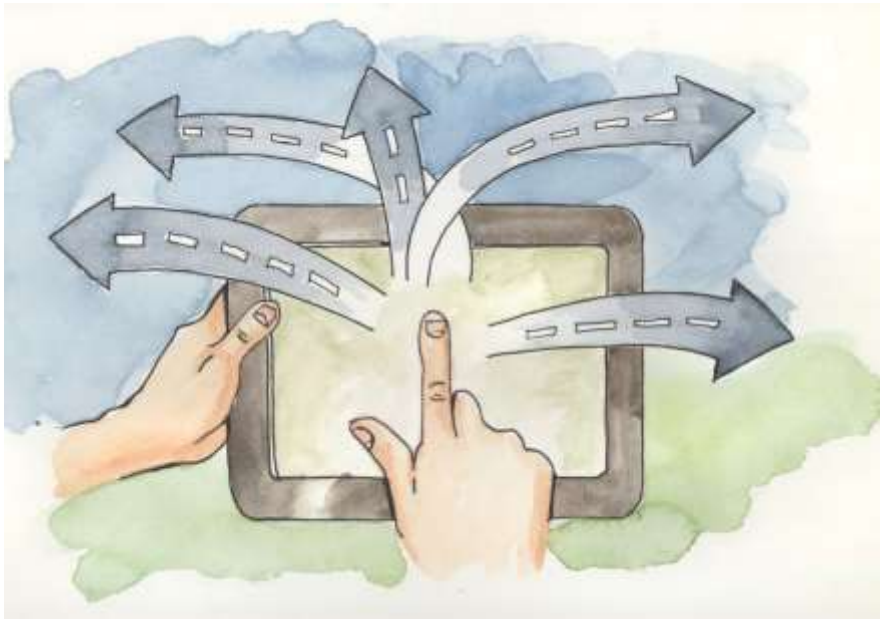

Flexible regulatory/ access pathways:

Are we there yet?

27-28 September 2017

Surrey, UK

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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Report date: September 2018

Section 1: Executive Summary

Background to the Workshop

There is broad agreement across companies, regulators, health technology assessment (HTA) bodies, patients, providers and payers that providing timely access to meaningfully better medicines at reasonable costs is an important aim of healthcare systems. A number of new regulatory initiatives to enable the flexible development and earlier licensing of innovative medicines have emerged over the last five years such as the US FDA Breakthrough Therapy Designation and Accelerated Approval pathway along with the US Congress 21st Century Cures Act to accelerate the development and delivery of new medicines. In Europe, the Priority Medicines (PRIME) scheme was launched by the EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier. In addition, within jurisdictions such as the UK, experience is being gained with approaches such as the Early Access to Medicines Scheme. The focus is on evaluating the benefit-risk profile in a restricted population where unmet medical need is highest and decision making can be based on robust evidence. These flexible regulatory pathways (FRPs) are playing an increasing important role in regulatory approvals worldwide. For the purposes of this meeting, FRPs include regulatory pathways to enable the more rapid development, availability, review and/or approval of medicines and flexible access and reimbursement pathways (FARPs) include the integration of HTA and payers into the accelerated access process.

While regulators do not consider product cost or comparative or incremental benefits in their assessments, these are key factors for health technology assessors and payers. Consequently, the outcomes of FRPs are not widely embraced by the payers due to the uncertainty around the effectiveness of new treatments and concerns as to whether their value to healthcare systems has been adequately demonstrated. In addition, payers, although sympathetic to early access for truly unmet medical need, do not support use of accelerated pathways for a wider set of indications. HTA agencies, on the other hand, are also looking at how to better ensure that they are not recommending coverage for medicines that are not clinically or cost effective by examining models such as coverage with evidence development, managed entry schemes and new models around pay-for-performance. Therefore, the need to better define the relationship between FRPs and FARPs has emerged.

Defining clinical certainty and translating it into a cost value is the primary source of tension between the two pathways. This might be mitigated to some extent if all parties agree to clearly define the initial target population that has the greatest and most urgent clinical need and for whom the medicine is likely to generate the greatest clinical benefit. However, challenges to implementing FRP and FARPs exist, and include regulators' concerns regarding the controlled use of medicines approved through these flexible pathways, health technology assessors' need to develop rules surrounding disinvestment for medicines that do not meet the burden of proof and industry's need to realise competitive pricing, potentially tied to an agreed, genuinely adaptive pricing model. However, there is a disconnect in that regulator and payer evidence requirements are diverging rather than converging as regulators' approval of quality, safety and efficacy evolves and becomes

more flexible. Faced with challenges of affordability, payers and some health technology assessors are becoming more stringent regarding evidence for incremental benefit. In addition, there is also sometimes a lack of agreement around what is perceived as unmet medical need among the stakeholders.

In 2014, CIRS held the Workshop entitled "Medicines adaptive pathways: A practical strategy to improve patient access to medicines". Since this Workshop, there has been an increased use of FRPs globally by regulators and the evaluation of different access schemes by health technology assessors and payers. The aim of this Workshop was to bring together companies, patient representatives and HTA, payer and regulatory agencies to discuss current perspectives and opportunities for FRP/FARPs as part of the regulatory/HTA toolbox to enable earlier patient access, especially where these is high unmet medical need.

Workshop objectives

- Determine if the current collaborative models being piloted or used are meeting different stakeholders' needs and what solutions are being used to enable an integrated, holistic and sustainable approach
- Ascertain how companies, regulators and health technology assessors would like to use regulatory FRPs together with FARPs and what systems are required to use these in an integrated manner to successfully to meet the needs of patients and healthcare systems
- Recommend how best to evolve and ensure success of new medicines FRPs and FARPs for patients and the critical success factors to manage uncertainty, ensure proper use and to interpret continuity with evidence generated during early phases of study

Introduction

The traditional development and regulation of medicine can take as much as 10 years, but as **Session Chair Prof Sir Alasdair Breckenridge,** *Former Chair, Medicines and Healthcare products Regulatory Agency (MHRA),* UK, reminded Workshop participants, earlier access can be obtained through the use of FRPs for promising medicines that address unmet medical need or serious disease. However, these medicines may be initially approved through the evaluation of surrogate markers of efficacy and subject to the collection of post-authorisation data and multiple stakeholders including companies, regulators, health technology assessors, payers, healthcare professionals and patients must accept a degree of uncertainty at the time of marketing authorisation. It was envisioned that through this Workshop, it could be determined how the predictability of the regulatory success rate and the positive HTA recommendations could be improved and which methods would allow stakeholders to achieve their aims.

Key points from presentations

SESSION: ENABLING TIMELY AVAILABILITY TO MEANINGFUL NEW MEDICINES - DO FLEXIBLE REGULATORY PATHWAYS DELIVER THIS AND ARE THEY MEETING STAKEHOLDER NEEDS?

Flexible pathways are needed to achieve the conflicting regulatory and health technology assessment goals of innovation and affordability, but the required work is scientifically complex and labour intensive and more platforms, resources and dialogue are needed. **Dr Sean Tunis,** *President and CEO, Center for Medical Technology Policy (CMTP), USA* detailed some of the requirements for flexible pathways, including adequate capacity for effective early dialogue, efficient generation of post-approval evidence to address key uncertainties and nimble mechanisms for policy revisions; additional requirements for flexible reimbursement include a solid legal platform, agreement as to the level of evidence for initial access, criteria and process for determining study protocol acceptability and adequate resources to implement studies. Acceptable study protocols evaluate whether an intervention improves meaningful, patient-relevant health outcomes and the coreHEM collaboration work in outcome standardisation advocates using core outcome sets in clinical trials designed using consensus techniques

Explaining the differences and commonalities of FRPs and FARPs, *CIRS Executive Director* **Dr Lawrence Liberti** said that FRPs speed the progressive development, authorisation and access to important new drugs with a positive benefit-risk balance. FARPs, on the other hand, provide options for managing the introduction of new medicines via pathways that include opportunities to decrease uncertainty present at the time of accelerated regulatory approval through an increasingly robust experience database. FARPs can address the limitations of payers and budgets and expectations of sponsors and provide opportunities for managed disinvestment. Common elements of FRPs and FARPs include early stakeholder interactions and early controlled release followed by real-world monitoring with progressive data collection to completely define the medicine's profile, leading to a full approval, withdrawal or limitation of use. Dr Liberti took the opportunity of the Workshop to conduct a short survey regarding FRPs and presented the results in comparison to a similar survey of industry participants in 2016.

Dr Tomas Salmonson, *Chair, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA)* discussed the background and status of the EMA Priority Medicines (PRIME) scheme, which is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation. PRIME eligibility review is robust with excellent collaboration across committees and rapid decisions are delivered in writing. The programme includes iterative, enhanced multi-stakeholder scientific advice and enables early identification of potential issues. Kick-off meetings include broad discussion of development and regulatory strategy with multiple issues identified for future scientific advice and planning for post-authorisation and stakeholder interactions. At the time of the Workshop, out of 130 requests, 28 products have been granted PRIME eligibility to date, mostly in rare diseases.

Because healthcare expenditures have escalated to nearly unsustainable levels, **Dr Ad Schuurman,** *Head of Business Contact Centre and International Affairs, National Health Care Institute (ZIN), Netherlands* explained that payers would like to control costs, potentially through mechanisms such as adaptive reimbursement, confidential national pricing, or agreement on mutually acceptable prices. As part of cost containment, payers would like to see programmes such as Medicines Adaptive Pathways to Patients (MAPPs) to be applied to special cases such as life-threatening diseases or urgent public health protection. Major improvements should be expected to be gained through use of these medicines and a realistic exit strategy should be agreed with the knowledge of patients and physicians if expectations are not met. Furthermore, patients and physicians should agree in writing in advance as to the possible withdrawal of the medicine if results are not as expected and that they have been informed regarding the uncertainties in the efficacy and safety of the medicine. In this plan, reimbursement can be decreased or increased according to mutually agreed possible results, market authorisation can be stopped and populations or indications can be reduced or changed.

New medicines can be expedited through enhanced regulatory guidance, faster regulatory review or licencing based on limited clinical data package. **Dr Jens Heisterberg**, *Vice President, Regulatory Affairs Intelligence, Novo Nordisk, Denmark* listed some of the reasons for expediting the licensing of medicines addressing a high unmet medical need, saying that these programmes can result in earlier and more frequent interactions between industry and regulators, the allocation of regulatory resources to provide high-quality scientific and regulatory advice to sponsors to facilitate fast development and approval and reduced or no fee for interactions. For patients, these expedited pathways provide early access to medicines for severe diseases for which no or limited treatment options exist. They provide regulators with a tool to balance unmet medical need and the severity of the disease against an increased number of uncertainties about efficacy and safety and for industry, they incentivise the development of innovative medicines. However, obtaining meaningful data post-licensing is challenging and there are many methodological problems in interpreting real-world data. Potential ways forward include joint rather than parallel regulatory HTA scientific advice and new outcomes-based pricing schemes in which payment is only made when benefit is achieved.

Valentina Strammiello is *Programme Manager of the European Patients Forum (EPF),* an independent, non-governmental umbrella organisation providing a voice for 74 patients groups, EU disease-specific organisations and national patient coalitions. The EPF vision calls for equitable and timely access to high-quality, patient-centred health and social care for all EU patients regardless of where they live in the EU. The EPF has actively participated in ADAPT SMART (Accelerated Development of Appropriate Patient Therapies a sustainable, multi-stakeholder enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities. EPF participation in ADAPT SMART programme has assisted in the identification of gaps in patient involvement in medicines development that need to be addressed. For example, a strong legal basis for FRPs and adaptive pathways is key for patients, particularly as it applies to the disinvestment in or withdrawal of new medicines, both of which have the potential to impact patient treatment options. Truly informed and comprehensive patient consent is also required, which includes a complete understanding of all potential implications of treatments and of inclusion and exclusion criteria prior to study enrolment and an awareness of the trade-off in benefits and risks for the expedited use of new medicines.

Evidence needs of regulators outside of the US and EU are being influenced by evolutions in situational contexts, evidence generation innovations and facilitated regulatory pathways (FRPs) than can narrow or shift focus. **Dr Robyn Lim,** *Senior Science Advisor, Health Products and Food Branch, Health Canada* pointed out that developers' and other regulators' choices about evidence generation and FRP implementation; for example, parallel vs sequential regulatory involvement, may influence the nature of the evidence produced and decisions of regulators outside of the US and EU could be affected by potential gaps between their evidence needs and received evidence packages. Potential pan-regulatory approaches include diversity assessment and management, in which there would be up-front decisions to exclude the possibility of generalisability and facilitated regulatory pathway applicability in other jurisdictions or generalisability/ applicability assessment and management, in which follow-on jurisdictions perform their own "applicability analyses" and options management. International discussions and upfront alignment may promote a needed balance between evidence and product needs to avoid inefficiencies that increase time to decision and global decision diversity.

SESSION: FLEXIBLE ACCESS AND REIMBURSEMENT PATHWAYS (FARPS): DO HTA AGENCIES AND PAYERS HAVE MECHANISMS ALIGNED WITH FRPS TO ENABLE TIMELY AVAILABILITY TO MEANINGFUL NEW MEDICINES?

In Australia, implementation of change in health technology assessment now has a defined timeframe but **Prof Andrew Wilson,** *Chair, Pharmaceutical Benefits Advisory Committee, Department of Health, Australia* described the existing Pharmaceutical Benefits Advisory Committee (PBAC) process, as likely the clearest of any aspect of Australian healthcare investment, saying that modifications to that process should recognise the full scope of the investment framework and full range of options. The sources of uncertainty around new medicines are not going to improve in the short term and that uncertainty plus the increasing requirements for alternative entry models with evidence development involve a change in the relationship between companies, regulators and funders; the payer shares a greater proportion of the risks of the uncertainty with the sponsor and should expect that the budget consequences of that shared risk are recognised and compensated.

Expedited regulatory processes mean that products come to HTA agencies and payers sooner in their development cycle, with less mature evidence. **Dr Nick Crabb,** Programme Director, Scientific Affairs, National Institute of Health and Care Excellence (NICE), UK said that further work is required to achieve consensus amongst HTA and payer agencies on some aspects of adaptive pathways, although these stakeholders are most supportive in principle of pathways that allow patients early access to transformative medicines in a financially sustainable way. NICE has participated in some of this necessary work, including the European Medicines Agency (EMA) Adaptive Pathways Pilots, designed to improve alignment of regulatory and health technology assessment processes, IMI2 ADAPT SMART, which supports policy makers and national governments to further develop adaptive approaches to the development and reimbursement of medicines and England's Cancer Drugs Fund, a source of funding for cancer drugs through which pharmaceutical companies, the National Health Service England and NICE address uncertainties surrounding the effectiveness of new cancer treatments, typically by the collection of additional data during a specified period of managed access.

The uncertainties surrounding the evidence on which decisions for expedited medicines are based have resulted in challenges in pricing and reimbursement. **Niklas Hedberg,** *Chief Pharmacist,* Tandvårds- och läkemedelsförmånsverket (TLV)*, Sweden* explained that to meet this challenge, TLV has established a national platform for collaboration and dialogue with pharmaceutical companies and Swedish county councils. This three-party dialogue identifies and seeks ways to address risks such as uncertainties about treatment populations and the duration and results of treatment. In addition, TLV revised its internal structure to allow for more therapeutic specialisation and increased analytical capacity and adapted its processes to accommodate different types of applications. Finally, to meet the important challenges surrounding real-world data, TLV aims to run several pilots with regards to drug assessment and use of real-world data.

Unaligned regulatory and HTA views lead to confusing signals, waste of resource, frustrated stakeholders and delayed patient access. **Claudine Sapede,** *Global HTA & Payment Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland* suggested several ways that all stakeholder decisions can become more agile while also being predictable and reliable for stakeholders, including the use of real-world data to provide an appropriate standard of care historical control and confirm the size of treatment effect after approval. Prices for the initial launch of a drug with confidential discounts could vary over time as more evidence become available and data-driven schemes including pay for performance, outcomes-based agreements should also be explored. However, implementing new payment models requires an appropriate infrastructure for data collection, including the ability to efficiently collect relevant data, compliant with all data privacy and information technology regulations and collective efforts are needed to invest in the appropriate infrastructure enabling outcomes-based agreements and an outcome-driven healthcare system.

Dr Marc Van de Casteele, *Coordinator Expertise Pharmaceuticals, Belgian Institute for Health Insurance and Invalidity (RIZIV-INAMI)*, Belgium reminded Workshop participants that to many payers, adaptive pathways are still a concept in development that requires more discussion and that for payers, the objective of flexible pathways is not early access but decent access to quality care. It has been reported that of 30 drugs that received conditional approval by the European Medicines Agency (EMA) from 2016 to 2016, 17 still maintain conditional status and of conditional approvals granted 2009-2010 at the US Food and Drug Administration (FDA), 25% of the commitments are still ongoing and 20% have never started. These statistics may understandably inspire caution among payers and remaining uncertainties as to the quality and safety of new medicines may cause payers to make conservative reimbursement decisions.

MAPPs seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product lifespan in a sustainable fashion. MAPPs is a prospectively planned, iterative approach to medicines development and access pathways within the current regulatory framework, making the best use of existing tools and methods such as conditional approval, scientific advice, and real-world data with multi-stakeholder engagement. **Solange Corriol-Rohou**, *Senior Director, Regulatory Affairs & Policy, Europe, AstraZeneca Global Medicines Development, France* discussed the Innovative Medicines Initiative Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from

Research to Treatment-outcomes (IMI ADAPT SMART) Consortium, which has established a platform to facilitate and accelerate the availability of MAPPs to all healthcare stakeholders. Moving forward, all stakeholders, whether from IMI ADAPT SMART and other IMI projects or regulatory or HTA initiatives or pharmaceutical companies must work together from the earliest stages of medicines' development and accept new R&D approaches and development paradigms to ensure innovative promising products can fulfil unmet needs as early as possible.

SESSION: A GLOBAL APPROACH– CAN THE DOTS BE CONNECTED ACROSS JURISDICTIONS?

Representing the Pharmaceutical Research and Manufacturers of America (PhRMA), **Camille Jackson,** *Senior Director, Science and Regulatory Advocacy,* said that regulatory harmonisation and convergence efforts are best focused on regulatory processes, tools, trainings, and best practices that each regulatory authority could reference to ensure resources are efficiently managed by each regulator, between regulators and by industry to support expediting patient access to innovative medicines. There are a number of existing tools through which regulatory convergence already happens such as the ICH Common Technical Document and the electronic Common Technical Document, bilateral and multilateral agency collaboration occurs through cluster and information sharing practices and mutual reliance recognition agreements and successful harmonisation fora include the ICH and the Asia Pacific Economic Cooperation (APEC) Centers of Excellence. Opportunities for future tools for regulatory convergence could include clinical trial applications, electronic clinical trial applications and common protocol templates. Technical guidelines to aid convergence could be developed such as risk-based submission of CMC information and post-approval planning and a common definition of terms such as l*ife threatening, serious* and *unmet medical need* could be agreed.

Dr Murray Lumpkin is the *Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation*, which determined that the total time for all assessments and approvals for health products in low-income countries averaged between 4 and 7 years after the completion of the development programme and the initial submission to the regulatory authority in the country of manufacture. Delays in prequalification and national regulatory review due to lack of reliance on previous stringent reviews were exacerbated by long spreads in timing from the first to last regulatory submission in a low-income country. It was determined that the greatest opportunities to expedite the availability of new medicines and vaccines was likely to be found in optimising some of the processes of WHO prequalification, in helping manufacturers from low-income countries better understand the international requirements of prequalification and working to help national regulatory agencies rely on the work products of other trusted agencies to help inform their own decision making both through joint reviews and work-sharing, and through more regional approaches to product regulation. As a result of these enhanced processes, the total timing for the abridged assessment of vaccines in low-income countries that had already been approved by stringent regulatory authorities was reduced by 49% for dossiers approved from 2013 to 2016, and during that same period, the timing for the full assessment of medicines in low-income countries that had not yet been approved by stringent regulatory authorities was reduced by 23%.

The European Network for Health Technology Assessment (EUnetHTA) comprises 81 partnering national, regional and not-for-profit agencies that produce or contribute to HTA. **Dr Wim Goettsch,** *Director, EUnetHTA JA3 Directorate, Zorginstituut Nederland* updated Workshop participants about EUnetHTA Joint Action 3 (JA3), which aims to contribute to a sustainable model for the scientific and technical cooperation in HTA in Europe through a series of work packages (WPs). Parallel HTA consultations with the European Medicines Agency (EMA) as part of WP5A and linking to EMA Priority Medicines (PRIME) might help to select the products that require facilitated regulatory and access pathways and also clearly define what is needed in the research programme. Joint relative effectiveness assessments (REAs) conducted in parallel with EMA as part of WP4 may speed access to needed treatments and also ensure a more consistent REA perspective across Europe. Collaboration on additional data collection as part of WP 5B can increase the number of patients included in registries and the trustworthiness of registry data and ensure the use of standardised tools for data analysis but despite these HTA tools it is likely that the management of pricing, reimbursement, managed entry and exit schemes will remain at the national level.

Recommendations from across the Syndicates

Prioritising important therapies– What are the criteria that will be used to determine which products should be considered for FRPs and FARPs and how should they address evolving unmet clinical needs?

- Using a multi-stakeholder approach, CIRS should assess the feasibility of developing a consolidated (core) list of factors to prioritise products for facilitated regulatory and access pathways.
- The core list of prioritisation criteria for facilitated regulatory and access pathways should be adapted by individual stakeholders to meet their needs.

Alignment of FRPs and FARPs – What are the elements needed to bridge the barriers and exploit the opportunities to promote holistic convergence to ensure effectiveness and efficiency of the regulatory and HTA approaches?

- Earlier joint discussions should be conducted among companies, regulators and health technology assessors. These discussions should result in agreements as to the core package for approval, evidence needs, post-authorisation effectiveness studies. Payers should be involved in determining post-authorisation expectations and health technology assessors and payers should provide input into risk management plans to manage uncertainty
- Stakeholders should improve the description and understanding of uncertainty; looking for guidance from ICH M4.
- It should be recognised that, along with randomised clinical trials, real-world data are an important element of evidence. It should also be recognised that patient-reported outcomes are an important aspect of real-world evidence; access and usability of these data are key and new technology should be embraced as a potential source of new data; progress is required in agreements as to what is needed and what approaches should be used for real-world evidence.

Understanding stakeholder differences on views of outcome and success of flexible regulatory/access pathways: How can stakeholders bring FRPs/FARPs to life?

- Life-cycle spanning, multi-stakeholder dialogue is fundamental to move FRPs and FARPs forward. All such discussion spaces need to be safe harbours and include data protection and confidentiality. Global differences in dialogue processes should be acknowledged.
- Earlier discussion, planning and agreement on potential post-approval commitments, including processes for enforcement and distinctions between commitments for FRPS vs FARPS may help address issues in timing and compliance of commitments.
- Stakeholders should be open to the use of FRPs/FARPs while understanding that they are still in the experimental phase. FRP experiences, potentially through pilots need to be publicly available for global learning.

WORKSHOP PROGRAMME

SESSION: ENABLING TIMELY AVAILABILITY TO MEANINGFUL NEW MEDICINES - DO FLEXIBLE REGULATORY PATHWAYS DELIVER THIS AND ARE THEY MEETING STAKEHOLDER NEEDS?	
Chair's welcome and introduction	**Prof Sir Alasdair Breckenridge**
Should flexible approaches to both regulation and access be healthcare policy?	**Dr Sean Tunis,** *President and CEO, Center for Medical Technology Policy, USA*
The flexible regulatory pathways (FRP) landscape: How do they fit into the development and regulatory toolkit?	**Dr Lawrence Liberti,** *Executive Director, Centre for Innovation in Regulatory Science*
EMA viewpoint on PRIME: Does early upstream agency/stakeholder involvement result in better designed development programs facilitating agency decision making downstream? How does scientific advice contribute to success?	**Dr Tomas Salmonson**, *Chair, CHMP, European Medicines Agency*
Payer perspective: Are these pathways fit for purpose?	**Dr Ad Schuurman**, *Head of Business Contact Centre and International Affairs, National Health Care Institute (ZIN), Netherlands*
Industry perspective: What are the strategic, opportunities, outcomes and pitfalls?	**Dr Jens Heisterberg**, *Vice President, Regulatory Affairs Intelligence, Novo Nordisk, Denmark*
Patient perspective – Is enough being done to ensure timely development and reviews of medicines?	**Valentina Strammiello**, *Programme Manager, European Patients' Forum, Belgium*
Non-EU/FDA regulatory agency perspective: How might an FRP in another jurisdiction affect evidence requirements and decision making?	**Dr Robyn Lim,** *Senior Science Advisor, Health Products and Food Branch, Health Canada*
SESSION: FLEXIBLE ACCESS AND REIMBURSEMENT PATHWAYS (FARPS): DO HTA AGENCIES AND PAYERS HAVE MECHANISMS ALIGNED WITH FRPS TO ENABLE TIMELY AVAILABILITY TO MEANINGFUL NEW MEDICINES?	
How could HTA agencies offer accelerated review pathways aligned with FRP processes and evidentiary requirements? HTA perspective	**Prof Andrew Wilson,** *Chair, Pharmaceutical Benefits Advisory Committee, Department of Health, Australia*
Reacting to rapid innovation: what is the impact on HTA/payer decisions of a newly submitted application on a product undergoing FRP? HTA perspective	**Dr Nick Crabb,** *Programme Director, Scientific Affairs, National Institute of Health and Care Excellence, UK*
Managing the uncertainty of the benefits, risks and value of medicines granted access through flexible pathways: What post-licensing mechanisms will be needed by HTAs and Payers? HTA perspective	**Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden*
Balancing early access with acceptable reimbursement – how do companies/payers view flexible access and reimbursement pathways? Company perspective	**Claudine Sapede,** *Global HTA & Payment Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland*
Payer perspective:	**Dr Marc Van de Casteele,** *Coordinator Expertise Pharmaceuticals, Belgian Institute for Health Insurance and Invalidity (RIZIV-INAMI), Belgium*
Flexible approaches – pushing regulatory, HTA and payer boundaries– how to connect and facilitate new models? IMI ADAPT SMART Perspective	**Solange Corriol-Rohou**, *Senior Director, Regulatory Affairs & Policy, Europe, AstraZeneca Global Medicines Development, France*

SESSION: SYNDICATE SESSIONS – ALIGNING STAKEHOLDERS	
Topic A: Prioritising important therapies– What are the criteria that will be used to determine which products should be considered for FRPs and FARPs and how should they address evolving unmet clinical needs? (what is the role of scientific advice in informing these decisions)?	**Chair: Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden* **Rapporteur: Dr Trevor Richter,** *Director, CDR and Optimal Use of Drugs, CADTH, Canada*
Topic B: Alignment of FRPs and FARPs – What are the elements needed to bridge the barriers and exploit the opportunities to promote holistic convergence to ensure effectiveness and efficiency of the regulatory and HTA approaches?	**Chair**: **Dr Thomas Lönngren,** *Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden* **Rapporteur: Paul Dearden,** *Head of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK*
Topic C: Understanding stakeholder differences on views of outcome and success of flexible regulatory/ access pathways: How can stakeholders bring FRPs/FARPs to life?	**Chair**: **Prof Adrian Towse,** *Director, Office of Health Economics, UK* **Rapporteur: Thomas Brookland**, *EU Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland*
SESSION: A GLOBAL APPROACH– CAN THE DOTS BE CONNECTED ACROSS JURISDICTIONS?	
What are the key regulatory enablers to create more opportunities for accelerated marketing authorisation approvals globally?	**Camille Jackson,** *Senior Director, Science and Regulatory Advocacy, PhRMA, USA*
Global development: Do FRPs enable more timely regulatory reviews and quicker access for patients outside of Europe and the US?	**Dr Murray Lumpkin**, *Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation*
Can HTA alignment efforts in Europe help to foster alignment of FRPs/FARPs within Europe?	**Dr Wim Goettsch,** *Director, EUnetHTA JA3 Directorate, Zorginstituut Nederland*
SESSION: ARE WE READY TO PRACTICALLY ALIGN FRPS AND FARPS?	
Chairman's introduction	**Dr Thomas Lönngren,** Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden
Interactive panel – How ready are we to practically align FRPs and FARPs and how can the whole process be brought to life?	
Patient viewpoint	**Dimitrios Athanasiou**, *Duchenne Patient Advocate, Muscular Dystrophy Association Hellas, Board Member in UPPMD and EMA Patient Expert for DMD, Greece*
Company viewpoint	**Prof Bruno Flamion,** *VP, Head Strategic Development, Idorsia, Switzerland*
Regulatory agency viewpoint	**Dr Siu Ping Lam**, *Director, Licensing Division, MHRA*
HTA agency viewpoint	**Dr Jan Jones**, *Principal Pharmacist, Scottish Medicines Consortium*
Payer viewpoint	**Evert Jan van Lente**, *Director EU-Affairs, AOK-Bundesverband, Germany*

Section 2: Presentations

Should flexible approaches to both regulation and access be healthcare policy?

Dr Sean Tunis, *President and CEO, Center for Medical Technology Policy, USA*

The goals of regulatory and reimbursement science

The US Food and Drug Administration (FDA) defines *regulatory science* as ". . . the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products." The agency goes on to state that "FDA will advance regulatory science to speed innovation, improve regulatory decision making, and get products to people in need" however, the affordability of those products is not mentioned. The importance of regulatory science surrounds its ability to provide clarity and consistency that is essential for regulated industries, to ensure that marketed products are safe and effective, to enable rapid patient access to promising new products and to promote innovation in life sciences. Whilst these objectives create tension with respect to evidence standards, regulatory science provides an opportunity to develop a scientific framework that balances multiple objectives and the FDA as well as the European Medicines Agency (EMA) provides platforms to support this process.

Adapting the above definition of regulatory science, *reimbursement science* is the science of developing new tools, standards, and approaches to assess the comparative effectiveness and value of products covered by public and private payers. The goals of reimbursement science are to improve reimbursement decision making, to maximise population health outcomes and to support efficient use of resources. This definition does not include innovation.

Requirements of flexible pathways

Flexible regulatory and reimbursement pathways offer the potential to work toward the equally important goals of both of these stakeholders, but there are few platforms to accomplish the scientifically complex and labour-intensive work associated with integrating these pathways and there are limited resources to support the sustained dialogue that is required. In fact, adequate capacity for effective early dialogue between regulators and HTA bodies is an essential ingredient of flexible pathways. Other needed factors include the efficient generation of post-approval evidence to address key uncertainties and nimble mechanisms for revisions in government policy. The US and EU differ in their abilities to achieve these needed factors and their acquisition could be improved in both jurisdictions.

Flexible pathways and acceptable study protocols

Flexible regulatory and reimbursement pathways offer the potential to work toward the equally important goals of both of these stakeholders, but there are few platforms to accomplish the scientifically complex and labour-intensive work associated with integrating these pathways

There are other requirements for flexible pathways, including a solid legal platform, the criteria and process to select technologies for pathways and a definition of what level of evidence is required for initial access. In addition, specifying the criteria and process for determining when a study protocol is acceptable is required as well as adequate resources to implement studies, a clear process to transition from study conclusion to access without study requirements and a robust

process and the capacity to efficiently manage all of these elements.

Acceptable study protocols are developed with the input of regulators, payers and other stakeholders and evaluate whether an intervention improves meaningful, patient-relevant health outcomes, follow research methods best practices and outline a study that is feasible to conduct in a reasonable period of time.

Recent gene therapy trials in haemophilia have reported promising results, demonstrating that gene therapy could yield a long-term "cure." However, outcomes associated with a "cure" may be different than outcomes used to assess a current standard of care. The project coreHEM seeks to develop a core outcome set for gene therapy in haemophilia using the COMET initiative (Core Outcome Measures in Effectiveness Trials). A Core Outcome Set is a minimum set of outcomes that should be measured and reported in all clinical trials of a specific condition. This does not mean outcomes in a particular trial should be restricted to those in core set. Outcomes should demonstrate the value of gene therapy from the perspective of patients, carers and healthcare professionals and the coreHEM project approach uses a multi-stakeholder collaborative process involving patients, carers, patient advocates, healthcare professionals, haemophilia researchers, US and international payers and health technology assessment groups, regulators, research funders and life science companies. A modified Delphi voting process was used to prioritise outcomes and the results of the first round of selection are shown in Figure 1.

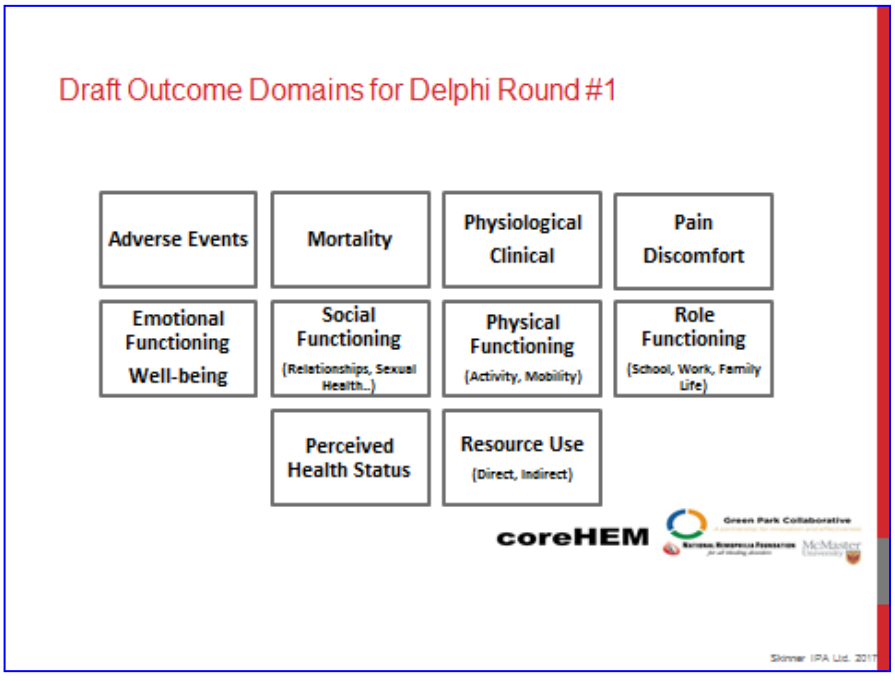


Figure 1. The outcomes to be measured and reported in clinical trials of haemophilia therapies as selected by multiple stakeholders in the first round of selection in the coreHEM project.

coreHEM is an example of the development of a platform for sustained communication among healthcare stakeholders that is required for the achievement of successful integrated flexible pathways for the development, regulation and reimbursement of innovative therapies.

How will flexible regulatory and flexible access and reimbursement pathways align?

Dr Lawrence Liberti, *Executive Director, Centre for Innovation in Regulatory Science*

Background

Flexible regulatory pathways (FRPs) are alternatives to standard regulatory pathways designed to speed the progressive development, authorisation and access to important new drugs with a positive benefit-risk balance. These pathways may increase the level of communication and commitment between the developer and the agency, give a larger role to the effects of surrogate endpoints and move some of the burden of evidence generation from the pre- to the post-authorisation phase. Examples of FRPs include the European Medicine Agency (EMA) Accelerated Assessment and Conditional Marketing Authorisation, the United States Food and Drug Administration (US FDA) Accelerated Approval, Breakthrough Therapy, Fast Track and Priority Review pathways, the Health Canada Notice of Compliance w Conditions and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) Sakigake.

Flexible access and reimbursement pathways (FARPs) give health technology assessment (HTA) agencies options to recommend access and reimbursement to new medicines. These pathways provide options for managing the introduction of new medicines via pathways that build opportunities for both payers and sponsors to benefit from increasing certainty around the effectiveness of a product, relying on an increasingly robust database of experience following the regulatory approval of a product. They can take any one of many forms to address the limitations of payers/budgets and return on investment expectations of sponsor while providing opportunities for managed disinvestment.

FRPs and FARPs pave the way for new approaches to development, access and reimbursement and may increase the level of communication and commitment between the stakeholders in new medicines including developers, HTA and regulatory agencies and patients. Their use is predicated on the fact that society is willing to accept uncertainty about benefits and harms versus the serious risks of disease, with the belief that the initial data generated are reasonably predictive of clinical benefit even though there is uncertainty regarding the ultimate “value” of the therapy.

FRPs and FARPs pave the way for new approaches to development, access and reimbursement and may increase the level of communication and commitment between the stakeholders in new medicines

Common elements include early stakeholder interactions, the early and controlled initial release of a product after an accelerated testing period followed by intensive real-world monitoring with progressive data collection. This data collection will more completely define the medicine’s profile and reduce the uncertainty about the product’s benefits, harms and value and lead to a follow-on full approval/access, recommendation or a withdrawal/limitation of use.

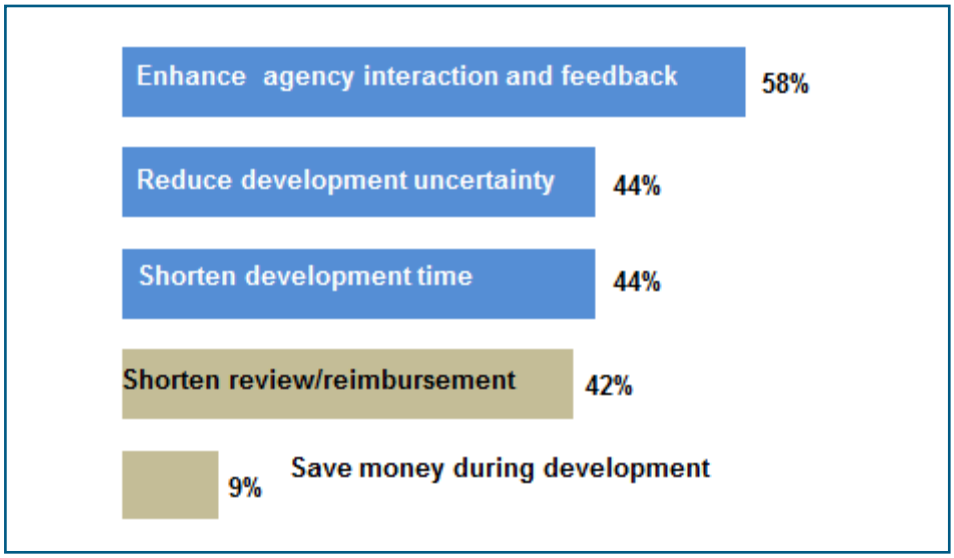
Interactive survey

Dr Liberti took the opportunity of the Workshop to survey 51 of the Workshop participants about flexible regulatory, access and reimbursement pathways. Some of the results of this survey were compared with survey results from 22 participants in a 2016 CIRS Technical Forum. However, it should be recognised that in

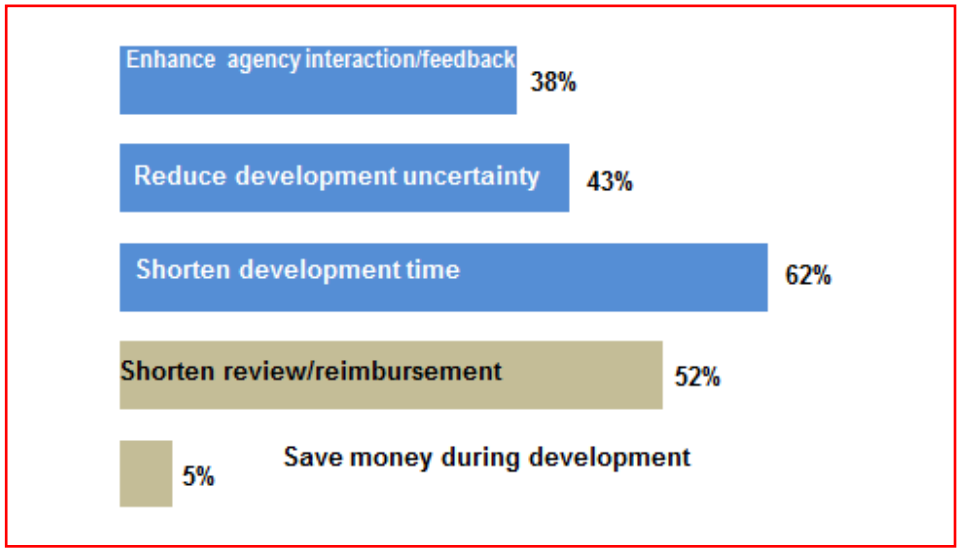
addition to a greater number of participants in the Workshop survey, the Technical Forum consisted exclusively of pharmaceutical industry attendees.

Question 1: What do you think would be the two main reasons an FRP could be used as part of a development programme? (pick two)

Perhaps not surprisingly, a greater percentage of the 2016 Technical Forum survey respondents, who were exclusively from industry, thought that shortening time for product development and for review and reimbursement were the most important reasons for use of an FRP.



2017 Workshop survey results N = 51

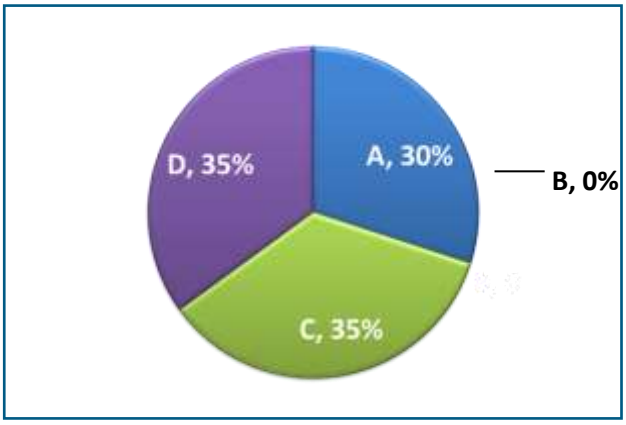


2016 Technical Forum survey results N =22

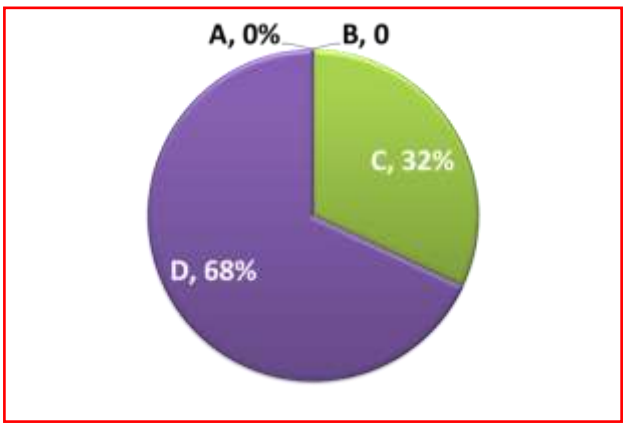
Question 2: How useful are regulatory pathways currently available at the US FDA to expedite reviews of important new medicines in the USA?

A higher percentage of participants in the 2016 survey indicated that expedited pathways available through the US FDA were fit for purpose (68%) compared with the 2017 Workshop (35%); whereas no respondents in 2016 and only 13% of respondents in 2017 felt that EMA expedited pathways met their needs

2017 Workshop survey results N = 51



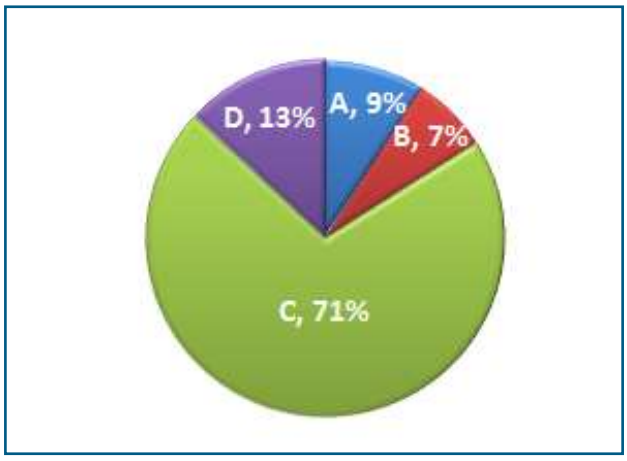
2016 Technical Forum survey results N =22



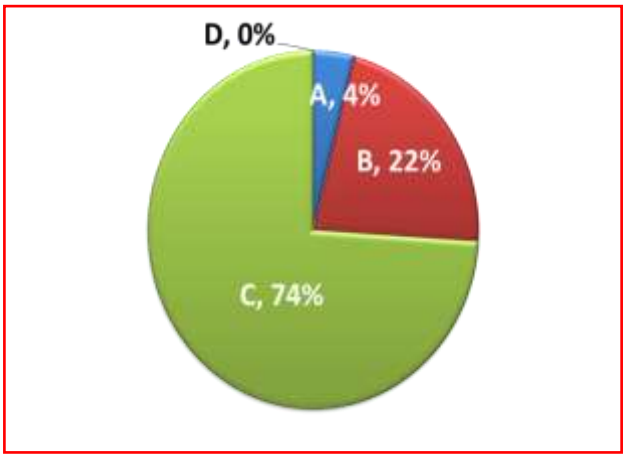
A = Do not know
B = Not useful or not meeting the need
C = Room for improvement
D = Meets the need

Question 3: How useful are regulatory pathways currently available at the EMA to expedite reviews of important new medicines in Europe?

2017 Workshop survey results N = 51



2016 Technical Forum survey results N = 22

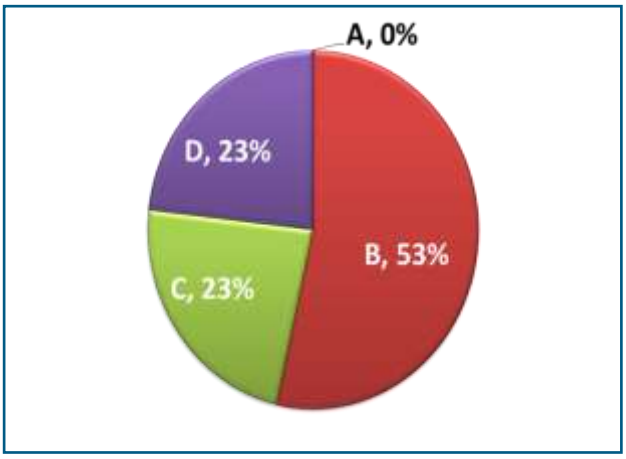


A = Do not know
B = Not useful or not meeting the need
C = Room for improvement
D = Meets the need

Questions 4 was unique to the 2017 Workshop.

Question 4: Does upstream regulatory/HTA agency involvement result in better meeting of downstream HTA and regulatory needs? (pick one)

The majority of participants indicated that they judge the value of early agency involvement on a case-by-case basis.



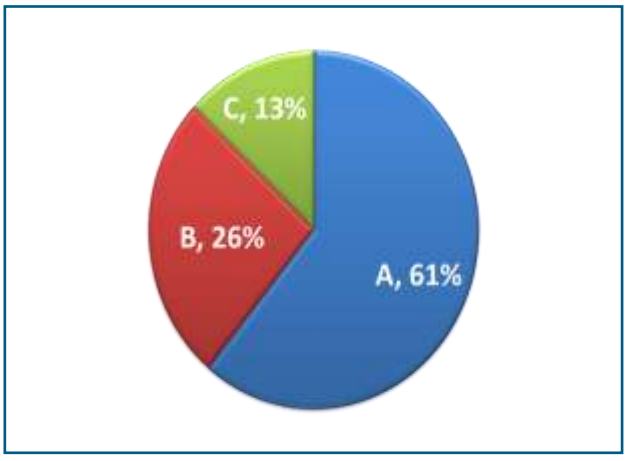
A = Not at all- not worth the effort
B = Case-by-case benefits
C= Always worth the effort
D = Still too early to tell

Question 5: Should aligned FRPs/FARPs be used only for products that meet an unmet medical need and that are considered to be prioritised medicines?

This question was posed to 2016 Forum participants in a slightly different format. Technical Forum question: **Aligned FRPs/FARPs should be used more widely for all therapy areas including chronic and lifestyle illnesses such as diabetes, obesity, high blood pressure.**

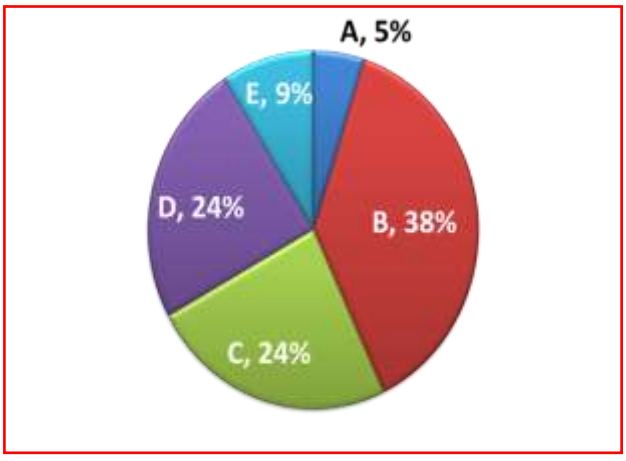
The majority of 2017 Workshop participants (61%) indicated that facilitated pathways should be reserved for medicines developed to treat an unmet medical need, whereas 41% of 2016 Forum participants indicated that the pathways should only be used for illnesses **not** characterised as chronic or life-style.

2017 Workshop survey results N = 51



A = Yes
B = No
C= Maybe

2016 Technical Forum survey results N =22

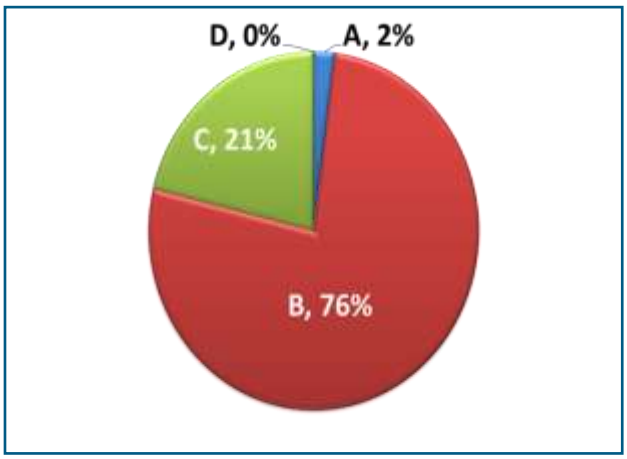


A = Strongly disagree
B = Disagree
C= Uncertain
D = Agree
E = Strongly agree

Question 6: What do you think is the main stumbling block for the adoption of an aligned FRP/FARP? Pick one

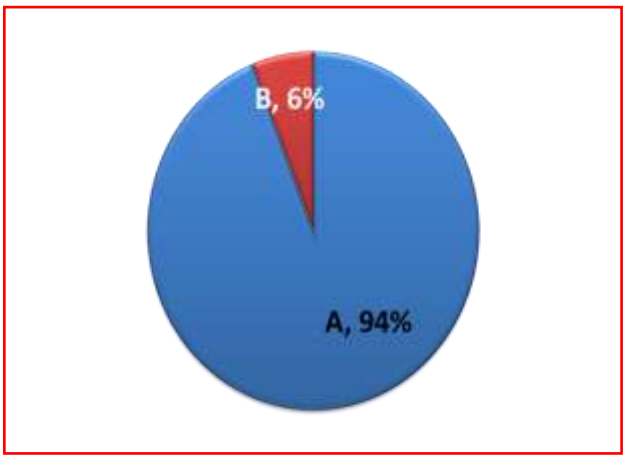
The same question was asked of 2016 Forum participants but only two possible answers were provided. The majority of respondents at both the 2017 Workshop and 2016 Technical Forum indicated that the lack of HTA agency or payer acceptance of the pathways was the biggest barrier to their adoption.

2017 Workshop survey results N = 51



A = Lack of regulatory acceptability to use such pathways
B = Lack of HTA agency/payer acceptability of medicines approved using such a pathway
C = Internal ambivalence or belief that such pathways are viable
D = External acceptance of FRP/FARPs by patients

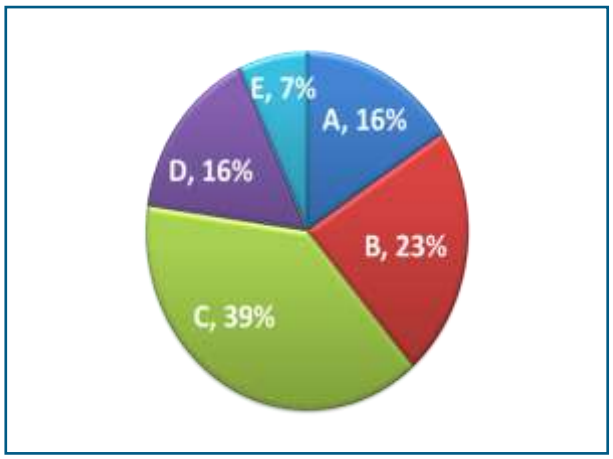
2016 Technical Forum survey results N = 22



A = Lack of HTA agency/payer acceptability of medicines approved using such a pathway
B = Internal ambivalence or belief that such pathways are viable

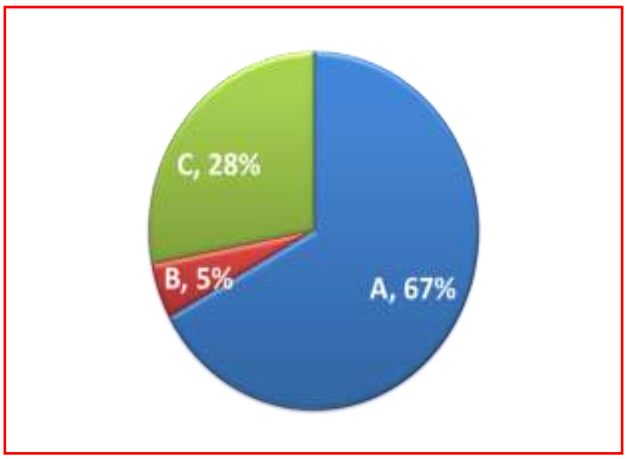
Question 7: By when do you think an aligned FRP/FARP pathway should be in place as a codified process within your geographic area of interest? A similar question was asked of 2016 Forum participants: **How likely do you believe it will be to see a fully implemented aligned FRP/FARP approach (integrating regulatory, patient, prescriber and HTA & payer needs) in a major jurisdiction (ie, US, EMA, Japan) within the next 5 years?** Thirty-nine percent of 2017 respondents felt that aligned pathways would be in place in five years whilst 28% of 2016 Forum respondents felt that this was likely to take place within 5 years.

2017 Workshop survey results N = 51



A = It is already in place
B = 1-2 years from now
C = 3-5 years from now
D = 6-10 years from now
E = Many years from now

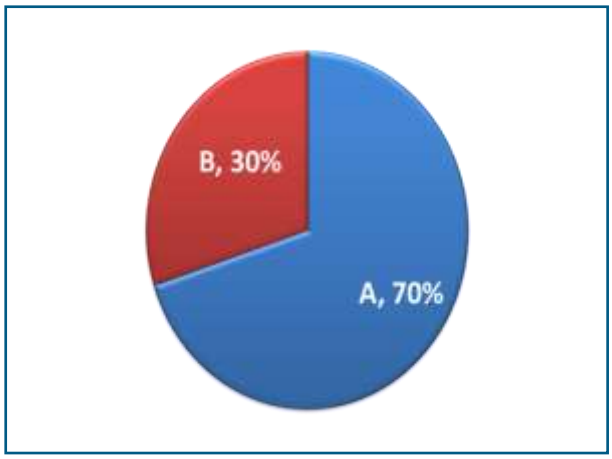
2016 Technical Forum survey results N = 22



A = Not all likely, not likely
B = Do not know
C = Likely or certain

Question 8 was unique to the 2017 Workshop.

Question 8: Use of an FRP pathway for products that meet a high unmet medical need should result in a higher proportion of positive HTA recommendations. The majority of Workshop attendees felt that FRPs for prioritised products should be more likely to be recommended for reimbursement.



A = Agree
B = Disagree

EMA viewpoint on PRIME: Does early upstream agency/stakeholder involvement result in better designed development programs facilitating agency decision making downstream?

Dr Tomas Salmonson, *Chair, CHMP, European Medicines Agency*

In 2016, the European Medicines Agency (EMA) launched the Priority Medicines (PRIME) programme to optimise development and regulatory review for earlier access to needed medicines. The programme includes provisions for accelerated review, conditional marketing authorisation and compassionate use. PRIME was designed toto be implemented along with adaptive pathways, registry initiatives, the collaboration of health technology assessment agencies and payer bodies and the involvement of patients.

Following written confirmation of PRIME eligibility and the potential for accelerated assessment, the programme includes the early appointment of a Committee for Medicinal Products for Human Use (CHMP) rapporteur during product development, a kick-off meeting with multidisciplinary expertise from the European Union (EU) network, enhanced scientific advice at key development milestones and decision points, an EMA dedicated contact point and fee incentives for scientific advice for small and medium enterprises and academics.

Eligibility

Eligibility to the PRIME scheme is based on accelerated assessment criteria. That is, the programme is designed for medicinal products of major public health interest, particularly from the viewpoint of therapeutic innovation. The product should have the potential to address, to a significant extent, an unmet medical need for which no satisfactory treatment exists, or if a method does exist, the product should bring a major therapeutic advantage. This advantage could be a meaningful improvement of efficacy creating an impact on onset or duration of disease or improvement in morbidity or mortality. Scientific justification for the product must be based on data and evidence available from nonclinical and clinical development. Small and medium enterprises and academia can make application to enter the PRIME programme at phase 1, based on proof of principle: sound pharmacological rationale, convincing scientific concept, relevant nonclinical effects of sufficiently large magnitude and duration, and tolerability in first-in-man trials. All other applicants can make application to enter the PRIME programme in the early clinical phase, based on proof of concept: sound pharmacological rationale, clinical response with efficacy and safety data in patients from exploratory trials showing substantial improvement, with the magnitude, duration and relevance of outcomes to be judged on a case-by-case basis.

By September 2017, 28 of 130 PRIME eligibility requests were granted, approximately 50% to small and medium enterprises. Applications have generally been of good quality, with only a few considered out of scope. Requests covered a wide range of therapeutic areas and product types, 44% were for oncology/haematology products and 28% for advanced therapy medicinal products (Figure 2). Assessment of eligibility requests is a short, robust, 40-day procedure involving multiple committees (Figure 3). Oversight group discussions of eligibility may focus on the product's stage of development, ability to satisfy unmet medical needs, requests based on literature rather than data or the extrapolation of data from other products.

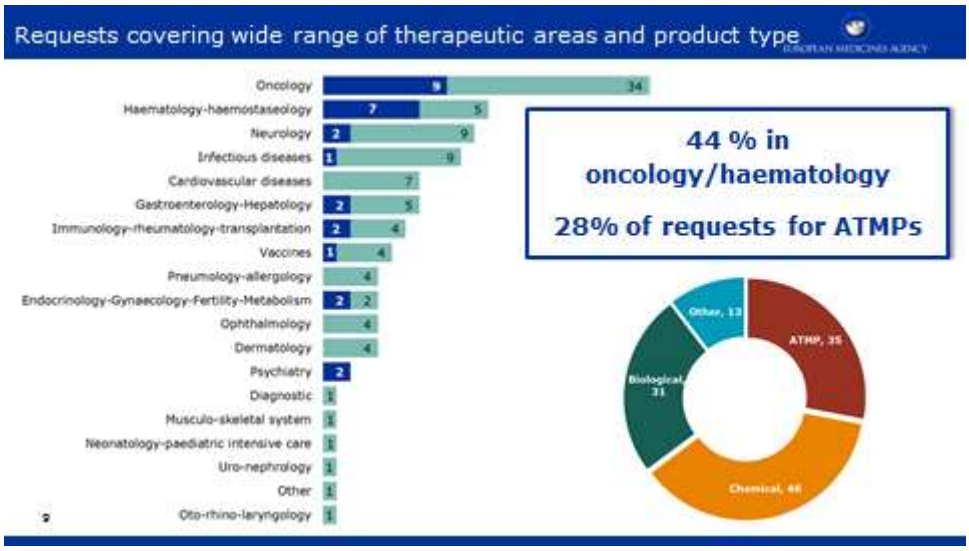


Figure 2. Requests for PRIME eligibility have encompassed all therapeutic areas.

Figure 3. Assessment of eligibility requests is a 40-day procedure employing several committees.

Only one in five requests for entry into PRIME based on proof of principle are granted. The main reasons for refusal are weak pharmacological rationale, insufficient nonclinical evidence on the claimed mechanism of action, limited relevance of animal models presented and insufficient pharmacokinetic exposure data to support the expected clinical outcome. Reasons for denial into the PRIME programme at proof of concept stage include trial design issues such as treatment effect not isolated from other factors, use of concomitant treatments, failed study, inconsistency of results, claim in subgroup insufficiently justified, sample issues and comparison to inadequate historical control data

PRIME kick off meetings

As of September 2017, kick-off meetings had been held for 15 products, each approximately 4 months after PRIME eligibility. Flexibility from applicants has been required to find the optimal timing for meetings.

Availability of a briefing document approximately 3-4 weeks in advance is essential for fruitful discussion and an internal preparatory teleconference is held approximately 2 weeks before the kick off meeting. The meeting itself is conducted through a tailored agenda with a broad discussion on development and regulatory strategy and many issues are identified for future scientific advice. Awareness is raised regarding the planning of post-authorisation aspects and HTA interface and a plan for future interactions is agreed.

Early rapporteur appointment provides opportunities for product knowledge accrual, the identification of relevant expertise, the building of an adequate team and the exertion of influence on development. Participants have expressed very positive views on the kick-off meeting, emphasising their ability to facilitate interactions across committees and with EMA. It was further underscored that the timing of PRIME eligibility is critical for fruitful engagement and that there was the need to improve follow-up communications/updates.

PRIME and scientific advice

Enhanced scientific advice had been provided for seven PRIME products and eleven requests for advice received following kick-off meetings. These were multi-stakeholder meetings, one with EMA/HTA parallel advice and two with patient involvement. All quality, non-clinical and clinical aspects were covered at the meetings and rapporteur involvement was coordinated though SAWP.

Moving forward

Additional PRIME programme developments that occurred during the EMA workshop held in May 2017, on the first anniversary of PRIME included the addition of an opportunity for an applicant to highlight particular characteristics of the development that warrant further support through PRIME and the ability for applicants to contact EMA for general guidance. It was decided that sponsors of eligible products are not prohibited from seeking national scientific advice during development and the EMA intention to engage health technology assessment bodies and patients as part of the PRIME programme and the importance of prospective planning of paediatric, orphan and post-authorisation aspects were emphasised.

Conclusions

Although it is still at an early time point in the PRIME programme experience, PRIME, which represents a significant EMA investment, has produced excellent collaboration across committees and covers all aspects of drug development. The programme includes both early access aspects and a life-cycle perspective with discussions across product type and class and provides an early focus on the post-approval development plan. In addition to the opportunity for enhanced iterative scientific advice, unexpected benefits to the programme to date include the opportunity for patient involvement, important links to parallel HTA advice and discussions with registry holders.

PRIME includes both early access aspects and a life-cycle perspective with discussions across product type and class and provides an early focus on the post-approval development plan

Payer perspective: Are these pathways fit for purpose?

Dr Ad Schuurman, *Head of Business Contact Centre and International Affairs, National Health Care Institute (ZIN), Netherlands*

It is understandable that payers, who are responsible for the dispersal of limited funds for healthcare services including medicines, would need to exert some controls over that dispersal. For example, payers would like to have some control of the volume of medicines that are reimbursed through more transparency from healthcare providers as to the indications, prescription timing and dosage of medicines after their approval.

All stakeholders need to assume co-responsibility for testing new medicines and to discuss what needs to be known and measured about those medicines

In addition, although payers are aware that the types of evidence being developed for the approval of medicines may be evolving, they would like to prevent a decline in evidence quality through stakeholder agreements. These would include an agreement that the quality of medicines should be judged through their measurable effects and through knowing what the measurement results mean as well as an agreement on the degree of the clinical relevance of those effects. All stakeholders need to assume co-responsibility for testing new medicines and to discuss what needs to be known and measured about those medicines, including what would constitute a convincing outcome. The right comparator must be used in testing with little delay between treatment and emergent results, clear alternatives and rapid implementation of decisions.

Because healthcare expenditures have escalated to nearly unsustainable levels, payers also want to control costs, potentially through mechanisms such as adaptive reimbursement, confidential national pricing, or agreement on mutually acceptable prices. As part of cost containment, payers would like to see programmes such as Medicines Adaptive Pathways to Patients (MAPPs) applied to special cases such as treatment for life-threatening diseases or urgent public health protection. Major improvements should be expected to be gained through use of these medicines and a realistic exit strategy should be agreed with the knowledge of patients and physicians if expectations are not met. That is, payer MAPPs collaboration requires guarantees.

Patients and physicians should agree in writing in advance regarding the possible withdrawal of the medicine if results are not as expected and that they have been informed regarding the uncertainties in the medicine's efficacy and safety. In this plan, reimbursement can be decreased or increased according to mutually agreed results, market authorisation can be stopped and populations or indications can be reduced or changed.

To avoid price differences in the EU during the adaptive period for new medicine, drug costs should come from an EU budget, with member states concluding their own pricing negotiations after full market authorisation. A low starting price may incentivise industry to complete development as soon as possible and would give member states a better starting point for negotiations. Payment after performance may be easier to realise than pay backs for non-performance, because if conditions for generous payment after performance cannot be agreed, pay backs would likely be even more difficult to implement. Strict criteria for performance must be developed and "what-ifs" must be clear to all concerned. The number of flexible deals must be limited and designed as to be as simple as possible. If the adaptation process is too time consuming, it may be declared unworkable before it has had a chance to prove its worth.

Strategic considerations, opportunities, outcomes and pitfalls: Company perspective

Dr Jens Heisterberg, *Vice President, Regulatory Affairs Intelligence, Novo Nordisk, Denmark*

Why expedite licensing of medicines addressing a high unmet medical need?

Although there are currently no uniform, globally accepted criteria for unmet medical need, it is generally considered to exist when there is either no available therapy or significant room for improvement with existing therapies for a severely debilitating or life-threatening disease. Examples of unmet medical need include many diseases within oncology and haematology, infectious diseases, neurodegenerative diseases and orphan diseases.

For patients, expedited pathways provide early access to medicines for severe diseases for which no or limited treatment options exist. These pathways also provide regulators with a tool to balance unmet medical need and the severity of the disease against an increased number of uncertainties about efficacy and safety and for industry, they incentivise the development of innovative medicines.

New medicines can be expedited through enhanced regulatory guidance, faster regulatory review or licencing based on a limited clinical data package. These programmes can result in earlier and more frequent interactions between industry and regulators, the allocation of regulatory resources to provide high-quality scientific and regulatory advice to sponsors to facilitate fast development and approval and reduced or no fee for interactions. Obviously, however, these programmes come with a cost, are resource demanding of regulators and questions remain regarding whether the programme funding will be adequate.

Examples of enhanced scientific advice include that provided through the PRIority MEdicine (PRIME) and Adaptive Pathways Approach in the EU and Fast Track and Breakthrough Therapy designations in the US (Table 1). Timing for regulatory review can typically be reduced by 2 to 4 months, depending on the programme but programmes aiming to reduce review time have strengths and weaknesses. They are good incentives for companies to promote the development of new medicines addressing an unmet medical need and they also serve the purpose of focussing regulatory resources on medicines that matter the most. However, the programmes will often allow a license only a few months earlier than standard, and thus the effect on public health may be limited, while shortened review times put assessors at regulatory agencies at increased pressure.

Programmes aimed at potentially granting a license to medicines with a certain amount or type of clinical data, for example, data on surrogate endpoints, enable an assessment of benefits and risks, but without a full, comprehensive data package that would normally be required (Table 2). They have the potential to significantly reduce the time to the approval of promising medicines by several years, but they are also associated with a markedly increased level of uncertainty about the benefits and risks of a medicine at the

Table 1. Programmes for shortened regulatory review time.

	EU	US			Japan				Canada	
	Accelerated Assessment	Fast Track	Breakthrough Therapy	Priority Review	SAKIGAKE package	Prior assessment consultation	Priority review	Expedited review	Priority Review	Notice of Compliance with Conditions (NOC/c)
Nature of programme	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment	Expedited regulatory assessment and expedited approval pathway
Candidate medicines	Major interest from the point of view of public health and in particular viewpoint of therapeutic innovation. Addressing unmet medical need and expected to have major impact on medical practice.	Demonstrated potential to address unmet medical need in serious condition; or designated as a qualified infectious disease product	Preliminary clinical evidence of substantial improvement over existing therapies in serious condition	Potential significant improvement in safety or effectiveness in serious condition; or labelling change related to certain paediatric studies; or designated as qualified infectious disease product; or submitted with priority review voucher	Medicines which meet all the following criteria: -Innovative medicine (i.e. new mechanism of action) -Medicine for serious disease -Medicine with extremely high efficacy -Company intends to pioneer in developing the drug in Japan	No particular criteria. Candidates are chosen twice a year considering the medical necessity	Significant improvement in safety or effectiveness compared to existing medicines or therapies for serious diseases	Medicines, which do not meet the priority review criteria but are regarded as associated with particularly high medical necessity	Serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness in a disease or condition for which no medicine is marketed; or -significant efficacy and/or safety advantage over existing medicines	Medicines with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.
Main features	Shortened review time (by 60 days).	Frequent interactions with review team. Rolling review.	Intensive guidance on development. Organisational commitment. Rolling review.	Shortened review time (10 months to 6 months).	Prioritised assessment consultation and shortened review time. Expected total review time: 6 month (regular review: 12 month)	Quality, non-clinical or clinical pharmacology data are reviewed before pivotal clinical trials are completed. Shortened review time (1 -2 months).	Shortened review time (by 3 month)	Shortened review time (by 1-2 month)	Shortened review target of 180 calendar days.	Approval based on surrogate endpoint or intermediate clinical endpoint. Shortened review target of 200 calendar days.

Table 2. Programmes for acceptance of limited data packages.

	EU		US	Japan		Canada
	Conditional Marketing Authorisation	Marketing Authorisation Under Exceptional Circumstances	Accelerated Approval	Approval with condition/ period	Approval with conditions	Notice of Compliance with Conditions (NOC/c)
Nature of programme	Expedited approval pathway	Expedited approval pathway	Expedited approval pathway	Expedited approval pathway	Expedited approval pathway	Expedited regulatory assessment and expedited approval pathway
Candidate medicines	Demonstrated positive benefit-risk and addressing unmet medical need in serious diseases, emergency situations or orphan diseases, and where immediate availability on the market outweighs risks.	Inability to provide comprehensive clinical data due to rareness of disease, the present state of scientific knowledge, or ethical concerns.	Meaningful advantage over available therapies in serious condition. Efficacy documented with surrogate endpoint likely to predict clinical benefit or clinical endpoint likely to predict effect on irreversible morbidity or mortality	Only applicable to regenerative products, e.g. cholinergic neuron cells. Does not apply to chemicals or antibodies.	No particular criteria. Depends on seriousness of disease and characteristics of endpoint. Medicines for life-threatening diseases or diseases, which seriously affect the activity of daily living is thought to be a target of this program.	Medicines with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.
Main features	Approval based on limited data package.	Approval based on limited data package.	Approval based on surrogate endpoint or intermediate clinical endpoint.	Approval based on limited data package.	Approval based on limited data package.	Approval based on surrogate endpoint or intermediate clinical endpoint. Shortened review target of 200 calendar days.

time of licencing. Most programmes will allow a license on the condition that confirmatory data can be obtained post-approval so approval based on surrogate endpoints and a limited clinical data package needs subsequently to be corroborated by post-approval data encompassing hard clinical endpoints establishing clinical benefit; however, once a medicine has been licensed, a number of challenges relating to the post-approval trials arise such as the ethical nature and feasibility of conducting placebo-controlled clinical trials. Moreover, the higher uncertainty makes it more difficult for health technology assessors and payers to evaluate the value of a medicine and whether needed evidence will ever be generated and what the role of real-world data may play in the evidence generation may remain unknown.

Conclusions

Programmes for early licensing based on limited clinical data have the potential to significantly accelerate the access of important medicines to patients. Good regulatory programmes have been developed although some refinement may still be required and more effective use – both by regulators and industry – is still needed. Global regulatory convergence has come far but there is still vast room for improvement. Global convergence is lacking on the access side and obtaining meaningful data post-licensing is challenging. There are many methodological problems in interpreting real-world data. Potential ways forward include joint rather than parallel regulatory HTA scientific advice and new outcomes-based pricing schemes in which payment is only made when benefit is achieved but there are no simple solutions for this complex area.

Global regulatory convergence has come far but there is still vast room for improvement. Global convergence is lacking on the access side and obtaining meaningful data post-licensing is challenging.

How can we ensure that FRPs address stakeholder needs? Patient perspective

Valentina Strammiello, *Programme Manager, European Patients Forum*

The European Patients Forum

Active since 2003, the European Patients' Forum (EPF) is an independent, non-governmental umbrella organisation providing a voice for 74 patients groups, EU disease-specific organisations and national patient coalitions. The EPF vision calls for equitable and timely access to high-quality, patient-centred health and social care for all EU patients regardless of where they live in the EU. The EPF supports investment in effective, beneficial technologies that improve the quality of life and disinvestment in those that do not.

Patients' perspective on traditional and facilitated regulatory pathways (FRPs)

Many patients recognise that strides are being made to ensure the timely development and review of medicines such as the European Medicines Agency-European Union Network for Health Technology Assessment (EMA-EUnetHTA) initiative on Scientific Advice/Early Dialogues, in which patients have played a role. In fact, the EMA has taken steps to involve patients at various time points across the review of new medicines (Figure 4).

Patients have also been part of the collection and use of real-world data to support the expedited approval of medicines, either data from the use of a medicine in routine clinical practice or routinely collected clinical, economic, health-related quality-of-life and patient-reported outcomes from registries, electronic medical records, and claims databases.

The EPF has actively participated in ADAPT SMART (Accelerated Development of Appropriate Patient Therapies) a sustainable, multi-stakeholder enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities. "MAPPs seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion." (www.adaptsmart.eu/home). MAPPs, broadly, are a multi-stakeholder approach to developing "randomised controlled trial (RCT)-plus" evaluation of new medicines. MAPPs involve a notable upstream shift in prospective planning and discussions on topics such as: design of the development plan, identifying sources of real-world data (RWD) and how they can be best utilised in combination with registries and RCTs, budget impact estimates, reimbursement and prescribing conditions, and resource planning. EPF ADAPT SMART participation has provided an excellent opportunity for patient interaction with industry and regulatory and health technology assessment (HTA) agencies (Figure 5).

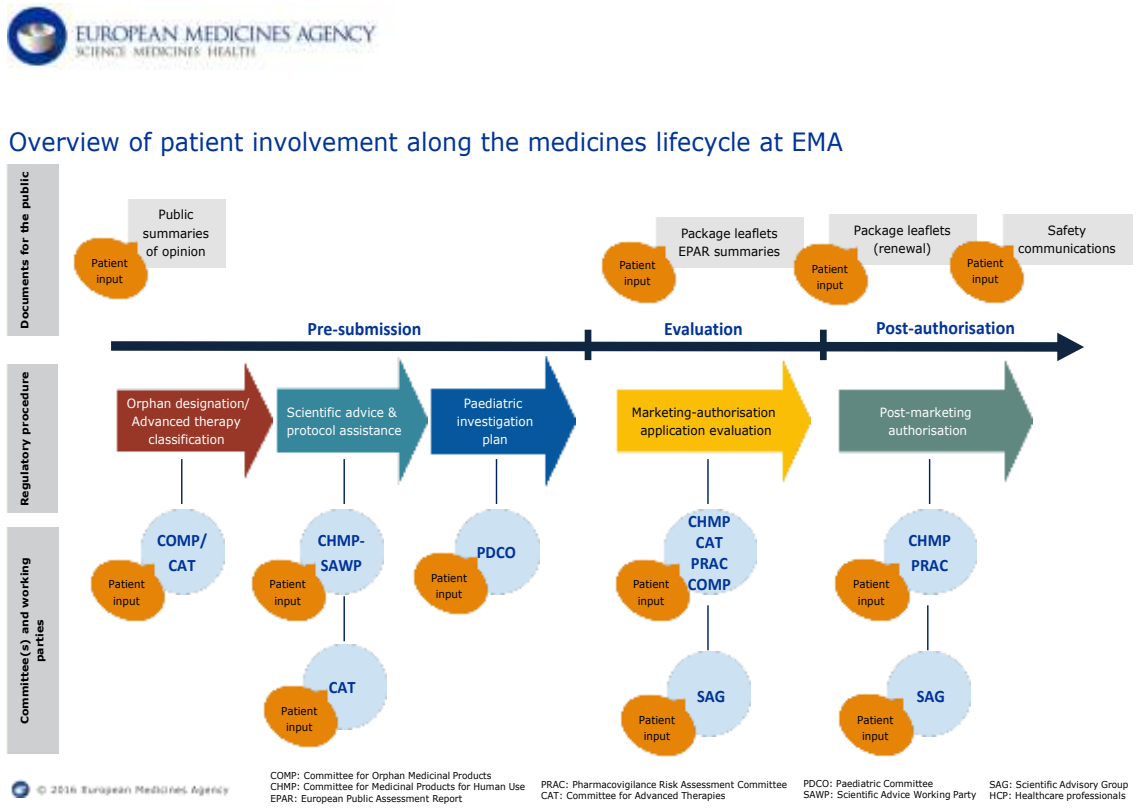


Figure 4. The European Medicines Agency has incorporated patient participation in the life cycle of medicines review.

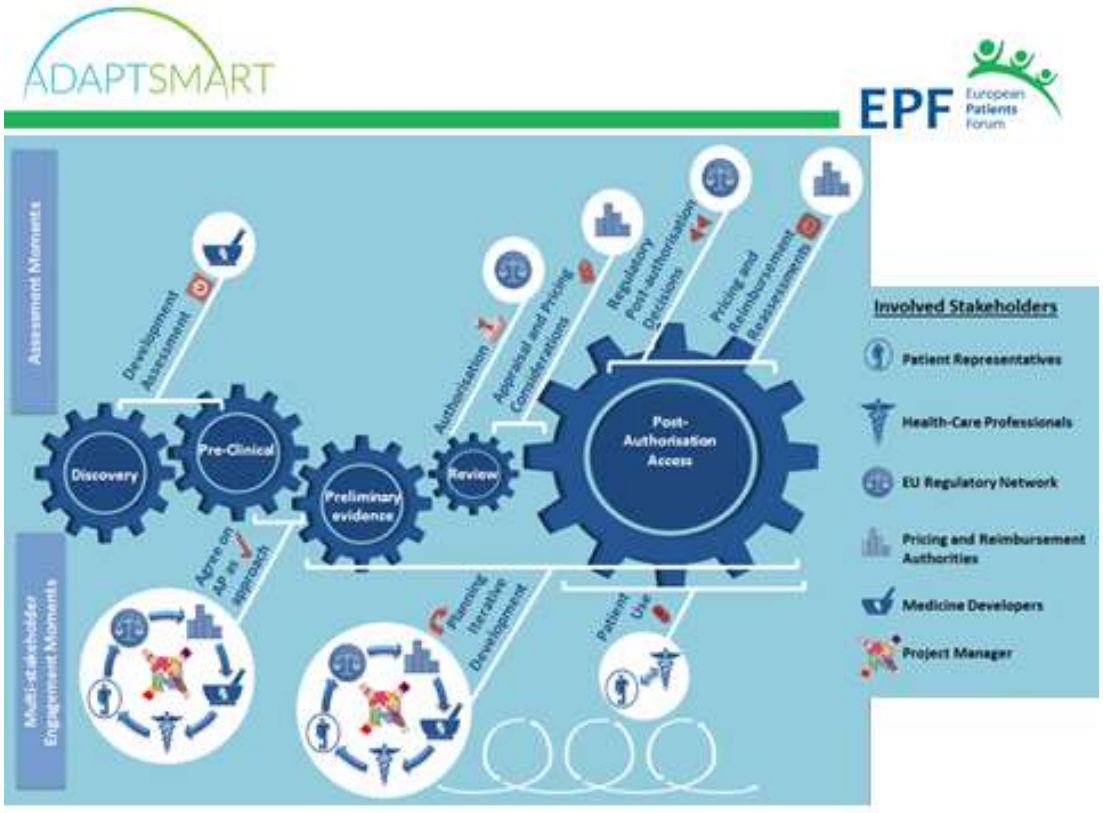


Figure 5. Stakeholder interaction in medicines development.

Moving forward

Patient participation in ADAPT SMART programme has also assisted in the identification of gaps in patient involvement that need to be addressed. For example, a strong legal basis for FRPs and adaptive pathways is key for patients, particularly as it applies to the disinvestment in or withdrawal of new medicines, both of which have the potential to impact patient treatment options. Some consideration of national and cultural variables in medicines' development is also required as is truly informed and comprehensive consent, which includes a complete understanding of all potential implications of treatments and of inclusion and exclusion criteria prior to study enrolment and an awareness of the trade-off in benefits and risks for the expedited use of new medicines.

. . . a strong legal basis for FRPs and adaptive pathways is key for patients, particularly as it applies to the disinvestment in or withdrawal of new medicines . . .

Communication and better promotion of early access to innovative treatments is needed as well as patient education and patient organisations and patient advocates make excellent sources for that information and education. The European Patients' Academy (EUPATI) is a consortium from the pharmaceutical industry, academia, not-for-profit, and patient organisations developed and implemented by the Innovative Medicines Initiative (IMI) and led by the EPF. EUPATI provides training for patient experts in medicines development, clinical trials, medicines regulations and health technology assessment, maintains a Toolbox on Medicine Development in many languages and coordinates a network of national platforms for patient advocacy. Patient involvement has become an integral part of the traditional regulatory process, but a new collaborative mind-set with a pragmatic, ethical, and transparent basis is required from all stakeholders.

How might a facilitated regulatory pathway in another jurisdiction affect evidence needs and decision-making? Non-EU/US regulatory agency viewpoint

Dr Robyn Lim, *Senior Science Advisor, Health Products and Food Branch, Health Canada*

Driven by domestic and international discussions concerning the democratisation of healthcare and health system sustainability, the reasons for agencies to update evidence requirements are increasing. Decision makers are also now determining how best to tackle up front the critical uncertainties that attend new medicines.

Other issues are also influencing current evidence policy development. All decision makers are confronted with multiple evidence generation and stakeholder innovations with global reach, such as patient-focussed drug development, real-world data/evidence, facilitated regulatory and access approaches, and parallel regulatory and health technology assessment; however, because many of these innovations are still in active development, implementation strategies and choices remain unclear. Furthermore, individual decision makers' evidence and decision models must also reflect a variety of context-specific considerations, such as variances in treatment approaches and/or in benefit-risk contexts and profiles, for example, between geographic areas and/or between patient subpopulations. Incomplete understanding of these heterogeneities is an added complication. Thus, technical and policy options for evidence generation and decision models are more numerous than ever, but many uncertainties still exist about which choices would be best.

The evidence generation choices made (for example, regarding potential populations and indications to be targeted) influence the nature of the evidence produced. The focus for evidence collection can be narrowed or shifted by these choices, affecting the resulting evidence package and potentially the consequent authorisation and reimbursement decision outcomes (Figure 6). Developers' options for regulatory approach to be taken, such as parallel versus sequential involvement of regulators and others, also can influence ultimate authorisation decision outcomes. For example, as a result of facilitated regulatory/reimbursement pathways which may not be broadly inclusive of jurisdictions, regulatory agencies not initially involved in evidence requirements discussions (that is, "follow-on" regulators) may find their decisions affected by gaps between their evidence needs and the evidence packages received. Jurisdictions without facilitated regulatory/reimbursement pathways would face additional misalignments and be further disadvantaged.

The focus for evidence collection can be narrowed or shifted by these choices, affecting the resulting evidence package and potentially the consequent authorisation and reimbursement decision outcomes

In some cases, however, regulatory heterogeneity in decisions may be inevitable due to unavoidable mismatches in evidence needs, in spite of active efforts to include multiple regulators' inputs up-front; generalisability of findings, as well as diversity of context-specific regulatory technical and value judgements, are contributing factors. Examples of diverging contexts include regional variations in prevalence of diseases or conditions such opioid use, obesity and attention deficit hyperactivity disorder in North America and Europe or infectious diseases that are endemic in particular regions. Available therapies and treatment approaches can also differ by region or jurisdiction, influencing standards of care and active comparator options; in turn,

judgements of optimal study design may also vary across jurisdictions. Lastly, efficacy, safety and benefit-risk balance conclusions are based on subjective value judgements, and where standards are still evolving or effects are finely balanced, differences in decision outcomes may be more pronounced. Thus, contexts and choices matter.

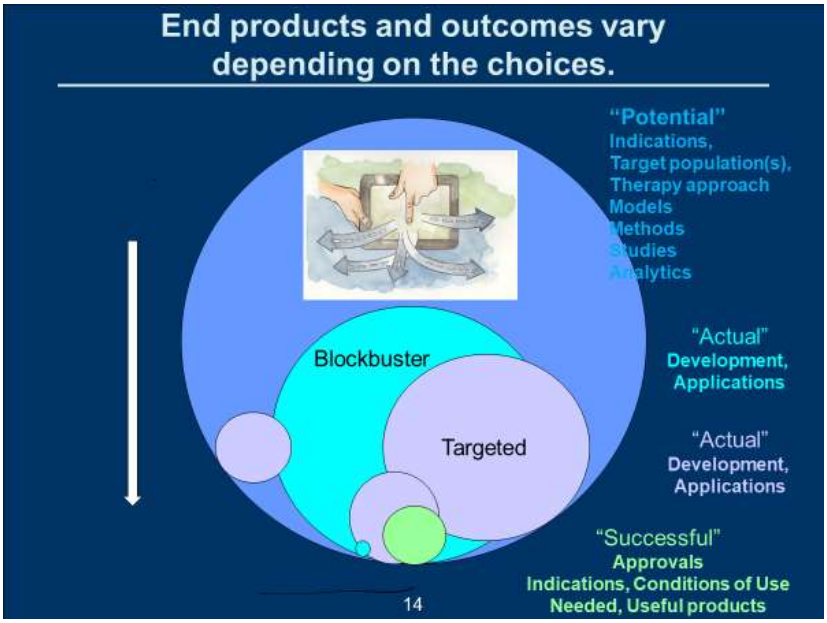


Figure 6. Developers' and regulators' choices may influence the nature of the evidence produced and narrow or shift focus and change outcomes.

The attributes for needed, well-performing drugs and the necessary evidence to substantiate drug quality and value are even more likely to elicit diversity in judgements when the broader spectrum of decision makers, such as reimbursers, is considered. Moreover, if the "traditional" evidence collected prior to authorisation is considered inadequate and novel "real-world" evidence solutions are needed, additional considerations for decision making may include an individual jurisdiction's capabilities to generate relevant post-authorisation evidence.

To address the evidence and choice challenges described, maps of regional or jurisdictional differences, regarding, for example, diseases, patients, unmet needs, available therapies, cultural values and methods/technical capabilities, could be developed to identify and better understand: 1) where commonalities can be leveraged during product development planning and execution to "pull" needed products through development; and 2) where differences need to be confronted and risk-managed during mapping of evidence needs and during options selection for evidence generation. Several strategy options to generate such maps could be considered. For example, individual product developers could generate these on a case-by-case basis for specific product development needs, either very early on in product development or at later stages; alternatively, more generalised and anticipatory multi-stakeholder mapping initiatives could be developed. A *post-hoc* approach would be for "evidence generalisability" analyses to be performed. Sponsors could submit these as part of their regulatory and reimbursement applications to "follow-on" jurisdictions (that is, those not included in initial evidence needs discussions). Alternatively, regulators could perform their own sponsor-triggered evidence "applicability analyses", to inform their decisions. It should be noted that the later on in the

development and/or regulatory/reimbursement process that such analyses are performed, the smaller the chance to avoid misalignments.

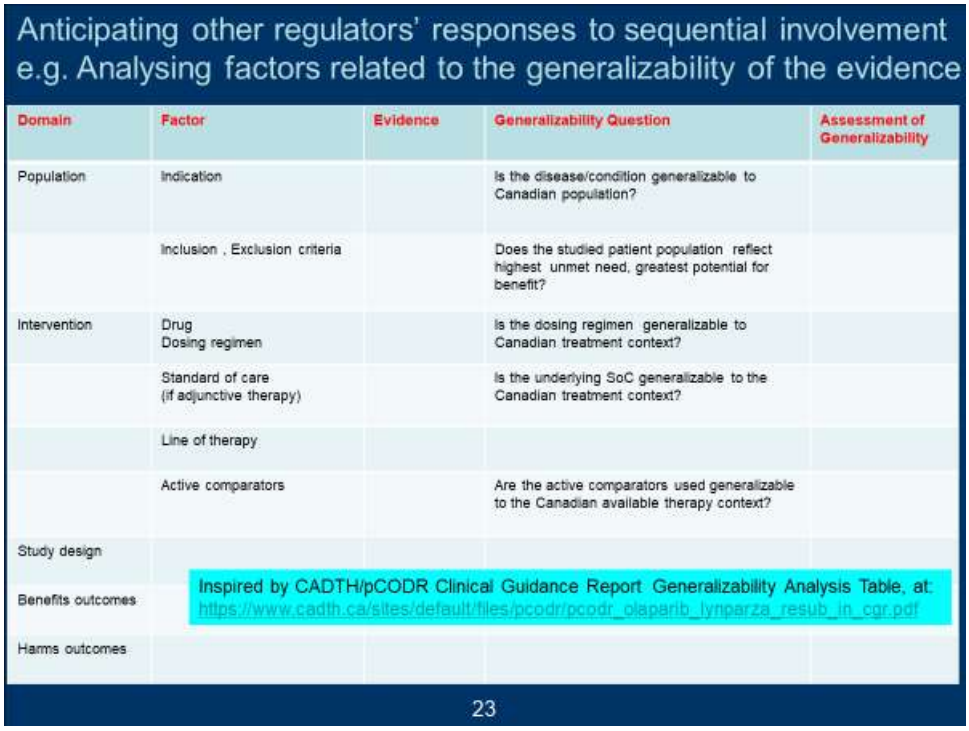


Figure 7. Additional potential regulatory approaches include generalisability/applicability assessment and management, in which follow-on jurisdictions perform their own "applicability analyses" and options management.

Conclusions

When considering the use of facilitated regulatory/access pathways, upfront alignment between jurisdictions would help achieve positive outcomes for all. To this end, current national discussions on this topic should expand and be coordinated globally to minimise the potential for systematic exclusion early on in the process of certain regulatory voices regarding evidence needs. Otherwise, if evidence complications and uncertainties must be tackled at late stages, various costs to multiple stakeholders are foreseeable such as increased regulatory review time or negative decisions. In other words, non-alignments at the front end may lead to inefficiencies and decision diversity at the back end.

How could HTA agencies offer accelerated review pathways aligned with FRP processes and evidentiary requirements? HTA perspective

Prof Andrew Wilson, *Chair, Pharmaceutical Benefits Advisory Committee, Department of Health, Australia*

Government investment in healthcare

Governments invest in healthcare to provide equity for its citizens, facilitating access for individuals who would not otherwise be able to afford therapy and protecting them from the financial hardship and the economic inequalities that may result from illness. In addition, healthcare can be regarded as an industry, providing direct and indirect employment and government support for this industry can facilitate innovation. The Australian healthcare system is a federation entity, with separate overlapping healthcare responsibilities. There is a high level of government subsidy for public and private services and 45% of Australians also have private health insurance. The Australian Pharmaceutical Benefits Scheme (PBS) subsidised more than 85% of prescriptions medicines, whilst the Medicines Benefits Scheme (MBS) subsidises medical services and diagnostic and therapeutic procedures. In operation for over 60 years, PBS is the main federal government subsidy programme for medicines, for which all Australian permanent residents are eligible. PBS covers over 5,300 brands/ products and over 209 million prescriptions were written in 2015-16 at a cost to the government of $13.4 billion, which was a 23% increase before rebates. An increasing proportion of the PBS budget is spent on high-cost drugs, especially cancer and immunomodulating drugs and since 1993, a cost-effectiveness evaluation for all drugs has been mandatory.

The Pharmaceutical Benefits Advisory Committee

To be chosen for subsidy, drugs must be registered with the Australian Therapeutic Goods Administration (TGA), after an assessment of their efficacy, safety and quality. The Pharmaceutical Benefits Advisory Committee (PBAC) recommends drugs for coverage after assessing their comparative effectiveness, comparative safety and comparative costs after which the Minister accepts or rejects this recommendation and the government provides the funding. According to the Australian National Health Act, the PBS cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health for at least some people.

Possible PBAC outcomes are to recommend a drug with cost-minimisation (for drugs with no price advantage) or to recommend a drug as having acceptable cost-effectiveness. The PBAC can reject a drug because its incremental cost-effectiveness ratio is unacceptably large, because it is associated with a high level of uncertainty because of the quality of its evidence, because of concerns about the total cost of the drug or because of concerns about usage beyond restriction. Finally, the PBAC can defer a recommendation because they request further information or because the drug has not yet been registered with the TGA. All

information about recommendations is made publicly available on the PBS website in a Public Summary Document. Quantifiable factors influencing PBAC decision making include comparative health gains, comparative cost-effectiveness, patient affordability in the absence of PBS subsidy, predicted use in practice and financial implications for the PBS and the Australian Government. Less quantifiable factors influencing PBAC decision making include overall confidence in the evidence and assumptions relied on in the submission, equity, the presence of effective alternatives, the severity of the medical condition treated, the ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most and other public health considerations such as the prudent use of antibiotics. Reasons that PBAC decision making has become more difficult include the fact that there is less certainty about comparative effectiveness and harms and the value of incremental gains, community expectations of earlier access, rare and rarer diseases, industry expectations for higher prices and changes within the pharmaceutical industry.

New opportunities and challenges

The 2015 Review of Medicines and Medical Devices Regulation and the 2017 Australian Government-Medicines Australia Strategic Agreement have presented new opportunities and challenges for healthcare in Australia. The 2015 Review of Medicines and Medical Devices Regulation resulted in 58 recommendations including increasing the use of overseas assessments with comparable regulators, while maintaining sovereignty of regulatory decisions; increasing flexibility in pre-market assessment processes for medicines and medical devices, including expedited and provisional approval and allowing the operation of commercial assessment bodies in Australia for medical device assessments; taking a risk-based approach to variations to medicines and medical devices and access to products not listed in the Australian Register of Therapeutic Goods (ARTG); enhancing post-market monitoring and improving integration of administrative arrangements relating to pre- and post-market processes for subsidy and other purposes.

The government-accepted TGA response to the review has been to establish a Priority Review system with the same standard, faster assessment of prescription medicines with a full data dossier in certain circumstances, a Provisional Approval system with a different standard, earlier access to certain promising new medicines that do not yet have a full dossier of clinical data. This is a time-limited registration pending evidence with enhance medicines vigilance that strengthens the post-registration monitoring of medicines and (and devices).

2017 Medicines Australia Strategic Agreement specifies that the Commonwealth and Medicines Australia will work to improve the efficiency, transparency and timeliness of the PBS listing process by targeting a 50% reduction in the number of resubmissions to the PBAC, including discussions regarding formalising solution orientated process for post-rejection discussion; and the feasibility of establishing faster consideration of resubmissions, including alternative pathways, submission dates and PBAC consideration dates. The Commonwealth and Medicines Australia will work to improve the efficiency, transparency and timeliness of the PBS listing process by reviewing the alignment of PBAC meeting times and additional arrangements to navigate with amendments to regulatory processes arising from the Medicines and Medical Devices Review implementation, including and in particular, provisional TGA approvals.

Parallel submissions to TGA/PBAC have already reduced the time to HTA decision. The mapping of TGA-PBAC processes suggests minimal areas of overlap and potential gains from the coordination of clinical assessment. The first pass rejection rate of 70% frequently reflects differences in sponsor vs PBAC views of the interpretation of results, comparators, appropriate models and model characteristics such as extrapolated benefits. Second pass (20%) and subsequent rejections (10%) are most frequently around cost-effectiveness, driven by requested price.

The PBAC defines investment and disinvestment activities as 'formal or explicit processes undertaken to consider the approval, refinement or removal of public funding for a health technology.' In 2009, the Australian Health Technology Review said 'HTA processes operate with the objective of ensuring that only safe and effective health technologies are permitted to be sold in Australia and that Australian Government funding is directed to priority technologies that are both clinically and cost effective.'

Health technology decision making in the ideal world

In the ideal world, formal horizon scanning and clinician and industry intelligence would facilitate the systematic active surveillance of emerging technologies. The assessment of these technologies would result in the prioritisation of which technologies to be assessed and the range of assessment outputs would be tailored to different policy questions. There would be clear methods for knowledge-based investment decisions, with the inclusion of all relevant evidentiary and contextual knowledge and costs. This method uses classic full health technology assessment and other methods such as rapid reviews and technology briefs. It also considers investment conditions under which technology is most cost effective. Investment decisions are explicitly linked to the introduction of technology and the co-ordination of policy levers across all service providers. Agreed frameworks allow the controlled adoption of technology with further collection of evidence. Technology could also be introduced under specified conditions such as fulfilment of research ethics requirements. Indicators for monitoring and evaluation of technology introduction would be prospectively defined. The interpretation of existing datasets collected by others would be harnessed and shared, with pre-specification of how particular findings will influence subsequent re-consideration of technology. There would be explicit processes for reconsideration of investment decision, identifying and prioritising when a technology should be reviewed, driven by local data from monitoring and evaluation activities and also informed by emergence of new evidence (Figure 8).

Broader public investment considerations include the traditional scope of health technology assessment such as clinical place, comparators, relative safety and effectiveness, cost-effectiveness, estimated patient populations, estimated costs. Considerations also include the scope relevant to investment decisions such as full operational costs, support/training requirements, staffing impacts and system efficiencies.

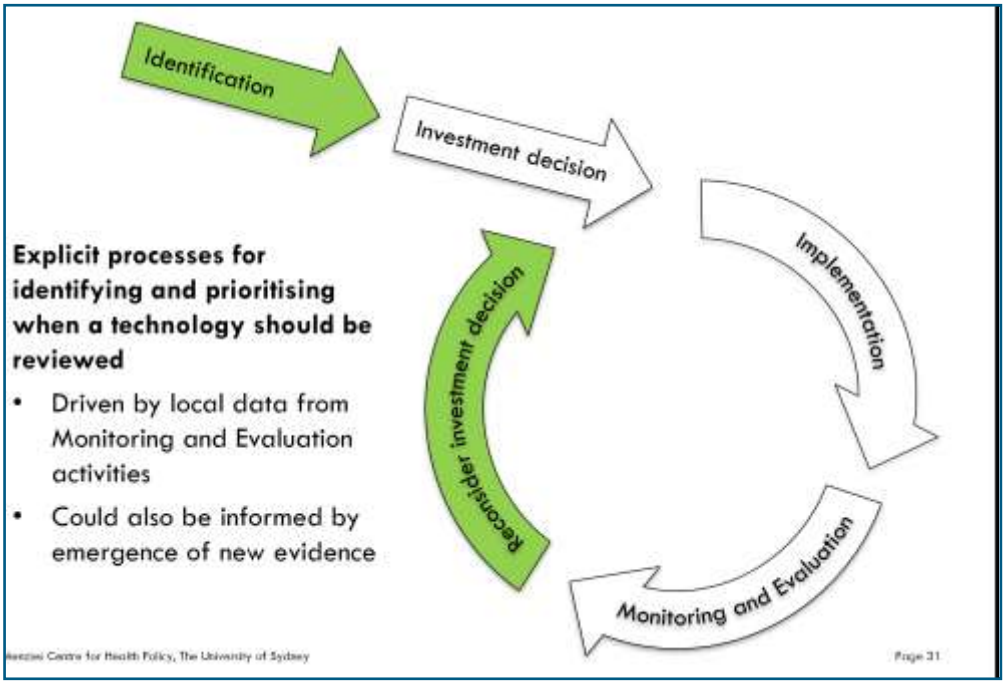


Figure 8. In an ideal world there would be explicit processes for reconsideration of investment decision, identifying and prioritising when a technology should be reviewed

Flexible access and reimbursement programmes with evidence development such as managed entry or managed access are highly consistent with the broader concept of investment/disinvestment. However, making health technology more flexible without the loss of value represents a challenge. Relevant questions for early access programmes include those that surround the benefits and safety of medicines in practice, the review of optimal practice or utilisation, the refinement of patient selection criteria, the adjustment of limits around frequency/interval for use, adherence to stepwise diagnostic/treatment pathways, changing who renders a service (limiting or broadening prescribing rights), narrowing where a technology can be used, the enforcement of technology as a replacement (if initial investment decision was predicated on this), and the (re)alignment due to technological advances. Challenges in early access programme include answerable questions about measuring outcomes efficiently, providing relevant timeframes, deciding on starting prices, negotiating final prices, managing clinician participation, managing exits for patients if the drug does not work as well, competitors, changing clinical practice, the capacity to manage multiple programmes with prioritisation, trust between parties.

Both flexible regulatory pathways and early access programmes change the relationship between the sponsoring company, the regulator and the payer. The payer, in effect, shares a greater proportion of the risks and possibly the benefits of the uncertainty with the sponsor. Governments as payers will expect that the budget consequences of that shared risk are recognised and compensated. Entry pricing expectations will be a rate-limiting step in the uptake of early access programmes.

Conclusions

Health technology assessment is a tool that assists with decisions about investment in healthcare including pharmaceuticals that should be flexible. In Australia implementation of change in health technology assessment now has a defined timeframe and the existing PBAC process, which ensures that the value of public expenditure on pharmaceuticals, is probably the clearest of any aspect of Australian healthcare investment. Modifications to that process should recognise the full scope of the investment framework and the full range of options. The sources of uncertainty are not going to improve in the short term and increasing requirements for alternative entry models with evidence development involve a change in the relationship between companies and funders for sharing risks in the unknown.

. . . increasing requirements for alternative entry models with evidence development involves a change in the relationship between companies and funders for sharing risks in the unknown.

Reacting to rapid innovation: what is the impact on HTA/payer decisions of a newly submitted application on a product undergoing FRP? An HTA perspective

Dr Nick Crabb, *Programme Director, Scientific Affairs, National Institute of Health and Care Excellence, UK*

EMA Adaptive Pathways Pilot

The National Institute of Health and Care Excellence (NICE) participated in the European Medicines Agency (EMA) Adaptive Pathways Pilots (2014-2016), "a scientific concept for medicines development and data generation which allows for early and progressive patient access to a medicine. These pilots were built on regulatory processes already in place and required no reform of the EU regulatory framework nor changes to the standards for evaluation of data for obtaining a marketing authorisation. The pilots were also intended to improve alignment of regulatory and health technology assessment processes.

Safe harbour discussions are non-binding multi-stakeholder dialogues that are a key component of adaptive pathways. In these talks, which generally precede formal scientific advice procedures, HTA and payer evidence requirements are covered and clinical development and real-world data collection plans are discussed before large confirmatory trials are planned. They are also considered to be an opportunity to discuss HTA processes and value frameworks and to start considering managed entry issues. The use of real-world evidence in support of marketing authorisation and health technology assessment is another key component of adaptive pathways. A pre-agreed strategy for post-approval data collection once a product receives marketing authorisation must be agreed. Use of real-world data does not remove need for appropriate confirmatory trials.

The need for and challenges of adaptive pathways

Expedited regulatory processes mean that products come to HTA agencies and payers sooner in their development cycle, with less mature evidence. Further work is required to achieve consensus amongst HTA and payer agencies on some aspects of adaptive pathways. These stakeholders are most supportive in principle of pathways that allow patients early access to transformative medicines in a financially sustainable way. It should be recognised that adaptive pathways are resource intensive and should not become the standard development approach. Rather these pathways should be applied where a product is targeting unmet need and there is reason to believe from the limited available evidence that the unmet need will be addressed in a meaningful way, providing substantial patient benefits.

What an adaptive pathway could look like

For medicines under development showing high promise of addressing unmet clinical need, wide-ranging multi-stakeholder early dialogue is available under safe harbour rules; for example, in England via NICE Office for Market Access. Developing companies would receive regulatory and HTA scientific advice and expedited approval through, for example, a conditional marketing authorisation. Submissions to HTA agencies would include available evidence and plans for further trials and real-world evidence generation. The developing company would propose managed access arrangements to achieve the fair sharing of risk, taking the value framework of the HTA agency or payer into account. Arrangements could include special pricing such as

discounts or outcomes-based payments based on further evidence generation. If proposed arrangements are considered satisfactory, the HTA agency or payer would recommend the product on a time-limited basis, subject to the agreed evidence development. After the defined period of use, the product is reviewed, taking the new evidence and any price changes into account. At the time of this Workshop, none of the projects that participated in EMA pilot had reached market.

IMI2 ADAPT SMART

Launched in 2015, the Innovative Medicines Initiative Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (IMI 2 ADAPT SMART) is a multi-stakeholder enabling platform for the coordination of Medicines Adaptive Pathways to Patients (MAPPs) activities and stakeholder dialogue. The National Health Care Institute (Zorginstituut Nederland; ZIN), Haute Autorité de Santé and NICE are partners in the consortium and broader HTA agency input is provided through the European Network for Health Technology Assessment (EUnetHTA). A scientific adviser at NICE is employed on the project coordinating HTA input within ADAPT-SMART activities. Outputs produced by ADAPT-SMART intended to support policy makers and national governments to further develop adaptive approaches to the development and reimbursement of medicines.

The Cancer Drugs Fund

The Cancer Drugs Fund is a source of funding for cancer drugs through which pharmaceutical companies, the National Health Service (NHS) England and NICE address uncertainties surrounding the effectiveness of new cancer treatments, typically by the collection of additional data during a specified period of managed access. Patients' earlier access to promising therapies is facilitated through a fast-track NICE process for companies to apply for appraisals and interim funding during the data collection period (Figure 9).

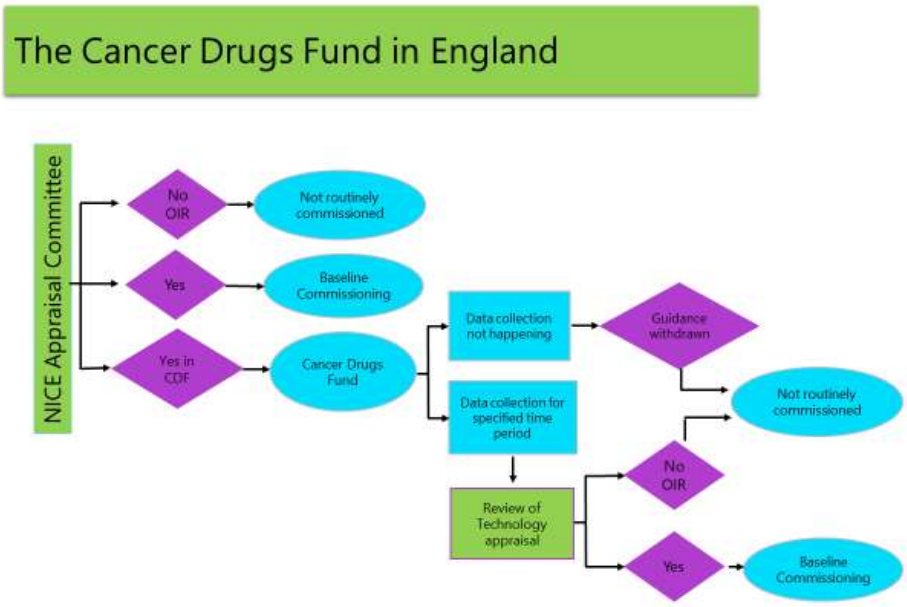


Figure 9. The Cancer Drugs Fund allows the interim funding of promising cancer therapies receiving expedited approval during the collection of additional data to resolve uncertainties.

Managing the uncertainty of the benefits, risks and value of medicines granted access through flexible pathways: What post-licensing mechanisms will be needed by HTA agencies and payers? An HTA perspective

Niklas Hedberg, *Chief Pharmacist,* Tandvårds- och läkemedelsförmånsverket (TLV)*, Sweden*

The context and challenges of Swedish healthcare

While the many regions and municipalities of Sweden ensure many potential sources of innovation, they also provide challenges in establishing synergies of scale in governance. Related challenges include difficulties in the joint collection and synthesis of knowledge and taking advantage of achieved volumes in certain healthcare procedures. The introduction of joint standards and the assurance of a strong digital infrastructure would assist the government in creating those synergies.

TLV achievements

The uncertainties surrounding the evidence on which decisions for expedited medicines are based have resulted in challenges in pricing and reimbursement. To meet this challenge, Sweden's Dental and Pharmaceutical Benefits Agency, Tandvårds-och läkemedelsförmånsverket (TLV) has established a national platform for collaboration and dialogue with pharmaceutical companies and Swedish county councils. This three-party dialogue identifies and seeks ways to address risks such as uncertainties about treatment populations and the duration and results of treatment (Figure 10).

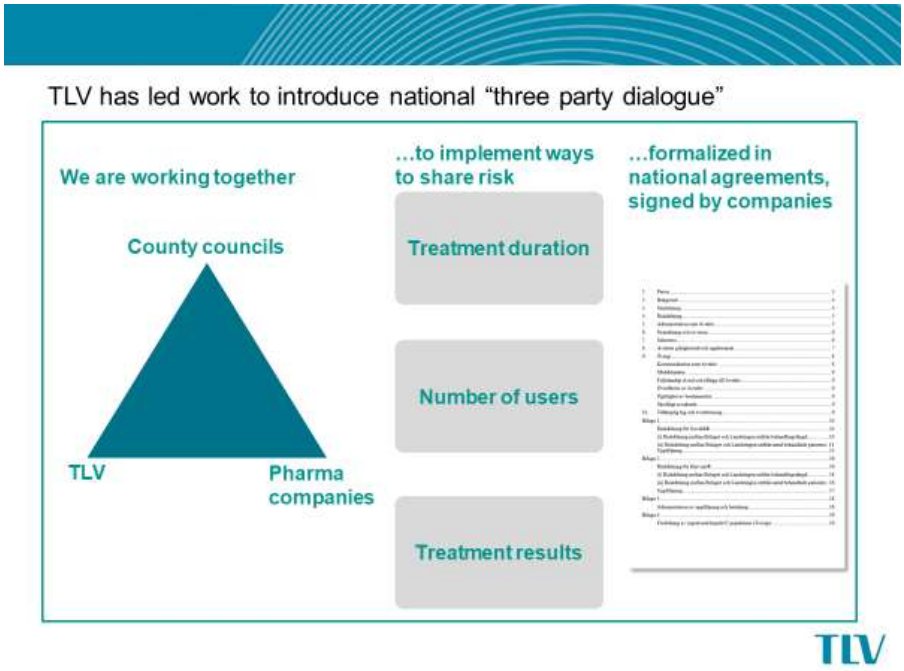


Figure 10. TLV dialogue to negotiate risk sharing.

One result of this process is negotiated agreements among the three parties as to how to manage uncertain parameters through a contract of risk sharing. In this process the county councils negotiate as one party, making reached agreements national. TLV can then incorporate the reduced uncertainties surrounding the new medicines into its reimbursement deliberations, resulting in more favourable decisions.

This work is now being implemented in practice and at the time of this Workshop, agreements had been reached in a number of therapeutic areas including hepatitis C, heart failure, oncology, ophthalmology and TNF-alpha and PC SK-9 inhibition. TLV is moving forward to institutionalise and expand the use of these risk-sharing models.

In addition, TLV revised its internal structure to allow for more therapeutic specialisation and increased analytical capacity and adapted its processes to accommodate different types of applications. The goal of these changes is increased transparency and efficiency to enable further increased focus on applications for high-cost medicines with a high degree of uncertainty.

More evidence generation is needed

Because value is created when a medicine is actually in use, health technology assessors are challenged in their use of regulatory-driven randomised clinical trial results. In fact, an increasing discrepancy has been observed between values from randomised clinical trials and those in the real world. In an attempt to fulfil unmet medical needs, new medicines now come to the market at an earlier phase. However, in addition to discrepancies in the definition of unmet medical need, there are large knowledge gaps about the relative effectiveness of these medicines at launch and prices are often high, which increase the payer's uncertainty about value.

Because value is created when a medicine is actually in use, health technology assessors are challenged in their use of regulatory-driven randomised clinical trial results.

However, important challenges surround real-world data, chiefly, challenges in methodology and the interpretation of and access to the data themselves. To help to meet some of those challenges, TLV aims to run several pilots with regards to drug assessment and use of real-world data:

- An in-market drug pilot to identify a framework and approach to predict the real-world effectiveness of new drugs in real-world circumstances through comparing real-world outcomes with the clinical data from the trials at time of application.
- An early-approval pilot to enable earlier, more equal and better structured market introductions of new and innovative drugs by tracking real-world data for an innovative newly approved oncology drug.
- A pilot to demonstrate that data can be integrated across markets on the EU level to generate better real-world evidence.

It is important to recognise that as stakeholders try to solve some problems in the access of medicines through the use of flexible pathways, new challenges occur to health technology assessors and payers such as evaluating comparable products with hidden or secret prices, evaluating and pricing of combination therapies and judging and grading unmet need and clinical benefit.

Balancing early access with acceptable reimbursement – how do companies/payers view flexible access and reimbursement pathways? A company perspective

Claudine Sapede, *Global HTA & Payment Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland*

The need for alignment in early access

Due to the confluence of different trends, including a deeper understanding of disease biology, new therapeutic modalities, comprehensive diagnostics, big data and advanced analytics and clinical decision support tools, the world of healthcare is evolving, creating the foundation and framework for more targeted, personalised patient care. One 2017 report showed that there were 7000 medicines in development that were potentially first-in-class medicines[1], meaning they use a completely new approach to fight a disease.

Regulators have adapted to these changes and new regulatory pathways allow earlier patient access to needed therapies in selected areas. Sixteen of the 2016 novel drugs (73%) approved by the FDA[2] were designated in one or more expedited development and review methods. In 2017, 18 Roche medicines/indications received a Breakthrough Therapy designation in the areas of oncology, multiple sclerosis, autoimmune disease and pulmonary fibrosis.

But health technology assessment (HTA) bodies and payers remain concerned. Payers have to balance expedited patient access to innovative medicines with the management of constrained drug budgets.
In addition, payers and regulators look at the degree of unmet medical need and the transformative potential of the medicine from different lenses. HTA/payer methods are still primarily focused on assessing evidence of added patient benefit in a way that made sense when most new medicines were in chronic disease areas with well-established standards of care and incremental long-term benefits. However, medicines with transformative potential in an era of rapidly changing standards of care require a different approach. In the face of the uncertainties that can accompany expedited pathways, HTA assessments tend to results in judgements of minor to absence of clinical benefit. Unaligned regulatory and HTA views lead to confusing signals, waste of resource, frustrated stakeholders and delayed patient access. How can decisions become more agile while also being predictable and reliable for stakeholders?

Ways toward collective progress

Evidence generation is inevitably context specific and joint parallel regulatory-HTA scientific advice can help align evidence expectations. In context of single-arm trials, real-world data could help establish an appropriate standard of care historical control and the size of treatment effect could be confirmed after approval. A life cycle approach to evidence generation is the way forward with real-world data providing growing opportunities to complement evidence available at initial approval.

Prices should evolve once more evidence becomes available. This model discussed in the context of the ADAPT SMART (Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes) project and the multi-stakeholder workshop held in July 2016, consisted in a flexible pricing model with variable discounts. A negotiated list price could be established for the initial launch of a drug with confidential discounts varying over time as more evidence become available (Figure 11).[2] In this scenario there should also be an upfront agreement as to pricing and

reimbursement consequences for successful or failed confirmation of a medicine's value proposition. In addition, managed entry agreements could accommodate a different value proposition for each of a medicine's different indications. Data-driven schemes including pay for performance, outcomes-based agreements could also be explored.

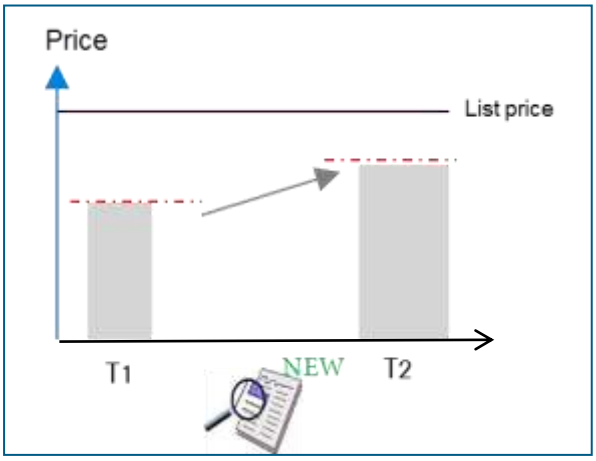


Figure 11. The price for expedited medicines should evolve as more evidence becomes available.

However, implementing new payment models requires an appropriate infrastructure for data collection, including the ability to efficiently collect relevant data, compliant with all data privacy and information technology regulations. Payers expect additional evidence to be provided within a limited time frame. Multiple single registries are costly to implement and do not contribute to public health knowledge. Collective efforts are needed to invest in the appropriate infrastructure enabling outcomes-based agreements and an outcome-driven healthcare system (Figure 12).

Collective efforts are needed to invest in the appropriate infrastructure enabling outcomes-based agreements and an outcome-driven healthcare system

Figure 12. New payment models require appropriate infrastructure for data collection.

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Payer perspective on flexibility in reimbursement pathways

Dr Marc Van de Casteele, *Coordinator Expertise Pharmaceuticals, Belgian Institute for Health Insurance and Invalidity (RIZIV-INAMI), Belgium*

The recently published paper" Adaptive pathways: Possible next steps for payers in preparation for their potential implementation" represents the views of some European payers and was the basis for this presentation.[1] Some of the important topics in this paper include:

- Flexible pathways for new medicines are associated with uncertainties in evidence.
- Although HTA reports have traditionally been individually regarded, repetitive HTA reporting from trusted and accepted sources is now required.
- Financial and legal responsibilities surround the accrual of real-life data.
- Clear exit scenarios are required for medicines receiving expedited approval.

Newer is not necessarily better

Researchers from the University of Birmingham investigating whether the increase in drug launches in recent years was related to an increasing number of highly innovating drugs found that highly innovative drugs comprised only around a quarter of all new drug launches in the UK. In contrast, drugs categorised as only slightly innovative comprised well over half of all new drugs and annual numbers in this category are increasing.[2] Worldwide pharmaceutical sales are also expected to continue to grow by 6.5% between 2017 and 2022.

Making more of randomised clinical trials

It should be recognised by all stakeholders that adaptive pathways are still a concept in development that requires more discussion and that for payers, the objective of flexible pathways is not early access but decent access to quality care. Payers, in fact, would prefer that more and better use be made of randomised clinical trials. A study published in *Lancet* showed that the results from only about 40% of clinical trials are published and that "Comparisons of protocols with publications showed that most had at least one primary outcome changed, introduced or omitted."[3] Conversely, a recent article in *Scrip* reported positive results from adaptive design in randomised clinical trials after years of experience.[4] This has raised payer confidence in adaptive design and many payers would like to see a similar accrual of published positive results from flexible pathways.

. . . for payers, the objective of flexible pathways is not early access but decent access to quality care.

Unfulfilled conditional approvals

It has also been reported that of 30 drugs that received conditional approval by the European Medicines Agency (EMA) from 2016 to 2016, 11 have since received standard marketing authorisation, 2 were withdrawn for commercial reasons and 17 still maintain conditional status.[5] Meanwhile other researchers report that of conditional approvals granted 2009-2010 at the US Food and Drug Administration (FDA), 25% of the commitments are still ongoing, 20% have never started and 48% have been fulfilled and "although the FDA approach has improved, work still remains to be accomplished".[6] These statistics may understandably inspire caution among payers and remaining uncertainties as to the quality and safety of new medicines may cause payers to make negative reimbursement decisions.

Advice for sponsors

In their sessions of parallel regulatory and HTA scientific advice, HTA advisors have brought the topic of comparators to the forefront of discussions[7] and more of this type of early dialogue would be beneficial and of interest to payers. To this, De Ridder and colleagues would advise that rather than using a commercially driven definition of *unmet medical need* to designate new medicines as appropriate for conditional approval, healthcare stakeholders should provide real access to real solutions for patients with real unmet medical needs. In addition, whilst registry data may be useful in compiling data on conditionally approved medicines, there needs to be agreement on research questions and outcomes parameters and the "use of real-life data should never have the ambition to replace randomised clinical trials.".

Finally, most payers would agree with the statement about the pricing of medicines that was written in the meeting report of the Fair Pricing Forum of the World Health Organization "We need transparency on the real costs of R&D for new products and anticipated profit margins."

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Flexible approaches – pushing regulatory, HTA and payer boundaries– How to connect and facilitate new models? IMI ADAPT SMART Perspective

Solange Corriol-Rohou, *Senior Director, Regulatory Affairs & Policy, Europe, AstraZeneca Global Medicines Development, France*

Medicines adaptive pathways to patients (MAPPs) seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product lifespan in a sustainable fashion. MAPPs is a prospectively planned, iterative approach to medicines development and access pathways within the current regulatory framework, making the best use of existing tools and methods such as conditional approval, scientific advice, and real-world data with multi-stakeholder engagement.

The Innovative Medicines Initiative Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (IMI ADAPT SMART) Consortium has established a platform to facilitate and accelerate the availability of MAPPs to all healthcare stakeholders. ADAPT SMART comprises 22 European Federation of Pharmaceutical Industries and Associations (EFPIA) members, 2 patients' organisations, 2 regulatory and 2 health technology assessment agency members and payers as observers.

The Consortium hoped to address issues such as unmet need, the potential lowering of evidence standards, randomised clinical trials and real-world data, conditional approvals and its promises, compliance and exit strategies and on-market utilisation. At the time of this Workshop, the ADAPT SMART Consortium had engaged some EU payers as observers and achieved a spread outside of the EU that included Canada, Australia, Japan and the US via its International Advisory Board. This resulted in the wide dissemination of the MAPPs idea – with interesting consequences. Workshops were convened to ensure discussion and alignment on a variety of selected topics with participants with a variety of expertise. Main deliverables of the MAPPs Consortium included the creation of a 143-item glossary of terms and the development of reports on

- Engagement criteria
- Seamless pathway and decision points
- Research gaps (identified through the review of mature IMI projects)
- Appropriate medicine use by targeted patient populations and
- Managed entry agreements (MEAs) [1]

Report: Engagement criteria for MAPPs

A framework of questions to be addressed by stakeholders when considering the MAPPs pathway for a given medicinal product was developed:

1. Can we define a target population with a high unmet medical need? Does the product hold sufficient promise to address unmet medical need?
2. Can a prospective iterative post-(initial) marketing authorisation development plan be proposed, developed, implemented and agreed?
3. Are there workable tools to ensure appropriate product utilisation?
4. Are there workable 'strategies' for payers in case the product under-performs?

5. Is there sufficient commitment and resources from relevant stakeholders to ensure successful interaction?
6. Which critical aspects for pharmaceutical development would need to addressed?

It was determined that a MAPPs pathway could be a conceptual structure within existing EU and national legal frameworks. EU and national competent authority mandates would remain unchanged. The pathway would make the best use of existing tools such as scientific advice and data registries. The pathway would incorporate coordinated dialogue with relevant stakeholders and an iterative development plan with decision points and formal stakeholder engagements (Figure 13).

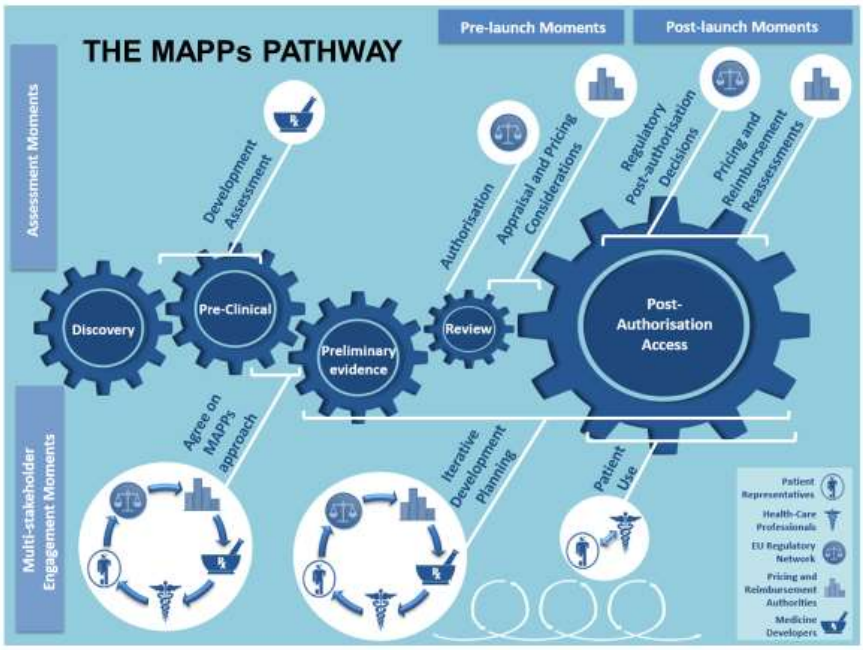

Figure 13. The MAPPs pathway: a conceptual structure within existing frameworks.

Report: Appropriate use of medicines by target populations

Twelve EU member states were surveyed through EFPIA companies to assess the availability of tools and systems in the EU that guide the appropriate use of medicines. Knowledge gaps were identified and a proposal for further study and recommendations were developed. Limited evidence is available on the impact of tools and systems and investing in evidence on successful tools and systems can help to identify which strategies could be suitable for a MAPPs product.

Report: Managed entry agreements

Eastern and central EU member states were surveyed to develop this report. The success of MEAs is dependent on the reduction of decision-making uncertainty, the improvement of cost effectiveness and the decrease of healthcare budget impact. Health technology assessment bodies and payers are often not convinced that MEAs will deliver these requirements. Simple financial agreements are preferred and commonly used in Europe, although they are known to be not fully transparent. Companies are more interested in outcome-based MEAs, the implementation of which would increase the workload of HTA bodies and payers. A lack of infrastructure for MEA implementation and issues with data collection are common and closer alignment of stakeholder expectations for the evidence generation plan, pricing and coverage status.

At the time of this Workshop, remaining work for the MAPPs Consortium included a gap analysis on evidence generation throughout a product life-cycle for MAPPs and recommendations for collaborative research proposals. Other open projects included:

- Evaluation of the resources needed for multi-stakeholder engagement in MAPPs and implications for an implementation roadmap
- Recommendations on patient engagement at critical decision points during the MAPPs process
- Recommendations on 'exit/disengagement' from MAPPs
- Recommendations on the appropriate use of MAPPs product by the targeted patient group
- Gap analysis of potential legal constraints for implementing MAPPs including on intellectual property rights and regulatory data exclusivity

Future publications are planned including decision points in current vs. future processes; Medicine Adaptive Pathways to Patients: why, when and how to engage? Addressing uncertainty - managed entry agreements for pharmaceuticals in the context of adaptive pathways in Europe.

After ADAPT SMART

The ADAPT SMART closing event was planned for 22 March 2018 in Budapest with the support of the Hungarian Regulatory Agency. It was envisioned that this meeting would include a proposal from NEWDIGS for adaptive pathways simulation/game and discussion, proposals for future research projects on topics such as single-arm studies, indirect comparison, observational studies, and payers' evidence requirements. The MAPPs Consortium hoped to maintain a platform for engagement, with broader involvement of payers and healthcare, enhance acceptance of the MAPPs concept, enable 'pilots' in MAPPs and integrate project outputs into everyday activities [ED: a report of the closing meeting are available at http://adaptsmart.eu/adapt-smart-closing-event-21-22-march-2018-budapest/] Moving forward, all stakeholders, whether from IMI ADAPT SMART and other IMI projects or regulatory or HTA initiatives or pharmaceutical companies must work together from the earliest stages of medicines' development and accept new R&D approaches and development paradigms to ensure innovative promising products can fulfil unmet needs as early as possible.

. . . all stakeholders . . . must work together from the earliest stages of medicines' development and accept new R&D approaches and development paradigms to ensure innovative promising products can fulfil unmet needs as early as possible.

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What are the key regulatory enablers to create more opportunities for accelerated marketing authorisation approvals globally?

Camille Jackson, *Senior Director, Science and Regulatory Advocacy, Pharmaceutical Research and Manufacturers of America (PhRMA), USA*

PhRMA

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the United States' leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. PhRMA is committed to advancing public policies in the United States and around the world that support innovative medical research, yield progress for patients today and provide hope for the treatments and cures of tomorrow.

Key regulatory enablers for accelerated marketing authorisation approvals

Regulatory agencies across the world have successfully implemented regulatory pathways to expedite the development and/or registration review of innovative therapies intended to treat serious conditions and address unmet medical needs. Criteria for expedited pathways are specific to each country/region and in many cases codified in laws or regulations. Harmonisation and convergence efforts are best focused on regulatory processes, tools, trainings, and best practices that each regulatory authority could reference to ensure resources are efficiently managed by each regulator, between regulators and by industry to support expediting patient access to innovative medicines.

General considerations

Expedited pathways are generally limited to those disease areas/conditions for serious, life-threatening conditions where there is an unmet medical need. Expedited pathways should be available not only for new molecular entities, but all products developing new indications, that is, add-on indications to already approved products, if those indications are for serious, life-threatening conditions where there is an unmet need. Approval under an expedited pathway still requires demonstration of safety and efficacy. However, it is important to note that the standards for safety and efficacy, as well as standards for quality, are not changed or lowered.

Development and regulatory capacity considerations

Open, transparent, and frequent communications with the health authority are required but the health authority must be adequately trained and resourced for these communications. Increased communication, especially during the development phase, is important to expediting drug development. As there is potential for approval based on phase 1 and 2 studies, with smaller patient populations, and/or use of modern drug development tools such as flexible trial designs, single-arm trials and modelling, the health authority must be willing to accept and understand the science behind such tools. In many cases there are requirements/commitments to conduct post-approval confirmatory studies.

Review and post-approval considerations

The use of 'rolling submissions' is beneficial, as the health authority can begin to review a dossier as key sections are completed. Gaining approval to use an expedited pathway generally requires a significant potential at an early stage and early planning of post-approval activities to confirm the benefit-risk profile and in many cases, there are requirements/commitments to conduct post-approval confirmatory studies. Often, the chemistry, manufacturing, and controls (CMC) aspects of a product that has been granted an expedited pathway designation may not be as well developed as the clinical programme, so there needs to be a flexible approach to demonstrate the quality of a product and allow for optimisation of a product after approval.

Convergence opportunities in regulatory processes and best practices

There are a number of existing tools through which regulatory convergence already happens such as the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Common Technical Document and specifically, the electronic Common Technical Document. In addition, bilateral and multilateral agency collaboration occurs through cluster and information sharing practices and mutual reliance recognition agreements. Successful harmonisation fora include the ICH, which has produced more than 60 harmonised technical guidelines and the Asia Pacific Economic Cooperation (APEC) Centers of Excellence Regulatory Training and Capacity Building Model.

Opportunities for future tools for regulatory convergence could include clinical trial applications, electronic clinical trial applications and common protocol templates. Technical guidelines to aid convergence could be developed such as risk-based submission of CMC information and post-approval planning and a common definition of terms such as l*ife threatening, serious* and *unmet medical need*. There are, in fact, multiple opportunities for convergence in regulatory practices and processes throughout the product life cycle, before and during development and before and after registration (Figure 14).

Opportunities for future tools for regulatory convergence could include clinical trial applications, electronic clinical trial applications and common protocol templates.

Existing strategic efforts in regulatory convergence

Strategic connections now exist across the global regulatory infrastructure that develop harmonised guidelines, tools, and templates to other regulatory training and capacity initiatives. For example, the APEC Regulatory Harmonization Steering Committee (RHSC) Strategic Framework for Regulatory Convergence for Medical Products by 2020 has developed six priority work areas aligned to the APEC Centers of Excellence (CoE) training model. The ICH Training Subcommittee has developed training pilots with trusted training providers on prioritised ICH guidelines. In a recent example of work in regulatory convergence, during the August 2017 Meeting of the APEC RHSC, members discussed a plan to expand the current Good Regulatory Management Priority Work Area to include a focus on expedited drug review and approval pathways. A step-wise approach was proposed, including building opportunities for APEC regulatory agencies to share with each other best practices and tools that can help facilitate their capacity to expedite regulatory reviews balanced against a country's regulatory framework such as full technical review or a reliance system. The goal is to foster greater regulatory convergence for simultaneous global drug development and regulatory approval specifically directed at products to treat serious, unmet medical needs – and build on the practices of more standard reviews.

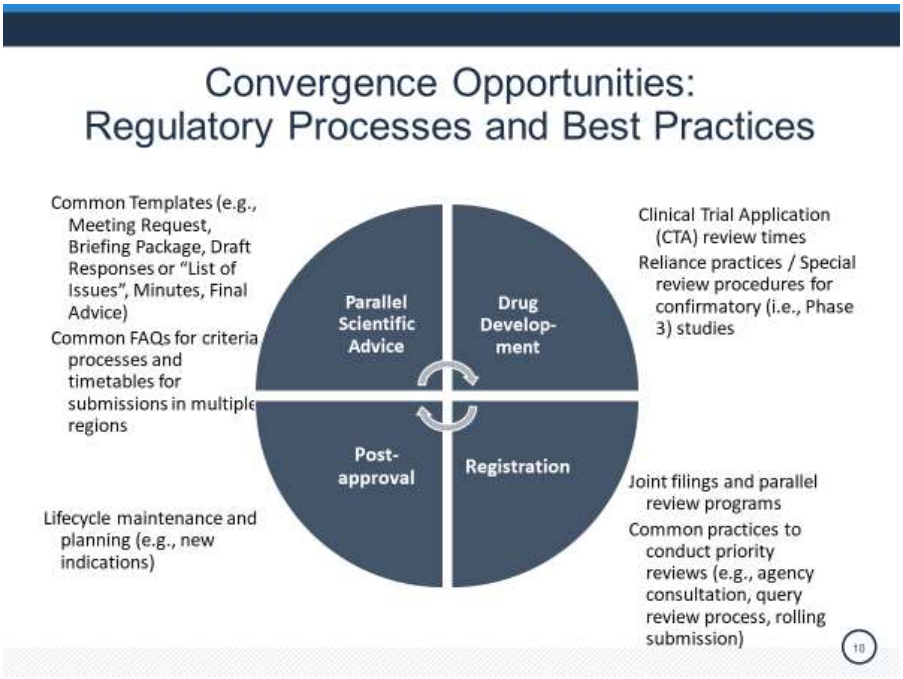

Figure 14. Multiple opportunities for regulatory convergence during the product life cycle.

Future considerations

Moving forward, regulatory training programmes could be developed that target expedited review case studies to foster better understanding by regulators – understanding expedited programmes in drug development such as the US FDA Breakthrough Therapy Designation, programmes in the registration or marketing application phase such as the Priority Review programme and facilitated pathways that are enabled through mutual recognition or reliance agreements. Finally, sustainable, systems-level training is needed to identify, prioritise and fund mechanisms for training and to train an agency rather than just a few key reviewers.

Facilitated regulatory pathways: Do they enable more timely regulatory reviews and quicker access for patients outside Europe and the US?

Dr Murray Lumpkin, *Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation*

The steps to medicines' access and impact in high- and low-income countries

In high-income countries, regulatory and health technology assessment activities are the key steps in patient access to health products. In these countries, treatment recommendations are not usually required for product approval and patient access. In addition, product safety and supply chain integrity are well established, and the impact of new medicines can be evaluated through a typically strong post-approval surveillance programme.

In low-income countries, the registration of many high priority health products is a three-step process in which a product first receives an approval in the country of manufacture (or in a high-income country); then, if the product is eligible, World Health Organization (WHO) prequalifies the product for purchase by various procurement agencies; and it is then evaluated by national or regional regulatory bodies, which are responsible for product licensure in the country of marketing. As in high-income countries, national registration in low-income countries and WHO prequalification are dependent on the quality and consistency of the product's manufacture and its preclinical and clinical safety and efficacy in the clinical trials setting. Finally, country suitability of the product must be assessed, with respect to stability in the local climate and transport circumstances. In addition, its utility in the local healthcare system and the appropriateness of its labelling must be evaluated.

A WHO (or other organisation) treatment recommendation is often required for procurement of health products in low-income countries. To receive a recommendation or be incorporated into a WHO guidance, the product must be evaluated for effectiveness, and often, affordability, in the population that will be using it. The impact of the product's use on public health and the feasibility of its implementation are also considered. Health economic evaluations may be carried out (these evaluations may also be performed by a procurement agency). The role of the product in the context of existing interventions and its community acceptability must also be assessed.

Most products in low-income countries must be either self-purchased or procured, either by local or regional groups or external organisations such as the United Nations. Other challenges to access include the fact that delivery of the product to patients may be hampered by challenges in storage (temperature and humidity) and poor physical transport infrastructure, in addition to theft or diversion. Finally, post-approval surveillance to determine the impact of a product in these areas and to monitor the supply chain is weak or non-existent (Figure 15).

Facilitated regulatory pathways in low-income countries

After examining registration data for more than 200 medicines and vaccines in 2012 to determine the timing for the registration of health products in low-income countries, the Bill and Melinda Gates Foundation determined that the total time for all assessments and approvals averaged then between 4 and 7 years after the completion of the development program and the initial submission to the regulatory authority in the country of manufacture. Delays in prequalification procedures and national regulatory review due to lack of reliance on previous reviews and inspections by trusted authorities were exacerbated by long spreads in timing from the first to last regulatory submission by manufacturers in low-income countries. Rationales for these long manufacturer submission spreads included a lack of a business imperative, language barriers and the complexities and disharmony in and between local registration systems.

Figure 15. In low-income countries, many factors besides regulatory review and health technology assessment are required for the approval and access of health products.

It was determined that the greatest opportunities to expedite the availability of new medicines and vaccines were likely to be found in optimising the systems through which these global health products must go to be ultimately licensed in low-income countries. Specific efforts that have been targeted in the past four years include: some of the PQ processes, outreach to manufacturers from low-income countries to facilitate better understand the international requirements of prequalification and working to help national regulatory agencies rely on the work products (inspection reports and scientific assessment reports) of the prequalification programme and other trusted agencies to help inform their own decision making, and initiation of both joint reviews and work-sharing by low-income national regulatory authorities, and through more regional approaches to product regulation. As a result of these enhanced processes, the total timing for the abridged assessment of vaccines by the WHO PQ programme (products that had already been authorised by a mature regulatory authority) was reduced by 49% for dossiers approved from 2013 to 2016, and during that same period, the timing for the full assessment of medicines (products that had not been authorised previously by a mature regulatory agency) was reduced by 23%. In addition, the establishment of a WHO PQ - local national regulatory authority collaborative registration programme has reduced the time to approval of products that

use this pathway to a median of 76 days in low-income countries that are a part of this programme. An overview of product pathways facilitated by the WHO in low-income countries is shown in Figure 16.

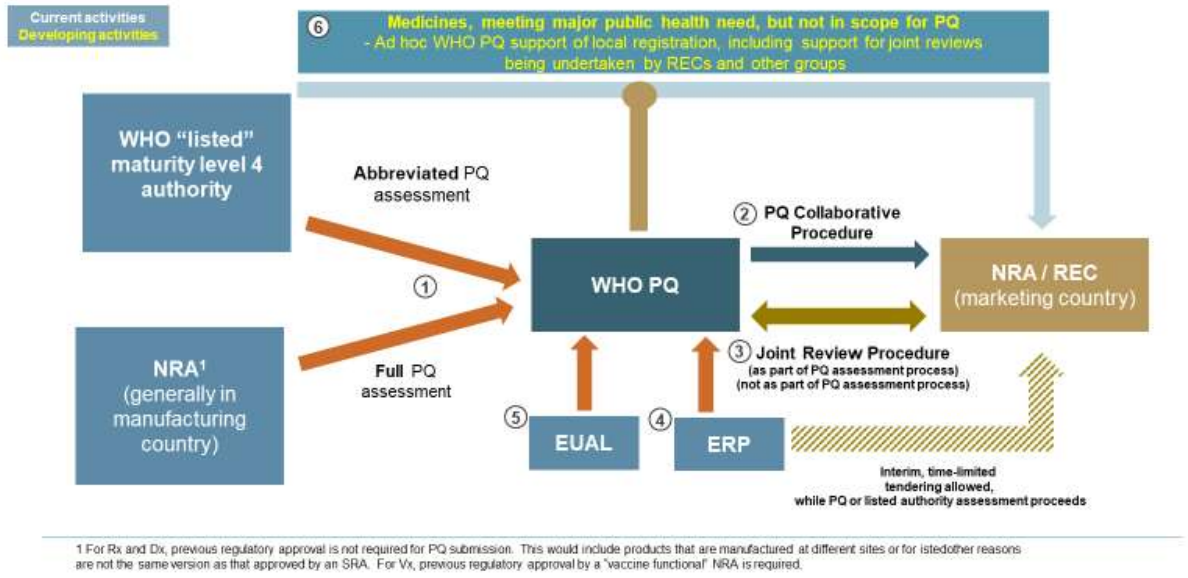

Figure 16. An overview of WHO-facilitated product pathways to low- and middle-income countries.

Challenge in reliance on high-income facilitated regulatory pathways

Most FRPs for high-income countries are based on benefit-risk profiles and the knowledge that strong down-stream systems exist that facilitate development of further information to iteratively refine the community's knowledge of those profiles even after they are released for larger marketing in the community. These include systems for vigilance (both active and passive), further specified clinical trials (infrastructure, regulatory and ethics board oversight), new data analysis and wide stakeholder communication - and the expertise to manage those systems. Many of these downstream systems simply don't exist or are not robust in low-income countries, making further knowledge enhancement and refinement of initial information difficult. Low-income jurisdictions are understandably reluctant to rely on the FRP decisions from high-income countries under circumstances where the benefit-risk profile in the high-income country is only through positive if the product is used under specific post-approval distribution and further study caveats, which are not feasible in low-income countries.

Facilitation through regionalisation

A significant proportion of medicines that are needed in low-income countries are not eligible for the WHO prequalification procedure and one way to facilitate the registration of these products is regionalisation.

A significant proportion of medicines that are needed in low-income countries are not eligible for the WHO prequalification procedure and one way to facilitate the registration of these products is through the development of regional approaches to product regulation (regionalisation). The pharmaceutical "Model Law" adopted by African Heads of State in January 2016 provides the basic legal foundation for a

modern medical product regulatory system and allows centralised registration procedures to be conducted through regional economic communities. Many African countries are currently using this model as the template for further refining their own national pharmaceutical laws.

The African Medicines Regulatory Harmonisation (AMRH) initiative seeks to harmonise and streamline regulatory processes for regulators and manufacturers and create a platform on which to build African regulatory capacity in each African regional economic community, leading to increased and timely access to quality products on the continent. As part of these efforts, the East Africa Community (EAC) product registration system was launched in January 2015 and performed its first joint regional review in October 2015, with technical support from WHO and Swissmedic. At the time of this Workshop, 32 products had been reviewed, none of which were previously pre-qualified, with 4 accepted and the rest awaiting manufacturer and/or local registration completion. Therapeutic areas for these products included oncology, cardiovascular, diuretics, epilepsy, HIV, antibiotics, antidepressants, herpes, diabetes, tuberculosis and others. Reviews will be expanding to other product streams such as vaccines, to other regulatory functions such as pharmacovigilance and clinical trials and to other geographies such as western and southern Africa.

Other regulatory regionalisation initiatives include that of the Caribbean Regulatory System, which has been developed under the auspice of the Pan American Health Organization (PAHO) in the 15 Caribbean community (CARICOM) countries. At the time of this workshop, 11 recommendations have been made as a result of the joint assessments and reliance on pre-qualification or PAHO regional reference agency reviews and inspection. Using this approach, the first national authorisation was granted less than 60 days from the joint review.

In addition to these regionalisation efforts, WHO is in the process of developing a guidance for good reliance practices, which will be an annex to its Good Regulatory Practices[1]. Finally, tailored pharmacovigilance strategies are being developed that are oriented to new products being initially introduced into low-income countries.

Reference

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Can HTA alignment efforts in Europe help to foster alignment of FRPs/FARPs within Europe?

Wim Goettsch, *Director, EUnetHTA JA3 Directorate, Zorginstituut Nederland*

The European Network for Health Technology Assessment (EUnetHTA) comprises 81 partnering national, regional and not-for-profit agencies that produce or contribute to HTA. Taking place from 2016 through 2020, EUnetHTA Joint Action 3 (JA3) aims to contribute to a sustainable model for the scientific and technical cooperation in HTA in Europe. The Dutch National Health Care Institute, Zorginstituut Nederland (ZIN) coordinates this effort, which is being accomplished through a series of work packages (WPs).

- *WP4: Joint Production,* will produce 37 rapid relative effectiveness assessments (REAs) on pharmaceuticals and 43 on other technologies, to provide a system for topic selection and prioritisation.
- *WP5: Evidence Generation,* will consist of the conduct of early dialogues (joint parallel HTA with regulators to link additional data collection to ongoing activities.
- *WP6: Quality Management* will provide quality management for EUnetHTA joint products to further develop methodologies and tools for joint work if necessary.
- *WP7: National Implementation and Impact* will facilitate the uptake of joint products at the national/local level to measure the impact of joint work in collaboration with other work packages.

WP5A

WP5A is the new European Medicines Agency (EMA) EUnetHTA Parallel Consultation Procedure. For prioritised products, this procedure may include participation of the Early Dialogues Working Party (EDWP), the EUnetHTA working party for the conduct of early dialogues including multi-HTA. To be prioritised by the EWDP, the products may be EMA Priority Medicines (PRIME) products, must target a life-threatening or chronically debilitating disease for which no satisfactory treatment is available and should aim to bring added benefit to patients by, for example, using a new mode of action for the indication. Early dialogues should cover a wide array of topics and therapeutic areas.

Most HTA agencies are aware of PRIME and are interested in participating in early dialogues as part of EUnetHTA WP5. In addition to having the view that HTA should be kept as a regular and independent process, HTA agencies may be concerned about the resource requirements for multiple instances of advice, continuous partnering or interactions and may prefer that there be only one occasion for early dialogue at a specific stage of development such as before phase II or IIB.

WP4

In the relative effectiveness assessments that are part of WP4, after the industry sponsor provides an expression of interest and a draft submission, a scoping meeting is held and a project plan developed. After the first two versions of the REA are drafted and a consultation meeting takes place, the third and final version of the consultation is created. At the time or this Workshop products that were the subject of joint relative effectiveness evaluations included midostaurin for acute myeloid leukaemia, regorafenib as monotherapy for adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib and alecensa as monotherapy for the first-line treatment of adult patients with ALK^+ advanced non-small cell lung cancer. Joint relative effectiveness assessments may contribute to FRAPs by providing the timely availability

of assessment data to ensure fast access to new medicines if the medicine's added value and value for money are proven. The assessment can also provide consistent information to support comparable processes in all European countries.

WP5B

The objectives of WP5B are to improve post-launch evidence generation (PLEG), with a special focus on the use of registries as a data source. The main activity has been in the development of PLEG pilots and the supporting activity was the development of Standards Tool for Registers in HTA. These efforts are based on the previous work of EUnetHTA JA2 and the Patient Registries Initiative (PARENT) Joint Action collaboration for cross-border PLEG for drugs and non-drug technologies.

Conclusions

EUnetHTA collaboration in different phases of the life cycle could contribute to facilitated regulatory and access pathways

EUnetHTA collaboration in different phases of the life cycle could contribute to facilitated regulatory and access pathways (FRAPs) (Figure17). Parallel consultations with EMA as part of WP5A and linking to PRIME might help to select the products that require FRAPs and also clearly define what is needed in the research programme. The use of joint relative effectiveness assessments (REAs) conducted in parallel with EMA may speed access to needed treatments and also ensure a more consistent REA perspective across Europe. Collaboration on additional data collection as part of WP 5B can increase the number of patients included in registries and the trustworthiness of registry data and ensure the use of standardised tools for data analysis but despite these additional tools, it is likely that the management of pricing, reimbursement, managed entry and exit schemes will remain at the national level.

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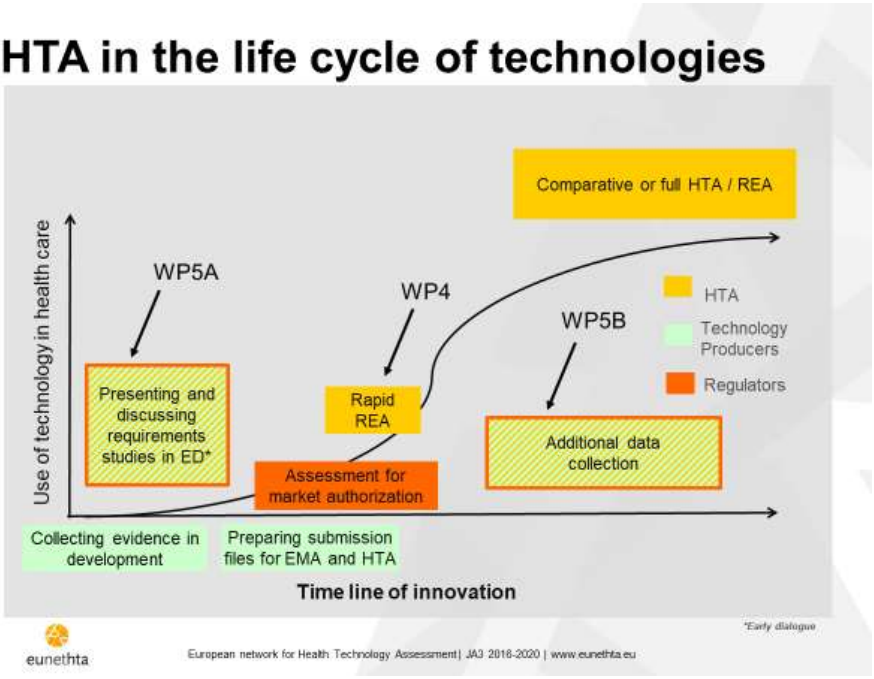

Figure 17. Activities of EUnetHTA JA3 Work Packages along the life cycle of medicines.

Section 3: Syndicate Discussions

Syndicate Discussion A

Prioritising important therapies– what are the criteria that will be used to determine which products should be considered for FRPs and FARPs and how they address evolving unmet clinical needs? (what is the role of scientific advice in informing these decisions?)	
Chair	**Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden*
Rapporteur	**Dr Trevor Richter,** *Director, CDR and Optimal Use of Drugs, CADTH, Canada*

Background

A CIRS survey in 2016 indicated that products that received conditional approvals experienced a higher level of scrutiny by health technology assessment (HTA) agencies.[1] This is perhaps not surprising, as it is reflective of the differences in the agencies' focus, with regulatory agencies' emphasis being on benefit-risk balance and product quality and the HTA focus being on relative and cost effectiveness, as well as on real-life effects. This divergence leads to the challenge for companies to find the right balance between timely access and optimal reimbursement and also for patients waiting for new medicines.

However, the fundamental question as to whether flexible regulatory pathways (FRPs) have an impact on recommendations for reimbursement by national HTA bodies could be considered from the perspective of two scenarios. First, use of the FRP pathway could result in a higher proportion of positive HTA recommendations because products that use FRPs typically address an unmet medical need. Alternatively, the use of the FRP pathway could result in a lower proportion of positive recommendations due to the less than complete data and the precautionary reluctance to pay for uncertainty. Interestingly, a study that investigated the impact of conditional versus standard regulatory pathways on HTA recommendations for new cancer drugs in Europe showed little to no difference in HTA recommendations for new oncology drugs approved by conditional versus standard pathways[2] and as such, the use of the EMA conditional regulatory pathway did not increase the likelihood of positive HTA recommendation.

FRPs have been established by regulators for medicines that address unmet medical need to enable more effective and efficient development, to prioritise regulatory review and to increase the early uptake of potentially beneficial medicines in clinical practice. Indeed, HTA agencies have also been testing new flexible access and reimbursement pathways (FARPs) and frameworks, which have the potential to support FRPs; these include, outcomes-based schemes, pricing and reimbursement controls and novel schemes such as deferred payments or indication-based pricing.

Defining clinical certainty and translating it into a cost value is the primary source of tension between the two pathways. This tension might be mitigated to some extent if all parties agree to clearly define upfront criteria

such as initial target population that has the greatest and most urgent clinical need and where the medicine is likely to generate the greatest clinical benefit. The focus of this Syndicate discussion was to discuss this lack of association between regulatory approval status and HTA decisions and make suggestions for criteria that can be considered for the aligned utilisation of both FRP and FARPs. This would drive clearer clinical evidence requirements for FRPs as well as potential trade-offs for post-marketing obligations that will be sufficient for both regulatory approval and HTA recommendation.

The objectives of the discussion were to

- Discuss the criteria needed to prioritise important medicines
- Determine the challenges to deciding which products should be considered for FRPs and FARPs
- Identify potential solutions to these challenges and discuss these in terms of criteria that could be considered and agreed
- Recommend two or three ways forward for this topic.

For purposes of this meeting, **flexible regulatory pathways (FRP)** specifically include regulatory pathways to enable the more rapid development, availability, review and/or approval of medicines.
For purposes of this meeting, **flexible access and reimbursement pathways** (FARPs) include the integration of HTA and payers into the accelerated access process

Questions for consideration

- Should important therapies be prioritised by regulatory and HTA agencies? If yes why?
- What is the syndicate group's perspective on the following statements?
    1. Use of the FRP pathway **should result in a higher proportion** of positive HTA recommendations because of high unmet medical need
    2. Use of the FRP pathway **should result in a lower proportion** of positive recommendations due to the less than complete data and the precautionary reluctance to pay for uncertainty
        - What would need to be in place for statement 1 to be predominant or the most predictable outcome? Please consider:
        - Kind of criteria to be used to identify eligible candidates
        - Interaction between stakeholders (eg, scientific advice)
        - Agreement between stakeholders
        - Timing of discussions

After identifying criteria above, select two or three key criteria and describe how these should be addressed by regulators and health technology assessors.

Discussion results

Critical issues

Describing *unmet medical need* is difficult and varies depending on the perspective used and the stakeholder involved. Current definitions of unmet medical need are imprecise and prioritisation criteria vary among and within jurisdictions. Factors important to stakeholders such as consideration of innovation and feasibility of

collecting marketing data are not captured within existing prioritisation frameworks. Prioritisation processes should have the involvement and endorsement of different stakeholders.

Strategies

This Syndicate advised the use of a common but flexible list of criteria for prioritisation that capture the needs of multiple stakeholders. This would avoid the limitations of using *unmet medical need* as a global criterion, obviate the need to satisfy all stakeholders in all situations and facilitate the prioritisation of products that meet the needs of multiple stakeholders.

It should be recognised that some early-stage considerations for prioritisation are challenging. For example, the affordability of a product is not relevant at the beginning of its development, as this type of value is difficult to determine at an early stage. Restrictions based on population size; that is, including rarity as a consideration, are also difficult to consider at an early stage of product development. Real-world evidence or other post-authorisation data collection are also difficult to address, as there is not clarity on what data are needed or are feasible to collect.

Criteria should be applied as a tool for relative assessment, rather than as a mechanism to include or exclude products. The involvement of multiple stakeholders will help this process succeed. The core list of criteria should explicitly address the following factors:

1. Severity of the disease

2. Availability of alternative treatments

3. Degree of benefit

4. Degree of innovation

5. Whether FRP access will accelerate development

6. Potential to collect post-authorisation evidence

7. Involvement of multiple stakeholders

Recommendations

- Using a multi-stakeholder approach, CIRS should assess the feasibility of developing a consolidated (core) list of factors to prioritise products for FRP and FRAP.
- The core list of prioritisation criteria should be adapted by individual stakeholders to meet their needs.

Syndicate Discussion B

Alignment of FRPs and FARPs – what are the elements needed to bridge the barriers and exploit the opportunities to promote holistic convergence to ensure effectiveness and efficiency of the regulatory and HTA approaches?	
Chair	**Dr Thomas Lönngren,** *Independent strategy advisor, PharmaExec Consulting Filial SE, Sweden*
Rapporteur	**Paul Dearden, Head** *of Emerging Markets, Regulatory Policy and Intelligence, AbbVie, UK*

Background

There is broad agreement across stakeholders, companies, regulators, health technology assessment (HTA) bodies, patients, providers and payers, that it is an important aim of healthcare systems today to provide timely access to patients to meaningfully better medicines at reasonable costs. Over the last five years, a number of new regulatory initiatives to enable the flexible development and earlier licensing of innovative medicines have emerged such as the US FDA Breakthrough Therapy Designation and Accelerated Approval pathway along with the US Congress 21st Century Cures act to accelerate the development and delivery of new medicines. In Europe, the Priority Medicines (PRIME) scheme was launched by the EMA to enhance support for the development of medicines that target an unmet medical need. These flexible regulatory pathways (FRPs) are playing an increasingly important role in regulatory approvals worldwide.

Whilst regulators do not consider product cost or comparative or incremental benefits in their assessments, these are key factors for HTA agencies and payers. Consequently, the outcomes of FRPs are not widely embraced by the payers due to the uncertainty around the effectiveness of new treatments and concerns as to whether their value to healthcare systems has been adequately demonstrated. In addition, although payers may be sympathetic to the need for early access for truly unmet medical need, they may not support the use of accelerated pathways for a wider set of indications. HTA agencies on the other hand are also looking at how to better ensure that they are not recommending coverage for medicines that are not clinically or cost effective by examining models such as coverage with evidence development, managed entry schemes and new models around pay-for-performance. Therefore, the need to better define the relationship between FRPs and flexible access and reimbursement pathways (FARPs) has emerged.

However, challenges to implementing FRP and FARPs exist, and include regulators' concerns regarding the controlled use of medicines approved through these flexible pathways, health technology assessors' need to develop rules surrounding disinvestment for medicines that do not meet the burden of proof and industry's need to realise competitive pricing, potentially tied to an agreed, genuinely flexible FARP. There is a disconnect in that regulator and payer evidence requirements are diverging rather than converging as regulators' approval of quality, safety and efficacy evolves and becomes more flexible. Faced with challenges of affordability, payers and some HTA are becoming more stringent on evidence around incremental benefit.

In addition, there is also sometimes a lack of agreement around what is perceived as unmet medical need among the stakeholders.

The focus for syndicate B was to discuss current perspectives and opportunities for FRP/FARPs as part of the regulatory/HTA toolbox to enable earlier patient access, especially where there is high unmet medical need, and to achieve alignment that will promote holistic convergence to ensure effectiveness and efficiency of the regulatory and HTA approaches to align FRP and FARPs. The objectives of this Syndicate discussion were to

- Discuss the key obstacles and opportunities are for aligning FRPs with FARPs
- Identify the critical elements needed to bridge the barriers that would enable alignment and how this alignment can best be achieved
- Recommend two or three ways forward for this topic.

Questions for consideration

1. What are the main obstacles for alignment of FRPs with FARPs and what is needed to bridge the barriers, from the perspectives of
    - Patients
    - Healthcare providers
    - Payers,
    - Health technology assessors
    - Regulators
    - Companies ?

2. What opportunities would such an alignment would bring for each of these groups?

Discussion results

Critical issues

Syndicate B participants agreed that it is now a new era of science generation and stakeholders are evolving at a different pace with different backgrounds, mandates and perspectives. Much progress has been made on the harmonisation of the regulation of medicines but health technology assessment and reimbursement are still at the beginning stages of their evolution.

In the EU, a single regulatory decision for a new product may result in more than 27 value and pricing decisions. Although frameworks have been available from the European Network for Health Technology Assessment (EUnetHTA) for some time, their use has been limited. Involving HTA stakeholders early in the development of new medicines does not seem to have had any effect on the ultimate national reimbursement decision making.

There are actually subtle disincentives for the generation of post-authorisation evidence as in the UK, where because of government classification of this type of evidence, it is not subject to the same tax breaks as research and development.

Organisational challenges to the development of FARPs include the variability in national preferences, processes and requirements. Resource constraints exist in many national environments, such as the lack of availability of health technology assessors or payers to provide scientific advice.

Challenges exist within industry in adapting to the concept of joint advice and in breaking down the internal barriers necessary for the cross-functional collaboration needed for the development of FARPs.

Evidence standards are extremely variable among stakeholders, especially as they apply to the acceptance of surrogate endpoints, patient-reported outcomes and the limited evidence that may be available at the time of expedited approval.

Global development for some products can be complicated because companies may devote the majority of their resources attending to the evidence needs for the US, which might be their single biggest market and they consequently may be challenged to change internal mindsets as to the necessity of preparing for other market requirements.

Recommendations

- Earlier joint discussions should be conducted among companies, regulators and health technology assessors. These discussions should result in agreements as to the core package for approval, evidence needs, post-authorisation effectiveness studies. Payers should be involved in determining post-authorisation expectations and health technology assessors and payers should provide input into risk management plans to manage uncertainty
- Stakeholders should improve the description and understanding of uncertainty; looking for guidance from ICH M4.
- It should be recognised that, along with randomised clinical trials, real-world data are an important element of evidence. It should also be recognised that patient-reported outcomes are an important aspect of real-world evidence; access and usability of these data are key and new technology should be embraced as a potential source of new data; progress is required in agreements as to what is needed and what approaches should be used for real-world evidence.

Syndicate Discussion C

Understanding stakeholder differences on views of outcome and success of flexible regulatory/access pathways: How can stakeholders bring FRPs/FARPs to life?	
Chair	**Prof Adrian Towse, Director**, *Office of Health Economics, UK*
Rapporteur	**Thomas Brookland**, *EU Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland*

Background

Using the same background as Syndicate B, the focus for this Syndicate was to discuss the different stakeholders' perspectives around the potential outcome and success of aligning and connecting flexible regulatory/access pathways, in particular, what each of the stakeholders need to do individually or in collaboration to make these routes work for both patients and healthcare systems.

The objectives of the discussion were to

- Understand and discuss the perspectives of patients, payers, health technology assessors, regulators and companies regarding a successful outcome from aligned flexible regulatory/access pathways
- Identify practical approaches or systems that need to be in place to enable the different stakeholders to achieve their expectations
- Recommend two or three ways forward for this topic

Questions for consideration

1. What would a successful outcome of flexible regulatory/access pathways look like from the perspective of patients, payers, health technology assessors, regulators and companies?
2. What could be measured to determine success?
3. From the above list, which would have the most impact to make flexible regulatory/access routes work for both patients and the healthcare systems and how could stakeholders enable those outcomes to be achieved? Please pick the top 2 or 3 for a discussion on what each of the stakeholders need to consider for the successful outcome to be realised.
4. Areas of concern have been raised by payers in respect to aligning with products approved through an adaptive licensing approach (Medicine Adaptive Pathways to Patients; MAPPs) .1 MAPPs have many similarities in common with FRPs and FARPs. What are options to address these concerns?
    - Scope and rationale for MAPPs— justification of the concept for adaptive pathways
    - Equity and allocation of public resources in the light of increased uncertainty
    - How beneficial are MAPPs? The risk-governance framework
    - Pitfalls of post-authorisation evidence generation—Ensuring efficacy and effectiveness
    - Stratification of the use of a medicine
    - Limiting the use of a medicine to specific patients—prescription control

- Implications for the pricing of new medicines including negotiations
- Shifting of research for new medicines to the post-authorisation phase—who should bear the costs?
- Enforcement—what if it doesn't work?
- Responsibility and liability for uncertainty and possible risk factors

1. Ermisch M et al. Payers' views of the changes arising through the possible adoption of adaptive pathways. *Front Pharmacol.* 2016. Available at http://journal.frontiersin.org/article/10.3389/fphar.2016.00305/full

Discussion results

Critical issues

This Syndicate discussed what a successful outcome for a FARP might look like from the perspective of different stakeholders, emphasising that there was likely an overlap of factors among the groups and that the list should not be considered exhaustive.

- *To patients*, a successful outcome would be a system where therapies are available to patients regardless of any potential reason for divestment other than safety and the opportunity to have an increased voice at regulatory and perhaps at HTA meetings.
- A successful FRAP outcome to *healthcare providers* would be one in which all stakeholders involved in deciding if a product should be assessed via an FRP would consider the burden on the healthcare system.
- *To payers,* success would be a system in which medicines prove their financial value in regard to alternative therapies and ultimately prove what was initially promised. They would also require stricter consequences for industry regarding delayed start or completion of post-approval commitments and a clear exit process.
- *Health technology assessors* would like to see timely patient access to transformative medicines in a financially sustainable way, a routine process whereby industry choose randomised clinical trial comparators from a more global perspective, along with regulators, the inclusion of health technology assessors, payers and patients in the decision as to which products proceed via FRPs and conditional acceptance based on smaller data packages followed by later re-evaluation.
- Successful FARP outcomes to *regulators* would include more industry accountability for the post-approval phase; for example, in oversight of appropriate medication use. According to regulators, FRPs should not allow the post-approval space to be used for correcting evidence pre-approval evidence gaps and rescue options such as the late conversion of standard marketing authorisation to conditional authorisation should not be possible with FRPs. Alternative options are needed for such situations.
- In successful FARP outcomes from a *pharmaceutical company* perspective, a single dossier is compiled and presented to satisfy both HTAs and regulators because the same data set would be used for evaluation and decision making. A single aligned, agreed definition of unmet need exists among health technology assessors, regulators, and patients and ideally,

payers; this would require effective, earlier multi-stakeholder dialogue and systems for facilitation. The place of FRPs in non-EU/US regions would be considered.

Strategies

The need for dialogue

Currently conversations are happening in silos and these need to be broadened to multi-stakeholder forums that include regulators, health technology assessors, payers and patients. Very early agreement as to which products could be assessed via FRPs/FARPs is needed; for example, stakeholders must decide if a product has the potential to fulfil an unmet need and where its value lies; these discussions need to be revisited at different time points throughout the procedure. It needs to be recognized that this iterative review could lead to situations in which an FRP is appropriate but an FARP is not – at least initially. A clear differentiation between FRPs and FARPs may be required as questions and criteria may differ. There should be fixed points and processes within the procedure to allow for the company, regulator or health technology assessor to exit the FRP because of a focus of resources and options to proceed by, for example, converting back to a standard procedure should be available.

Resources and planning are key to all stakeholders. Pipeline meetings and horizon scanning with regulators, health technology assessors and payers may be a good opportunity for planning. All such discussion spaces need to be safe harbours and include data protection and confidentiality. Global differences in dialogue processes should be acknowledged. The US context is more complicated and one potential option there would be an independent actor to mitigate between payers, companies and FDA. Such shared dialogue, engagement and agreements across stakeholder could help to reduce the current sense that FRPs being forced on HTA agencies and payers and make them more part of the decision-making process, leading to shared ownership

Agreement on post-approval commitments

Earlier discussion, planning and agreement on potential post-approval commitments would help address the situation of late starts and completions, which should be revisited throughout the life of the procedure. Enforcement of start and completion timing needs to be stronger through a legally binding contract. Distinctions may need to be developed between post-approval commitments for FRPs vs FARPs. Therefore, post-approval requirements could differ for FRPs vs FARPs and these need to be discussed – FRP studies need to be relevant for FARPs and uncertainties need to be resolved for health technology assessors and payers within a timely manner.

The learning phase with FRPs/FARPs

Stakeholders need to acknowledge and understand that FRPs and FARPs are still in the experimental phase and their ability to achieve desired outcomes is still unknown. Whilst these pathways should be welcomed, it must be recognised that they may not be the final solution. FRP experiences need to be publicly available for learnings, potentially through pilots. A systems-level approach may be needed to learn from global FRPs.

Recommendations

- Life-cycle spanning, multi-stakeholder dialogue is fundamental to move FRPs and FARPs forward. All such discussion spaces need to be safe harbours and include data protection and confidentiality. Global differences in dialogue processes should be acknowledged.

- Earlier discussion, planning and agreement on potential post-approval commitments, including processes for enforcement and distinctions between commitments for FRPS vs FARPS may help address issues in timing and compliance of commitments.

- Stakeholders should be open to the use of FRPs/FARPs while understanding that they are still in the experimental phase. FRP experiences, potentially through pilots need to be publicly available for global learning.

Panel Discussion of Syndicate Results: Key points

How ready are we to practically align FRPs and FARPs and how can the whole process be brought to life?

Patient viewpoint

Dimitrios Athanasiou, *Duchenne Patient Advocate, Muscular Dystrophy Association Hellas, Board Member in UPPMD and EMA Patient Expert for DMD, Greece*

Rare and genetic diseases such as Duchenne Muscular Dystrophy represent true unmet medical need; 30% of children with these types of diseases will not live to see their fifth birthday. These immediate needs of patients make the alignment of facilitated regulatory and access pathways crucial and it is important to recognise that there is no scientific, economic or policy rationale for a lack of alignment.

Potential areas of regulatory and access collaboration should be targeted at the regional and global levels and procedures harmonised and coordinated. We need to find ways to build sustainable global drug development models together with effective regulatory and access procedures. Innovative processes in R&D, licencing and reimbursement and most importantly, in thinking must be identified. What is more, a continuum approach should be used from basic research to evidence generation to budget spending.

To tackle fear, build trust and promote transparency among stakeholders and harmonise procedures and decisions, we must incentivise progress and promote and demand data and information sharing. Conflict must be handled in an organised and transparent way and the “rules of the game” be made clear. Compassionate and early access should be promoted and all the resulting data from this use collected and analysed. A total system change is not needed as we have the building blocks and only require the willingness to draw a common new future. We have the necessary scientific advances, information technology tools and technologies for data capture, analysis and modelling. Successful registry models exist such as that of the Italian regulatory agency Agenzia Italiana del Farmaco (AIFA). Health technology agencies have joined with the European Medicines Agency (EMA) to provide parallel scientific advice and experience is being accrued in the use of adaptive pathways in licencing and reimbursement.

More work, however, is still required such as the creation of common guidelines for the development of therapies in specific disease area. New technologies and information technology tools must be developed for regulatory and HTA evaluations and decisions, New statistical tools are required for patient and disease registries. Alignment work must begin at the earliest timepoint, when medicines are being researched and developed. The process must deepen and include stakeholders farther downstream. We must look beyond innovation in scientific platforms, products and technologies and look for innovation in strategy, policy, access and thinking.

HTA agency viewpoint

Dr Jan Jones, *Principal Pharmacist, Scottish Medicines Consortium*

The Scottish Medicines Consortium (SMC) conducts health technology assessment (HTA) for all new medicines / indications / formulations. Three types of assessment process exist, with an increasing flexibility of decision-making, moving from 'standard' medicines to medicines for end-of-life and orphan conditions to ultra-orphan medicines. Currently, there are three SMC decision options in National Health Services (NHS) Scotland: accepted for use, accepted for restricted use and not recommended.

Where is SMC on the facilitated access and regulatory pathways (FARP) curve? Relatively near the bottom - SMC is observing other HTA organisations such as NICE, with its managed access agreements (MAAs) and Cancer Drug Fund (CDF). The agency is developing the option of conditional SMC acceptance and is also learning from experience in EAMS, as discussed by Dr Lam in this panel discussion. SMC is exploring the practical issues surrounding real-world data, with a focus on using NHS datasets and is seeking to develop a realistic flexible HTA pathway to handle uncertainty.

Following Scottish Government policy changes in 2014, SMC has taken a more flexible approach to the assessment of medicines for end-of-life (cancer) and very rare conditions. This involves the output from a SMC Patient and Clinician Engagement (PACE) meeting designed to describe 'added value' which may not be fully captured in conventional clinical and economic analysis. PACE has facilitated the acceptance of higher incremental cost-effectiveness ratios (which has allowed the committee to handle greater uncertainty).

SMC's flexibility is to be extended shortly with the introduction of a fourth decision option of 'conditional acceptance', which will initially apply to medicines that have a conditional marketing authorisation. This will align HTA with regulatory processes and call for reassessment at the time of full marketing authorisation, when more mature data such as overall survival are available to reduce the initial uncertainty. In the future, conditional acceptance could include MAAs and be extended to other groups of medicines, for example: ultra-orphans, EAMS-designated medicines and end of life/orphan products. Real-world data using NHS datasets could then be used to support reassessment once clinical outcomes are available.

Robust real-world data require the routine collection of clinically relevant outcomes in everyday clinical practice. This information is particularly beneficial to supplement clinical trial data to reduce uncertainty. Experience of EAMS has highlighted the importance of early company engagement with HTA bodies and the health service to shape data collection.

Challenges to conditional HTA acceptance in NHS Scotland include the information technology infrastructure in the hospital setting, where electronic prescribing is not routinely available. There is also the need for a robust information governance framework. From the HTA perspective, questions exist as to whether real-world data are complete and sufficiently robust, and whether 'adaptive disinvestment' is possible if a medicine is found not to be cost-effective on reassessment.

Considering how the whole process of FRP and FARP alignment could be brought to life, the first steps for Scotland are a focus on real-world data use, on addressing gaps in electronic prescribing, the routine collection of meaningful outcomes (including clinical and patient-reported outcome measures) in everyday clinical practice and concentrating on practical issues surrounding information governance to ensure the framework is fit-for-purpose.

Company viewpoint

Prof Bruno Flamion, *VP, Head Strategic Development, Idorsia, Switzerland*

It's important to realize that pharmaceutical development is a regulated world in which industry has to comply with national legislation, which they do, despite occasionally lobbying for change. As has been discussed in the Syndicate sessions, rather than trying to engage in extremely lengthy efforts to change legislation in this regulated world, it is important to use existing tools for facilitated regulatory pathways. In this way, implementation of new pathways can occur relatively soon.

Even though this is not the first workshop on facilitated pathways, it remains critical to remind ourselves of the starting premise for this topic. The reason facilitated pathways exist, as the Senior Medical Officer of the EMA, Professor Hans-Georg Eichler, has often pointed out, is that patients want them. Patients cannot wait. Based on that foundational premise, patient buy-in has to be starting point of any facilitated pathway.

Syndicate A had a very interesting discussion on the criteria and tools for prioritisation of products for facilitated pathways. Regarding the first criterion, unmet need, Syndicate A was in complete accord with the US FDA breakthrough designation, which is reserved for treatments for serious or life-threatening disease. Of course, "serious" is a broad term that can encompass many different diseases. Another important criterion is the provision of some preliminary clinical evidence based on clinically significant endpoints. Two other criteria suggested by Syndicate A, the participation of multiple stakeholders and the collection of post-marketing data, may be more appropriate for Europe and would not apply to the FDA breakthrough designation. Nonetheless, this designation is important in the US, not only for facilitated marketing authorisation system but also for market uptake after authorisation, because breakthrough designation by the FDA can mean that the product is considered very important. One would hope that a similar EMA designation along with HTA collaboration would have the same impact, but this is not certain.

As Dr Jones pointed out, effectively collecting post-authorisation data is crucial but the quality of the system needs to be considered and we must consider how to improve the current information technology and registry systems. Even if an FARP is not achieved, if HTA agencies and EMA succeed enhancing post-authorisation data collection, it would be considered a success in itself.

As has been mentioned many times, we need collaboration among regulators and HTA bodies along medicines' continuum, starting early but continuing during and after market authorisation. This means that more than joint advice, we need parallel discussions among EMA, HTA bodies, and the companies, and this

can be implemented relatively quickly. Additionally, payers should also be invited to the discussion, although it has not been decided if they should be offered the same type of flexibility as other stakeholders. Some payers have commented that performance-based managed entry schemes may be too difficult to implement, too resource consuming and too challenging to control through the system. However, it is possible that these challenges can be overcome. Other payers have said that putting a managed entry scheme into place transforms companies' premarketing responsibility into payers' post-marketing obligation. I disagree with this opinion and believe that the responsibilities will be shared. Other challenges to fully empowering payers as stakeholders include their diversity across Europe and the diversity of their experience and available tools and resources. More discussion on these topics are required.

Regulatory agency viewpoint

Dr Siu Ping Lam, *Director, Licensing Division, Medicines and Healthcare products Regulatory Agency (MHRA)*

Flexible regulatory pathways include US Food and Drug Administration (FDA) Breakthrough Therapy Designation and Accelerated Approval, the European Medicines Agency (EMA) Priority Medicines (PRIME) initiative and the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS). EAMS aims 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.'

EAMS is a two-step process consisting of the Promising Innovative Medicine (PIM) Designation and the EAMS Scientific Opinion. The scheme covers medicines that are not yet available as licensed treatments and the programme is primarily aimed at medicines toward the end of their development. Companies agree to supply the product free of charge during the EAMS period. EAMS was launched in 2014, the first PIMS designation was granted in September 2015 and the very EAMS scientific opinion was granted in March 2015.

Step 1: A PIM Designation is an early indication that a medicinal product is a potential candidate for the EAMS and is awarded on the basis of non-clinical and clinical data available with the product, in a defined disease area. The PIM designation gives a company reassurance that its clinical development is on track through an early review of its data by the UK medicines regulator. Specific MHRA and National Institute for Health and Care Excellence (NICE) contacts are provided, with opportunities to engage on patient-access issues along with the opportunity to request a joint MHRA NICE scientific advice meeting. From April 2014 to September 2017, 57 EAMS PIM applications were received, 41 PIM designations were granted, 8 refused and 2 applications were withdrawn. MHRA expressed particular interest in applications for the therapeutic areas of oncology, anti-infectives, central nervous system, musculoskeletal, dermatology, blood disorders, cardiovascular and ophthalmology.

Step 2: An EAMS scientific opinion is rendered as the result of a fast track benefit-risk evaluation. A positive scientific opinion is issued after a 75- to 90-day timetable if the criteria for the EAMS are considered to be fulfilled and the benefit-risk balance is positive. Receiving an EAMS positive scientific opinion can result in

patient access for that product through the National Health Services (NHS) before marketing authorisation. The scientific opinion describes the benefits and risks of the medicine and supports both prescriber and patient in making a decision about using the medicine before its licence is approved. From April 2014 to Sept 2017 19 EAMS scientific opinion applications were received, 16 opinions were awarded and 2 opinions were refused. Pembrolizumab was the first medicine to be awarded an EAMS positive scientific opinion and a case study published on the UK government website describes some of the lessons learned: "EAMS undoubtedly accelerated access to pembrolizumab for patients with advanced melanoma and demonstrates a world-leading example of how healthcare agencies and industry can work together to get treatments to patients more quickly (MSD)."

PIM-designated products are prioritised by NICE in its Topic Selection process and the Office for Market Access offers companies the opportunity to have a supplementary meeting (NHS England are also invited) for discussion on data collection and technology appraisal evaluation. EAMS products are also prioritised in the Therapeutic Area work programme. NICE starts the evaluation during the EAMS period (before marketing authorisation), and the company prepares its submission during this period. The first Committee decision is published within 3 months of marketing authorisation, rather than the usual 6 months. Products recommended by NICE are usually commissioned within 3 months of publication of the guidance. NHS England reduces this to 30 days for EAMS products.

Post-launch, an Office of Life Science (OLS) EAMS Government-Industry Stakeholder Task Group was established to bring together key stakeholders from the pharmaceutical industry, government and arms' length bodies to inform the development of EAMS procedures, establish consistent lines of communication between stakeholders and to clarify, address and accelerate the resolution of emerging issues since launch. Membership of the group includes: MHRA, NICE, NHS England, OLS, Department of Health, Devolved Administrations, Scottish Medicines Consortium, All Wales Therapeutics and Toxicology Centre, the Association of the British Pharmaceutical Industry (ABPI), BioIndustry Association (BIA), Ethical Medicines Industry Group (EMIG), invited representative companies and other stakeholders including the Centre for the Advancement of Sustainable Medical Innovation (CASMI).

An independent 2016 review of EAMS said "From an industry perspective, the EAMS has offered a valuable opportunity for early dialogue with government and arm's length bodies about product uptake within the NHS." Applicants praised the introduction of the PIM designation, the support offered by the MHRA, and the role of the EAMS task group as key strengths of the current EAMS process:

According to a report and recommendations made to the UK government in 2016, a new transformative designation should be applied to those innovations with the potential for greatest impact and Accelerated Access Review (AAR): an accelerated access pathway for strategically important, transformative products should align and coordinate regulatory, reimbursement, evaluation and diffusion, with EAMS as an essential component. The pathway should be suitable for medical technologies, diagnostics and digital products as well as medicines. For medicines, analysis shows that patient access can be brought forward by up to four years

where an EAMS scientific opinion is used. Some funding should be available for small-to-medium enterprises and not-for-profit organisations with products on the EAMS pathway before NICE assessment. EAMS will be an integral part of the accelerated access pathway, providing pre-licence access for strategically important products.

Payer viewpoint

Evert Jan van Lente, *Director EU-Affairs, AOK - Bundesverband, Germany*

Facilitated access and reimbursement is an extremely complex topic that is not easily handled. I hope to explain this in the framework of the German system.

In the German Social Health Insurance system, the AOK group represents 26 million insured persons. Germany has a complex multiple-payer system, with decentralised decision making that can make certain issues even more complicated. In addition, Germany health policy is rather conservative and does not follow all international trends. For example, during the recent hype of personalised medicine, Germany consistently attempted to define the concrete benefit of this type of treatment without taking immediate action to change the regulation. The fact that the number of products in this area have not approached original estimates may point to the virtue of this reasoned approach.

In the meantime, several German organisations recognise that the way additional benefits are assessed, in the framework of the AMNOG-Law has its limits. This is especially true for new drugs that receive a conditional approval and for which marketing authorisation cannot be adequately assessed with current instruments. For Germany, this is very unsatisfactory, because products that receive EMA marketing authorisation are almost immediately available and reimbursed by the health insurance system – at least in outpatient care.

The German HTA agency Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) has increasingly assessed the additional value of new products without enough scientific evidence as having “no added value”. IQWiG reports serve as the basis for the Gemeinsamen Bundesausschuss (GBA) binding rating of additional value and as the basis for the price negotiations of the umbrella social health insurance organisation (GKV-Spitzenverband) with manufacturers. If the product is assessed to be without added benefit and the comparator is a generic medicine, the price will be set at the level of this generic medicine, and this may lead to withdrawal of this product after one year. On the other hand, if the comparator is an oncology drug that costs for example, 100,000 Euros per year, GKV-Spitzenverband will authorise payment for the new drug at that level, even without proven added benefit. Moreover, Germany does not have a framework and infrastructure to generate real-world evidence, partially because new drugs are available to patients in Germany outside of their target population.

Managed entry agreements and evidence generation frameworks will be necessary to accommodate products coming onto the German market through new regulatory approaches, but those agreements will require legislation that is not yet in place. Managed entry agreements that are in place in other countries would require also require more transparency in Germany so that data collected are available to all other countries.

APPENDIX: WORKSHOP ATTENDEES

Health technology assessment agencies		
Luc Boileau	*President and CEO*	*Institut national d'excellence en santé et en services sociaux (INESSS), Canada*
Dr Jacoline Bouvy	*Scientific Adviser*	*National Institute for Health and Care Excellence (NICE), UK*
Dr Nick Crabb	*Programme Director, Scientific Affairs*	*National Institute of Health and Care Excellence, (NICE) UK*
Dr Wim Goettsch	*Director, EUnetHTA JA3 Directorate*	*EUnetHTA, The Netherlands*
Niklas Hedberg	*Chief Pharmacist*	*TLV, Sweden*
Dr Jan Jones	*Principal Pharmacist*	*Scottish Medicines Consortium, UK*
Evert Jan van Lente	*Director EU-Affairs*	*AOK- Bundesverband, Germany*
Dr Trevor Richter	*Director, CDR and Optimal Use of Drugs*	*CADTH, Canada*
Ad Schuurman	*Expert on Secondment at the European Medicines Agency*	*Zorginstituut Nederland*
Dr Sean Tunis	*President and CEO*	*Center for Medical Technology Policy, USA*
Dr Marc Van de Casteele	*Coordinator expertise pharmaceuticals*	*RIZIV-INAMI, Belgium*
Patient groups		
Dimitrios Athanasiou	*Duchenne Patient Expert*	*MDA Hellas, United Parent Project Muscular Dystrophy (UPPMD), Greece*
Valentina Strammiello	*Programme Manager*	*European Patients' Forum, Belgium*
Pharmaceutical companies		
Sabine Atzor	*Head, EU International Regulatory Policy*	*F. Hoffmann-La Roche Ltd, Switzerland*
Dr James Barnes	*Director, EU Regulatory Policy and Intelligence*	*Vertex Pharmaceuticals (Europe) Ltd, UK*
Simon Bennett	*Director, Global Regulatory Policy EU Lead and GEMS Interim Lead*	*Biogen, UK*
Dr Kate Betteridge	*Director Worldwide Regulatory Strategy, Rare Disease*	*Pfizer Ltd, UK*
Fabio Bisordi	*Global Head, International Regulatory Policy*	*F. Hoffmann-La Roche Ltd, Switzerland*
Dr Patrick Brady	*Vice President, Head of Regulatory Policy and Intelligence*	*Bayer, USA*
Dr Gabriele Braeunlich	*Head RA Strategy*	*Bayer AG, Germany*
Thomas Brookland	*EU Policy Lead*	*F. Hoffmann-La Roche Ltd, Switzerland*
Dr Solange Corriol-Rohou	*Senior Director, Regulatory Affairs and Policy, Europe*	*AstraZeneca Global Medicines Development, France*
Paul Dearden	*Head of Emerging Markets, Regulatory Policy and Intelligence*	*AbbVie, UK*

Eric Dollins	*Director, Global Regulatory Lead*	*Merck KGaA, Germany*
Dr Felipe Dolz	*Head, Global Regulatory Affairs Science and Policy*	*Sanofi, USA*
Dr Roz Eijgenhuijsen	*Vice President, Europe Regulatory Affairs and London Site Head*	*Takeda, UK*
Dr Bruno Flamion	*Vice President, Head Strategic Development*	*Idorsia, Switzerland*
Dr Susan Forda	*Vice President, Global Regulatory Affairs – International*	*Eli Lilly and Company, UK*
Ine de Goeij	*Senior Regulatory Affairs Director*	*Astellas Pharma Europe, The Netherlands*
Angus Gunn	*Head of Access and Innovation Strategy, Global Medical Affairs*	*UCB Pharma Ltd, UK*
Ian Hawkins	*Executive Director, Regulatory Affairs*	*Celgene Corporation, UK*
Dr Adam Heathfield	*Senior Director, Centre for Health Systems Innovation*	*Pfizer, UK*
Dr Jens Heisterberg	*Vice President, Regulatory Intelligence*	*Novo Nordisk A/S, Denmark*
Claudia Hey	*Senior Director, Head Europe Global Regulatory and Scientific Policy (GRASP)*	*Merck KGaA, Germany*
Stefan Holmstrom	*Senior Director, HTA Strategy and Pro Excellence*	*Astellas Pharma, The Netherlands*
Camille Jackson	*Senior Director, Science and Regulatory Advocacy*	*PhRMA, USA*
Dr David Jefferys	*Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety*	*Eisai Europe Ltd, UK*
Gabriele Kapfer	*Market Access Policy*	*Bayer AG, Germany*
Dr Thomas Lönngren	*Independent Strategy Advisor*	*PharmaExec Consulting Filial SE, Sweden*
Rebecca Lumsden	*Director – EM Regulatory Policy*	*Pfizer, UK*
Brian Mayhew	*Executive Director*	*Novartis Pharmaceuticals, USA*
Karen Miller	*Senior Director, Global Regulatory Affairs*	*GlaxoSmithKline, UK*
Robert Morgan	*Head, EU Regulatory Strategy*	*Shire, UK*
Dr Filip Mussen	*Vice President, Head of Regulatory Affairs*	*Janssen Research and Development, Belgium*
Shevani Naidoo	*Director Global HEOR, Medical Affairs*	*Astellas, UK*
Jacqueline Paardekooper	*Associate Regulatory Affairs Director*	*Astellas Pharma Europe, The Netherlands*
Marie-Laurie Prudhomme	*HTA Analyst*	*Sanofi, France*
Dr Christine Sandford	*Senior Regulatory Specialist*	*Merck, Sharp & Dohme, UK*
Susan Sandler	*Director, Global Regulatory Policy and Intelligence*	*Janssen R&D, UK*
Claudine Sapede	*Global HTA and Payment Policy Lead*	*F. Hoffmann-La Roche Ltd, Switzerland*
Dr Sybil Skinner-Robertson	*Area Head Regulatory Affairs International (RAI), Western Europe*	*AbbVie, UK*
Dorte Strobel	*Senior Regulatory Intelligence Manager*	*Novo Nordisk A/S, Denmark*
Louise Timlin	*Senior Director International HTA/HO*	*Eli Lilly and Company, UK*
Andrew Wilkinson	*Head of Regulatory Affairs UK/Ireland/Nigeria, East and Southern Africa*	*Pfizer, UK*

Regulatory agencies		
Dr Claus Bolte	*Head of Marketing Authorization, Management Board Member*	*Swissmedic*
Lindsay Blaney	*Senior Advisor to the Director General, Biologics and Genetic Therapies Directorate*	*Health Canada*
Prof Sir Alasdair Breckenridge	*Former Chair*	*MHRA, UK*
Dr Siu Ping Lam	*Director, Licensing Division*	*MHRA, UK*
Dr Robyn Lim	*Senior Science Advisor, Office of Legislative and Regulatory Modernization*	*Health Canada*
Dr Tomas Salmonson	*Chair*	*CHMP, EMA*
Prof Andrew Wilson	*Chair, Pharmaceutical Benefits Advisory Committee*	*Department of Health, Australia*
Universities and non-profit organisations		
Dr Anke Hövels	*Assistant Professor*	*Utrecht University, The Netherlands*
Dr Murray Lumpkin	*Deputy Director – Integrated Development and Lead for Global Regulatory Systems Initiatives,*	*Bill and Melinda Gates Foundation, UK*
Prof Sam Salek	*Director – Public Health and Patient Safety Research Group*	*University of Hertfordshire, UK*
Prof Adrian Towse	*Director*	*Office of Health Economics, UK*

Centre for Innovation in Regulatory Science	
Dr Madga Bujar	*Project Manager*
Patricia Connelly	*Manager, Communications*
Dr Lawrence Liberti	*Executive Director*
Dr Neil McAuslane	*Director*
Prisha Patel	*Manager, Global Development Programme*
Professor Stuart Walker	*Founder*
Tina Wang	*Manager, HTA Programme*