requested at market entry for 22 products and although the costs of conducting these studies appear substantial, they were not a source of safety information in subsequent license

listings. The report goes on to stress the need to understand the business rationale for the use of new regulatory pathways. "'Adaptive licensing has been discussed for a long time with very little action . . . new regulatory pathways will only be useful if they are considered in a holistic approach including health technology assessment (HTA) and payers."[2]

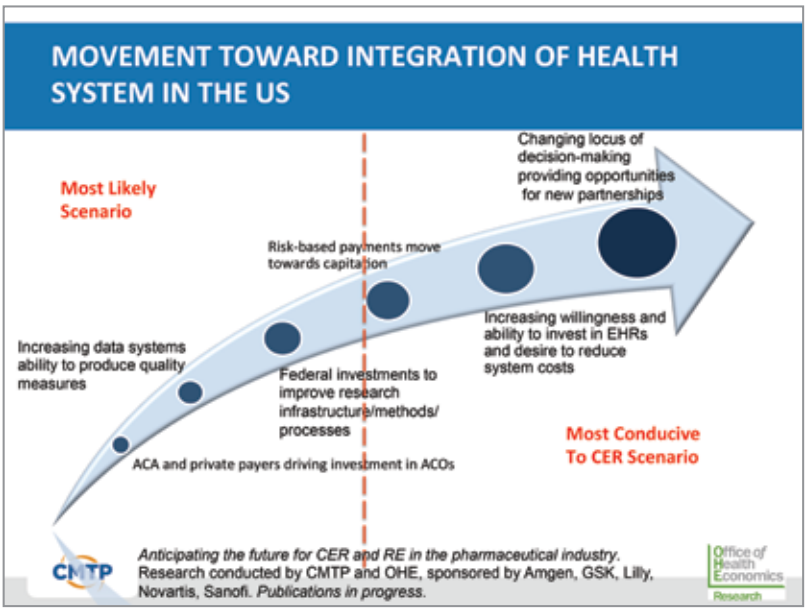
Industry is interested in adaptive pathways but is concerned about the lack of HTA and payer buy in, recognising that a coordinated European Medicines Agency- and health technology assessment-invested approach is needed.

The role of managed entry agreements and performance-based risk sharing

Managed entry agreements (MEAs), which give access to new technologies when traditional reimbursement is not appropriate, should take the form of a formal written agreement among stakeholders. These should, clearly identify the rationale for the agreement, aspects to be assessed, methods of data collection and review and the criteria for ending the agreement.

The three approaches to MEAs are management of the uncertainties of clinical outcome and cost-effectiveness; management of utilisation to optimise performance and management of budget impact and the rationale for using these approaches and their advantages and disadvantages differ. The 2013 report of the ISPOR Good Practices for Performance-based Risk-sharing Task Force provided the specific aspects of the three MEA management

Figure 26. Future scenarios for generating relative effectiveness evidence in the United States.



Industry is interested in adaptive pathways but is concerned about the lack of HTA and payer buy in, recognising that a coordinated European Medicines Agency- and health technology assessment-invested approach is needed.

approaches. In the management of budget impact, a cost-sharing arrangement covers budget and utilisation capping, discounts and price for volume. The uncertainties of clinical outcomes and cost effectiveness and utilisation to optimise performance are managed with performance-based risk-sharing arrangements, one to manage real-world utilisation through performance-linked reimbursement and a second to provide evidence regarding decision uncertainty, in which coverage is provided with evidence development.[3]

The study design for MEAs and performance-based risk sharing has to address uncertainties. Transaction costs, mostly evidence collection, are a key barrier and if the health gain is greater than expected, the payer should expect to pay a higher price; however, discounts should be withdrawn or increased, rather than prices changed. Retrospective price adjustments will be an issue in MEAs and the ability to manage differential pricing across indications will be key to a successful adaptive pathway. Uncertainty matters only if the decision makers can do something about it. Performance-based risk agreements allow assessors to concentrate on making sure they have got the correct expected value.

Future scenarios for the EU and the US for generating evidence for relative effectiveness

According to research performed by the Office of Health Economics and the Centre for Medical Technology Policy, the most likely scenario for the future involves the implementation of post-authorisation efficacy studies, establishment of disease registries and progress in electronic health records, greater pre-launch coordination between HTA and EMA and coordination across HTA bodies in the demand for post-launch studies. The scenario most conducive to determining relative effectiveness involves both pre- and post-launch coordination between HTA and EMA, collaborations across large registries, with full use of electronic health records, good

progress in methods and a major role for public-private partnerships. The key drivers for these events are HTA coordination, regulatory innovation, regulatory/HTA interaction, data availability and the evolution of methods. (Figure 25).

In the US, the most likely scenario for the future has the Affordable Care Act and private payers driving investment in accountable care organisations, increasing data systems ability to produce quality measures, risk-based payments moving towards capitation and federal investment to improve research infrastructure, methods and processes. The scenario most conducive to comparative effectiveness research will require changing the locus of decision-making, providing opportunities for new partnerships and increased willingness to invest in electronic health records and a desire to reduce systems costs. The two critical points that affect the situation are that there is currently no significant regulatory reform and no interaction between the FDA and payers. (Figure 26).

Conclusions

The commercial model for an adaptive pathway requires coverage with evidence development in the form of managed entry agreements and also needs performance-based risk sharing and pricing and the use of flexibility. Adaptive pathways require a transformation in evidence collection costs through electronic health and disease registries and methods evolution. Regulatory, health technology assessment and industry interactions post-launch will be key and use of post-authorisation efficacy studies in the EU has to be linked to managed entry and performance-based risk sharing requirements. Although this may be complex, the alternatives to adaptive pathways are not likely to succeed.

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Is there a viable commercial strategy for the use of adaptive approaches, now and in the future?

Dr Jens Grueger

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Adaptive licensing (AL) holds great promise for all stakeholders including faster patient access to new therapies, a focus on areas of high unmet medical need, innovative trial designs that include real-world data and earlier engagement with stakeholders. AL also allows for de-risking of the development programme and carries the potential for a reduction in development cost.

Oncology in personalise healthcare: a problem statement

In the area of oncology, there are increasing delays in approval and reimbursement in Europe partially because of the difficulty in completing mortality trials after a significant progression-free survival benefit has been demonstrated. In addition, drug manufacturers are unable to achieve an acceptable price based on surrogate oncology endpoints, even where there is a scientific rationale that this will translate into a benefit in overall survival. Furthermore, extrapolation from later stages of disease to earlier stages is not accepted, as in the example of pathologic complete response in neoadjuvant treatment of breast cancer.

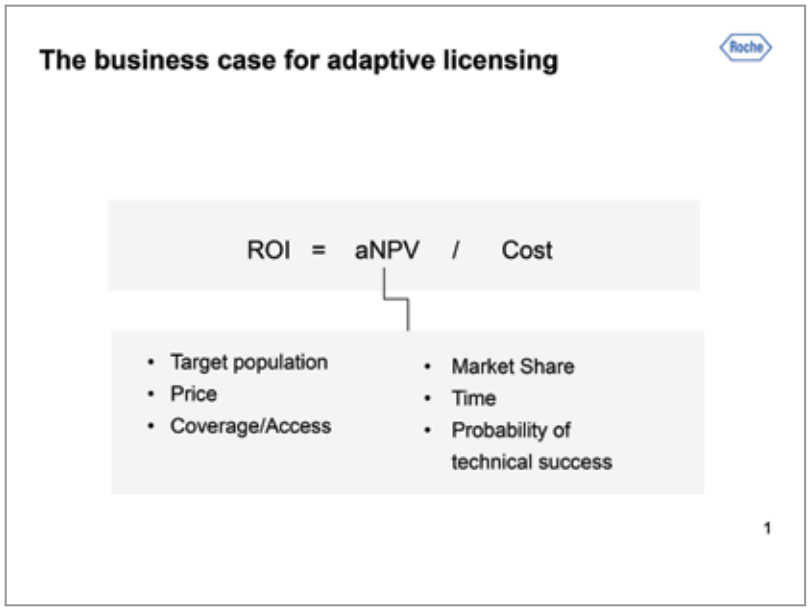

Figure 27. Factors driving return on investment for medicines.

An efficient infrastructure to collect utilisation and outcomes data after launch is also required and treatment registries. . . can fulfil this function . . . Treatment registries can also be used to manage the entry of medicines . . .

Other specific issues center on the demonstration of value. Cancer medicines are typically developed in late-stage metastatic disease where clinical benefits can be demonstrated quickly and although metastatic disease is the most difficult to treat, successful treatment has the least value from a payer perspective, because survival is extended by relatively short periods. Whilst extending the indication to early disease may demonstrate the greatest value, it can take years to demonstrate overall survival benefits in that setting. Another key issue is the absence of flexible pricing mechanisms; which is especially serious because oncology medicines for metastatic disease are usually introduced at a very aggressive price point.

Currently, there is a great deal of interest in the concept of survival tails in which clinicians are able to extend the survival of a significant proportion of patients through the combination of targeted medicines and immunotherapies. This may be an important area in which to test adaptive approaches, from both a scientific and commercial perspective.

The business case for adaptive licensing

Return on investment (ROI) is the adjusted net product value (aNPV) divided by the cost of development. In the case of oncology drugs, the aNPV is the product of the target population, price, coverage and access, market share, the time it takes to get to market and the probability of technical success (Figure 27).

With earlier engagement of stakeholders under AL, the likelihood of achieving coverage and access at an appropriate price can be improved. The questions of whether costs will be reduced in clinical development and what proportion of costs will be shifted to the post-approval stage remain to be resolved.

Commercial requirements and issues for adaptive licensing

To make AL work from a commercial perspective,

there must be early dialogue with regulators and health technology assessment (HTA) agencies and payers. Points of discussion must include the acceptability of study endpoints and the patient population, a lifecycle perspective on evidence and value and mechanisms to adjust price on the basis of value.

An efficient infrastructure to collect utilisation and outcomes data after launch is also required and treatment registries like those of the Agenzia Italiana del Farmaco (AIFA) in Italy and the Systemic Anti-Cancer Therapy database in the UK, can fulfil this function with their potential to add disease- and treatment-specific endpoints with a focus on early response, progression and toxicity. Treatment registries can also be used to manage the entry of medicines but disinvestment procedures also have to be established to manage a drug's exit, if needed.

In the collection of real-world data, it will not be possible to monitor off-label use in every jurisdiction in which a drug is licensed; therefore agreement is needed on reference countries to be used for evidence generation. In addition, there must be accord on the appropriate identification of evidence needs, with care taken to distinguish parameter uncertainty from decision uncertainty.

Management of price over the lifecycle of a drug should take into account price by indication and managing uncertainty through selective discounts and rebates. In this regard, it is useful to look at cost-effectiveness in different phases of disease and overall. For example, the initial price of curative treatments with long survival tails should be set high with long-term follow-up to confirm cures.

Expectations from adaptive licensing pilot

The results of pilot tests of AL show that this approach is well aligned with development in oncology. A distinct population for initial approval can be defined through biomarkers. Existing treatment registries can assist in the development of clear explanations of post-approval real-world data in the initial approved population. Finally, there is a clear approach to expansion into other populations post-approval, using biomarker-defined populations in other cancers, earlier stages of the disease or both.

UK Early Access Scheme (EAMS): What is it and how will it work?

Dr David Jefferys

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European Product Safety, Eisai Europe Ltd, UK

Early Access to Medicines Scheme background

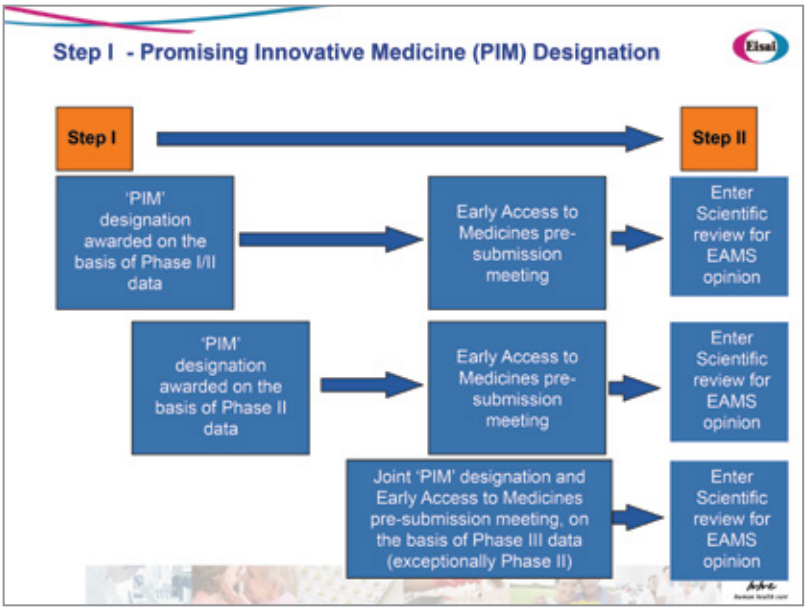
The Early Access to Medicines Scheme (EAMS) – which may become a precursor for wider schemes in other parts of Europe – is an example of adaptive licensing. EAMS is set against an international background of facilitated regulatory pathways such as the US FDA Breakthrough Therapy Designation and the Seskadake initiative in Japan and issues of early access surrounding the response to the Ebola virus.

Amidst rising demands for patient inclusion in the development and decision-making processes for new medicines, implementation of EAMS may help to overcome the public perception that regulatory agencies and systems are risk averse and address the European Parliament's medical expert panels' conclusion that the views of patients and their families have not been taken into account.

Arising from the Ministerial Industry Strategy Group's (MISG) medicines initiative scheme, the goal of EAMS is to provide earlier access to drugs that fulfil an unmet medical need among patients with life-threatening or seriously debilitating conditions without adequate treatment options, for which medicines are being developed that cannot yet be made available as licensed treatments. Candidate drugs must have a positive benefit-risk profile and must represent a significant advance in treatment. This would bring the decision point for these medicines to the end of phase 3 or, in very exceptional cases, to the end of phase 2B, making potentially life-saving treatments available one year earlier than is possible with traditional review.

The MHRA launched the scheme on the 7 April 2014 with a dedicated EAMS webpage (https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams), coordinator and guidance. The scheme is voluntary and the opinion from MHRA does not replace the normal licensing procedures for medicines.

Figure 28: PIM designation process (Step I)



EAMS Step I

A Promising Innovative Medicine (PIM) designation is an early indication that a medicinal product is a promising candidate for the EAMS and is a prerequisite to enter the programme. If data from early stages of clinical development indicate that a medicinal product is likely to demonstrate significant benefit for patients in life-threatening or seriously debilitating conditions, the sponsoring company may apply to be granted PIM designation to the Medicines and Healthcare Products Regulatory Agency (MHRA) at entry into phase 2 development.

The PIMS designation is issued after an MHRA scientific meeting and is based on non-clinical and clinical data available for the product in a defined disease area. The application, in addition to presenting administrative and product-specific information and brief details of current pharmaceutical development, must also include three criteria: details of the condition and details of the high unmet need; evidence that the medicinal product is likely to offer major advantage over methods currently used in the UK; and evidence that the potential adverse effects of the medicinal product are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit-risk balance. After review by an assessment team, a one-hour, face-to-face meeting will be scheduled, normally within 4 weeks. The MHRA will not publish either positive or negative

designation decisions. A fee will be charged, based on the cost-recovery model. (Figure 28.)

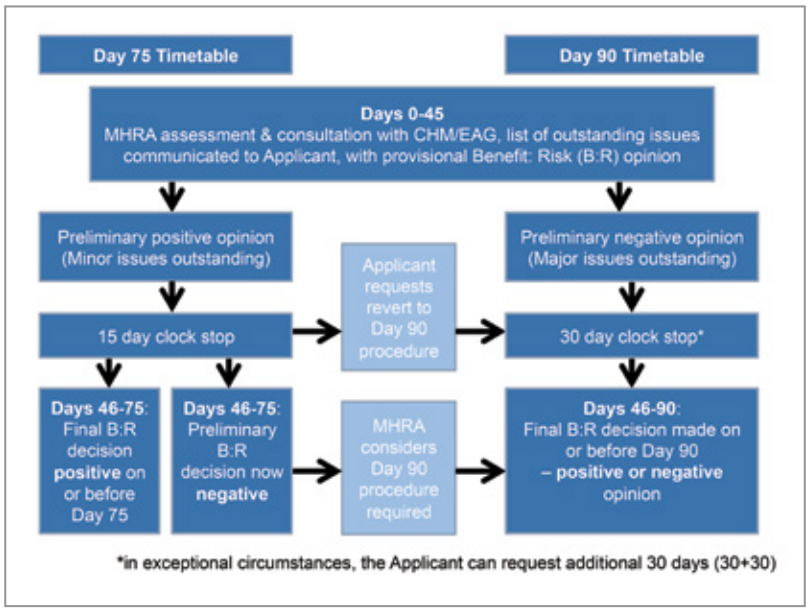
EAMS Step II

After a pre-submission meeting, the applicant, at its own discretion, may proceed towards receiving an EAMS Scientific Opinion, according to a 75-day or 90-day timetable (Figure 29). The timetable represents a faster cycle than the 150- to 210-day cycle in the EMA centralised procedure. The 75-day timetable applies if the preliminary opinion is positive and the 90-day timetable applies if the preliminary opinion is negative.

This opinion process describes the benefits and risks of the medicine; makes a public assessment report (PAR) available on the MHRA website; and provides more detailed product information in an EAMS Treatment Protocol, setting forth conditions for use and ensuring safe and efficacious use of the product. Negative opinions will not be published.

The protocol also provides information for the patient and physician and establishes a requirement for pharmacovigilance. The scientific opinion requires a fee based on the cost-recovery model and is valid for one year, with renewals as necessary and appropriate. It is expected that the EAMS protocol will have a two-year lifespan with possible extension to three years, while the drug proceeds through the normal regulatory process. During the period of validity for the EAMS Scientific Opinion, the opinion holder is expected to provide periodic updates and the MHRA will amend the PAR and the treatment protocol as necessary.

Figure 29. Obtaining a scientific opinion (StepII)



The concept underlying EAMS is that industry gains experience in the marketplace with real-world data in very specialised circumstances.

The opinion holder should submit relevant quality, safety and efficacy data generated during the EAMS opinion during the marketing authorisation application. While the EAMS opinion is in effect, Commissioned Research Groups under the National Health Service in the UK draw up treatment protocols. The PIM is available only through designated specialist centres and the applicant is responsible to provide the PIM and any special diagnostics free of charge.

Conclusions

The goal of EAMS is to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The MHRA is responsible for the scientific aspects of the scheme and the scientific opinion will be provided after a two-step evaluation process. Detailed guidance and templates can be found on the EAMS webpage and support regarding any aspect of the scheme is provided through the EAMS coordinator.

The concept underlying EAMS is that industry gains experience in the marketplace with real-world data in very specialised circumstances. EAMS provides a way forward to bringing the decision point for innovative and needed medicines earlier into phase 2B and has opened the door, allowing earlier control points.

How to move from current mindset to an "adaptive mindset":

What do companies, regulatory and HTA agencies and payers need to adopt?

An HTA perspective

Dr Sarah Garner

Associate Director, R&D, National Institute for Health and Care Excellence, UK

Health technology assessment (HTA) agencies are extremely diverse. Some are gatekeepers, some are recommenders and others are decision makers but regardless of their roles, there are a myriad of opportunities for them to support innovation by determining which products will actually provide benefits, providing scientific advice and infrastructure for those products and supporting them through the system. Some HTA agencies have a positive attitude about adaptive licensing and already have the necessary building blocks to support this type of development. However, to determine if there will be support for this or any type of research and approval process and payment for access to new medicines, there needs to be greater and earlier engagement and alignment among healthcare systems and health technology assessment agencies.

When confronted with the uncertainties surrounding some new medicines, particularly those approved through adaptive licensing procedures, HTA agencies frequently request additional research. The challenge lies in the fact that many committees that have been convened for HTA decision making may not necessarily have the necessary skillsets to design research projects. For example, HTA decision makers often request head-to-head trials between two drugs with very similar efficacy results, necessitating unfeasible trials of prohibitive size and expense to demonstrate potential differences.

The users of medicines need to be especially and explicitly aware of the additional uncertainty surrounding medicines that are approved earlier.

Ethical conundrums are among the other issues that healthcare assessment agencies face in consideration of the need for new and different types of research. In May 2014, the Centre for the Advancement of Sustainable Medical Innovation (CASMI) held a Workshop on the topic of Ethics in Adaptive Licensing. The key takeaway message for this meeting was the potential collision of healthcare and research represented by the necessary equipoise in randomised trials versus the ethics of patient care.

Patient participation in risk taking is another issue in adaptive licensing trial design. Patients and trial subjects need to be engaged in conversations regarding the amount of risk they are willing to undertake and what trade-offs they would consider to be participants in research and partakers of new medicines. Public awareness needs to be raised regarding the fact that regulatory approval does not mean that drugs are completely safe and the users of medicines need to be especially and explicitly aware of the additional uncertainty surrounding medicines that receive early approval.

For new, extremely expensive medicines to be of optimal value for public funds a new social contract and shift in perceptions are required. However, the willingness of stakeholders to advocate for change depends on their perspectives and whether they feel change is needed. These are joint challenges that require joint solutions and opportunities and enablers abound if all stakeholders make the best use of prospects for group discussion and adaptive study design.

How to move from current mindset to an "adaptive mindset":

What do companies, regulatory and HTA agencies and payers need to adopt?

A regulatory perspective

Prof Alasdair Breckenridge

Former Chairman, MHRA

Novel pathways for novel medicines?

Conditional marketing authorisation and accelerated assessment in Europe and fast track and accelerated approval in the United States are all examples of accelerated regulatory review, otherwise known as facilitated or incremental regulatory pathways. These methods of regulatory review are all based on traditional, decades-old developmental pathways.

Whilst adaptive licensing (AL) may be considered to be another type of these incremental pathways, it may be appropriate instead to consider its potential for use as a "disruptive regulatory pathway" for the regulation of new medicines for which a regulatory paradigm has not yet been developed and for which novel facilitating processes may be required. Examples of the type of medicine that would benefit from AL would be custom-made RNA antisense oligonucleotides for specific patients, new cancer drugs based on novel gene sequences or non-biological complex drugs such as amino acid sequences used to treat multiple sclerosis.

Social media for post-authorisation data

Another important issue in AL and other forms of early approval is their attendant need for real-life post-authorisation data. These data are currently being obtained through sources that include pragmatic clinical trials, registries and electronic health records although electronic health records were designed to be used for billing purposes and may therefore not be advisable sources for effectiveness and safety data.

Social media . . . have emerged as an important data collection resource whose full utility remains to be determined.

Social media, which consist of collaborative projects such as Wikipedia, blogs and microblogs such as Twitter, social networks such as Facebook and sources for content communication such as YouTube, have emerged as an important data collection resource whose full utility remains to be determined. Ten percent of all social media content concerns healthcare and half of that is about the safety and effectiveness of drug treatments and much of these data are from a new generation of people who may not normally visit physicians.

Many regulatory authorities are beginning to investigate ways in which these media can best be used. Some are using them to provide public information and safety alerts but others are monitoring healthcare discussions and requesting public feedback and some are even investing in developing methodologies to extract meaningful data.

The use of novel pathways for the development and regulatory review of important new medicines and research into the most effective use of social media to acquire post-authorisation data should both be considered to move healthcare stakeholders into an adaptive mindset.

How to move from current mindset to an "adaptive mindset:

What do companies, regulatory and HTA agencies and payers need to adopt?

Company regulatory perspective

Sharon Olmstead

Global Head, Development and Regulatory Policy, Novartis Pharmaceuticals, USA

In the traditional model for pharmaceutical research and development, a drug that is fortunate enough to be the 1 in 10,0000 to be eventually approved, takes ten to fifteen years to be developed and costs as much as two billion dollars. Additionally, clinical trials for global development plans have been geographically non-representative, stakeholder input has been largely limited to key opinion leader advisory boards and decisions regarding pricing and reimbursement have been conducted in isolation.

It is commonly agreed that this model is no longer sustainable and the development paradigm has begun to shift accordingly. In the new model of drug development, targeted drug research increases the likelihood of success and there has been an increasing recognition of the importance of the inclusion of all healthcare stakeholders, including patients, clinicians, health technology assessment agencies, with joint regulatory/HTA scientific advice meetings becoming more common. The development and use of new facilitated regulatory pathways is also part of that paradigm shift and the question remains, how do we adapt our current model?

Currently, industry seems to be retrofitting yesterday's regulatory submissions to today's adaptive pathways, sometimes in an effort to rescue a project that is otherwise destined for failure. Approximately one third of retrofit applications meet with regulatory approval. To increase the rate of success, tomorrow's adaptive regulatory thinking should identify potential candidates much earlier in development, potentially pinpointing the sub-populations that would best fit the adaptive model and building adaptive licensing development into portfolio management with decision gates.

. . . new regulatory pathways provide all stakeholders the opportunity to develop a better understanding of national and local priorities and to rethink approaches for delivering new therapies to patients .

The timing of pre-market discussions with regulatory and HTA agencies regarding progressive evidence development for particular candidates must also be considered. Progressive discussions to match progressive development may be the best option, with the first occurring before approval in an initial sub-population. Although initially shortened regulatory timing is a positive feature of adaptive licensing, it should be recognised that a shortened period of technical development will have to be aligned with this decreased regulatory timing to ensure available drug supply.

Methodologies for real-world evidence development must be established, including the use and linkage of databases and the creation of a consistent database infrastructure. Once collected, the evidence must be analysed and synthesised into the development programme. Approaches for industry engagement with external stakeholders such as patients, clinicians and health technology authorities are already under development but companies must also consider the engagement of internal stakeholders such as research, clinical, technical and market access teams as well personnel in alliance development departments who are typically charged with patient involvement issues.

Industry must also consider the labelling implications of adaptive licensing. The US FDA has begun to include notations for products approved through the use of accelerated approval pathways stating that the surrogate or clinical endpoints that were evaluated for approval may or may not represent clinical benefit. Industry must decide if these labelling issues should also be part of their developmental decisions.

The convergence of multiple pathways, some adaptive and some more traditional, may be required for a global development programme appropriate for multiple regions and the shifting of development costs throughout a development life cycle is yet another industry consideration for adaptive licensing. Industry must identify these and other challenges to

adaptive licensing through discussion and propose solutions to these challenges. One of those obstacles may be public health benefit versus the pricing models that are necessitated to make up for the potentially lost data exclusivity time associated with faster approval for smaller patient populations. Ultimately, however, new regulatory pathways provide all stakeholders the opportunity to develop a better understanding of national and local priorities and to rethink approaches for delivering critical new therapies to patients.

How to move from current mindset to an "adaptive mindset":

What do companies, regulatory and HTA agencies and payers need to adopt?

A company HTA perspective

Dr Eric Giesen

Director, Market Access Policy, Bayer Pharma AG, Germany

Maximising the positive impact of new medicines through timely access to patients is the central rationale behind adaptive licensing. In a 2014 Question-and-Answer document developed following its initial experiences with the Adaptive Licensing Project, the European Medicines Agency said that adaptive licensing "can be described as a prospectively planned, adaptive approach to bringing medicines to patients and is intended to maximise the positive impact of new medicines on public health by balancing the need for timely patient access with the importance of providing adequate, evolving information on a medicine's benefits and risks."[1]

It remains to be determined, however, if all stakeholders are ready for the changes necessitated by the adoption of the adaptive licensing pathway. In classical change management, from awareness through desire, capability and action to sustainability, the readiness of the various healthcare stakeholder groups to accept and implement adaptive licensing lies at different points along this process.

Differences in perception also exist within stakeholder groups; for example, some health technology assessment agencies are willing to accept adaptive licensing, while others are lagging (see presentation by Liberti in this report) and in some pharmaceutical companies it may be a challenge to bring all the different functional teams to a single united view on this topic. It remains critical, however, that all parties come to the same conclusion regarding adaptive pathways and are able to participate in the process from the outset.

Political mandates in various jurisdictions are moving toward the use of novel processes to expedite the review of medicines and new solutions to unanswered questions about the processes of adaptive licensing may emerge through dialogue and collaboration. These unanswered questions surround decision making and include the best methods for dealing with uncertainty; the willingness of HTA agencies and payers to accept uncontrolled data for initial recommendation; the course of action to be taken if the results of an evidence-generation plan are non-conclusive and the determination of the frequency of iterative decision making. There are also questions about data for adaptive licensing such as: what data to collect; how to collect the data in market; the infrastructure to be used and the role of healthcare professionals; the identity of the research funders and directors; how to analyse the data and new methodologies for real world evidence developing. Other open questions surround price, such as how to price products at the initial launch and over time; whether a smaller patient population should signal a

higher price and whether prices will increase or decrease as treatment populations expand and uncertainty is reduced.

There are specific steps that companies can take to fully engage in an adaptive licensing model such as taking a proactive rather than reactive position in moving toward continuous evidence generation and using new study designs. Company knowledge and capabilities should be enhanced through an education programme for adaptive approaches and new trial designs and company teams must be aligned around these approaches. Capabilities in post-licensing study design and implementation need to be strengthened and action scenarios built around different potential outcomes. Finally, a business model should be adopted that accepts certain levels of uncertainty and alignment with external stakeholders must occur.

All stakeholders can provide solutions to the challenges represented by adaptive licensing by actions such as bridging the knowledge gap among stakeholders and redefining data requirements and acceptable uncertainty. Health technology assessors and payers, especially those in major markets can be aligned through political mandates and through use of common accepted methodologies. Appropriate financial incentives can be supplied for all stakeholders by establishing predictability of decision making to ensure investments for promising candidates and by working for product reimbursement after regulatory approval.

It is now time to act. The first adaptive license pilots have started and it is expected that the products in those pilots will receive their initial licenses within the next few years. All stakeholders are facilitators for better treatments for patients. Although adequate pricing and reimbursement are fundamental to the success of adaptive licensing, all must move from the mindset that asks "What's in it for me?" to "What's in it for the patients" and from needing more data for decision making to a willingness to accept and manage uncertainty.

References

1. European Medicines Agency. Questions and answers following the initial experience of the Adaptive Licensing Pilot project, Sept 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/09/WC500172810.pdf Accessed May 2015.

Appendix: Workshop Attendees

REGULATORY AGENCIES		
Dr Claus Bolte	Division Head – Clinical Review (Marketing Authorization)	Swissmedic
Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Amy Egan	Deputy Director, Office of Drug Evaluation III, CDER and Acting FDA Liaison to the EMA	Food and Drug Administration, USA
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Dr Wim Goettsch	Advisor	National Health Care Institute, The Netherlands
Dr Andrew Mitchell	Strategic Adviser, Evaluation	Department of Health and Ageing, Australia
Kelly Robinson	Director, Bureau of Metabolism, Oncology and Reproductive Sciences	Health Canada
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Prof Tomas Salmonson	Chair	CHMP, EMA
Dr Almath Spooner	Pharmacovigilance and Risk Management Lead	Health Products Regulatory Authority, Ireland
PHARMACEUTICAL COMPANIES		
James Anderson	External Partnerships Director	GSK, UK
Dr Indranil Bagchi	Vice President and Head, Payer Insights and Access, Global Health and Value	Pfizer Inc, USA
Mireille Collombat	Group Leader, DRA Project Management	Actelion Pharmaceuticals Ltd, Switzerland
Frank DeFelice	Director, Global HTA Public Policy	Merck, Canada
Anna Forsythe	Global Head, Global Value and Access Strategy	Eisai Inc, USA
Dr Veronique Frechin	Portfolio Management and Prospective Director	Institut de Recherches Internationales SERVIER, France
Dr Eric Giesen	Director, Market Access Policy	Bayer Pharma AG, Germany
Sharon Gorman	Director, EU Regulatory Policy	Pfizer, UK
Dr Jens Grueger	Vice President, Global Pricing and Market Access	F. Hoffmann-La Roche, Switzerland
Dr Sanjay Gupta	Head of HEOR	Daiichi Sankyo Inc, USA
Michiel Hemels	Director, EMA HEMAR	Janssen, Denmark
Dr Mark Higgins	Senior Clinical Director, CF	Vertex Pharmaceuticals, UK
Dr Claire Hill-Venning	Director, Global Regulatory Policy and Intelligence	Janssen, UK
Mark Hope	Global Head of Neuroscience and Ad Interim Head EU/International Regulatory Affairs	F. Hoffmann-La Roche Ltd, Switzerland
Dr Paul Huckle	Chief Regulatory Officer and Senior Vice President	GlaxoSmithKline, USA
Dr David Jefferys	Senior Vice President	Eisai, UK
Dr Hiroki Kato	Director of R&D	Zeria Pharmaceutical Co Ltd, Japan

Dr Stephanie von Klot	PV – Strategic Data Analysis	Boehringer-Ingelheim Pharma GmbH, Germany
Dr Ashish Kohli	GEP Portfolio Regulatory Strategy Lead EU/ NZ/AU	Pfizer, UK
Dr Kinga Komar-Malinowska	Director, Global Regulatory Affairs Oncology Early Projects	Bayer Pharma AG, Germany
Carol McConnell	Regulatory Affairs Director, Oncology TA	AstraZeneca, UK
Diane Mackleston	Senior Director, Regulatory, Bio-Medicines	Eli Lilly and Company Ltd, UK
Jesús Muñiz	Senior Director, Regulatory Policy and Intelligence	Shire, USA
Bharti Navsariwala	Director – Oncology	Takeda, UK
Sharon Olmstead	Global Head, Development & Regulatory Policy	Novartis Pharma, USA
Dr Otmar Pfaff	Senior Regulatory Affairs Manager	Boehringer-Ingelheim Pharma GmbH, Germany
Corina Schmidt	Director – Head of Regulatory Policy and Intelligence, Europe	GlaxoSmithKline, Belgium
Merete Schmiegelow	Senior Director of Regulatory Policies and Intelligence	Novo Nordisk A/S, Denmark
Regina Seidel	Head, Global Regulatory Affairs DM CVI	Bayer Pharma AG, Germany
Andrew Storey	Vice President, Regulatory Affairs, US/ Canada	AbbVie, USA
Louise Timlin	Senior Director International HTA/HO	Eli Lilly and Company, UK
Chris Walker	Executive Director	Amgen Ltd, UK
Pauline Walstra	Director, RAE Development	Astellas Pharma Europe, The Netherlands
John Way	Director, Regulatory Affairs	Biogen Idec, UK
HEALTH TECHNOLOGY ASSESSMENT AGENCIES		
Meindert Boysen	Programme Director, Technology Appraisals	National Institute for Health and Care Excellence
Prof Sarah Garner	R&D Associate Director	National Institute for Health and Care Excellence
Anne Lee	Chief Pharmaceutical Adviser	Scottish Medicines Consortium
Aileen Muir	Vice Chair	Scottish Medicines Consortium
Dr Brian O'Rourke	President and CEO	Canadian Agency for Drugs and Technologies in Health
Prof Robert Peterson	Executive Director, Drug Safety Effectiveness Network	Canadian Institute of Health Research
Prof Angela Timoney	Director of Pharmacy	NHS Lothian, UK
ACADEMIC AND NON-PROFIT INSTITUTIONS		
Prof Richard Barker	Director	CASMI
Dr Donald Berry	Professor, Department of Biostatistics	University of Texas M.D. Anderson Cancer Center, USA
Prof Bruno Flamion	Professor of Physiology and Pharmacology	University of Namur, Belgium
Dr Tony Hoos	Core Member MIT NEWDIGS and President M4P Consulting	MIT NEWDIGS and Medicines 4 Patients Consulting Ltd, UK
Alastair Kent	Director	Genetic Alliance, UK
Dr Pieter Stolk	Project Manager	IMI GetReal Consortium/ UMCU, The Netherlands
Prof Adrian Towse	Director	Office of Health Economics, UK

Centre for Innovation in Regulatory Science (CIRS)	
Patricia Connelly	Manager, Communications
Lawrence Liberti	Executive Director
Dr Neil McAuslane	Director
Prisha Patel	Manager, Emerging Markets Programme
Professor Stuart Walker	Founder