



# Regulatory, HTA and payer interactions and collaborations: optimising their use and outcome success

10-11<sup>th</sup> March 2021

## WORKSHOP REPORT

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

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## Section 1: Executive Summary

### Background to the workshop

CIRS workshops have focused on how to align or understand the divergences and/or synergies between regulatory agencies and health technology assessment (HTA) bodies, with the results of making recommendations on how to further improve evidentiary alignment. In the last three years these workshops have focused on: different flexible regulatory and access pathways; upstream early interactions with regulators or HTAs to enable better downstream decision making; the challenges around early access medicines, and how best to manage these uncertainties pre-approval or mitigate them post-approval.

These workshops highlighted and made recommendations around issues such as: how best to demonstrate value from trial design (e.g. comparators) to meet stakeholder needs; how to bridge the gap between efficacy and effectiveness so evidence is available at the time of decision; and in regard to regulatory early access pathways, how HTA and payers seek to deal with less certainty and what mechanisms they have in place to mitigate these uncertainties. As regulators and HTA and payers have different remits, these workshops also identified common ground as well as what are the nature and rationale for divergences.

There are now a number of stakeholders that play a significant role in the process of getting a medicine to patients. The interactions between these different stakeholders (regulatory, HTA, payer, patient and company) were raised consistently as key components of building improved predictability into development and enabling more positive regulatory and access outcomes.

### Rationale for the workshop

Over the last five years, regulatory and HTA interactions, as well multi-HTA and multi-regulatory interactions and collaborations, have evolved in thinking and mutual activities both at a product level as well as at a policy and cross jurisdictional level. This is not just around providing early scientific advice, but also activities related to horizon scanning, ways to collaborate on registries and other forms of post-approval evidence generation to ensure work done by one agency can be reused by another.

At the global level there has been increased collaboration on both technical and policy issues, for example through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), International Coalition of Medicine Regulatory Authorities (ICMRA) and International Network of Agencies for Health Technology Assessment (INHATA). Examples at the jurisdictional level include between the UK National Institute of Health and Care Excellence (NICE) and Healthcare Products Regulatory Authority (MHRA); Dutch National Health Care Institute (ZIN) and Medicines Evaluation Board (MEB); and the Canadian Agency for Drugs and Technologies in Health (CADTH) and Health Canada. Although regulators have a long history of collaborations across jurisdictions, and in Europe the European Network for HTA (EUnetHTA) has worked to align HTA methodology, there are increasing opportunities for other collaborations including cross-continent HTA interactions, such as that recently seen between NICE and CADTH.

Indeed, these channels of communication and the networks for interactions are being tested in the current COVID-19 pandemic, which may illuminate both challenges and opportunities as both new medicines and repurposed medicines are developed, and their assessment accelerated.

CIRS, therefore, proposed that its 2021 March workshop should provide a platform for discussion on the new ecosystem of interactions and collaborations between and within the different stakeholders (HTA agencies, regulators, payers and companies), informed by the learnings on new development and regulatory models discussed in the [CIRS December 2020 workshop](#). The aim is to understand the impact of these collaborations on the development, regulatory review and HTA assessment/reimbursement space.

## Workshop objectives

- Discuss the current and future landscape for interactions and collaborations within and across the key stakeholders: companies, HTAs, regulators, payers.
- Identify through case studies the key areas, types of interactions and collaborations between stakeholders that are effective, as well as the challenges and opportunities.
- Understand the value-add these interactions and collaborations bring to enabling improved decision making by the stakeholders as well as how to address divergences and limitations.
- Make recommendations on what can be learnt across jurisdictions from the current initiatives so as to inform the future evolution of stakeholder interactions and collaborations and how they can enable better evidence generation as well as improved outcomes for patient access.

## Venue

This workshop was held virtually over two days; 10-11<sup>th</sup> March 2021.

## Workshop Programme

Affiliations are stated as they were at the time of the meeting (10-11th March 2021).

<b>Session 1: Interactions and cross-regulatory jurisdiction collaborations – enabling efficient and effective development</b>	
CIRS welcome and introduction	<b>Dr Neil McAuslane</b> , Director, CIRS
Session Chair introduction	<b>Dr Tomas Salmonson</b> , Director, Consilium Salmonson & Hemmings, Sweden
ICH at 30 years: driving convergence of technical standards for global regulatory acceptance – has this decreased divergence of requirements across agencies?	<b>Lenita Lindstrom-Gommers</b> , Chair of ICH Assembly (European Commission)
Jurisdictional regulatory early scientific advice – does this enable a more effective and efficient medicines development?	<b>Sharon Gorman</b> , Director, Regulatory Intelligence and Analysis, Pfizer, UK
ORBIS – A new model of regulatory cooperation	<b>Michael Shum</b> , Director, Application and Advisory Management, Prescription Medicines Authorisation Branch, Therapeutic Goods Administration, Australia
Stakeholder perceptions of regulatory, HTA and payer interactions and collaborations: results of the CIRS pre-workshop surveys	<b>Tina Wang</b> , Senior Manager, HTA Programme and Strategic Partnerships, CIRS
<b>Session 2: Focus on HTA-HTA interactions and collaborations – is this supporting future convergence and work-sharing across HTA agencies?</b>	
Session Chair introduction	<b>Dr Wim Goettsch</b> , Associate Professor of HTA, Utrecht University, The Netherlands
HTA Global collaboration – International collaborations on policy and technical issues - What outcome would be of value and most benefit to patients?	
INAHTA perspective	<b>Prof Tracy Merlin</b> , Chair, INAHTA; Director, Adelaide Health Technology Assessment; Head, School of Public Health, University of Adelaide, Australia
Company perspective	<b>Dr Indranil Bagchi</b> , Senior Vice President and Head, Global Value & Access, Novartis, USA
European multi HTA early dialogues – are these enabling improved evidence generation, quality of submission and HTA assessment outcomes at the time of HTA assessment over single HTA early advice?	
HTA agency perspective	<b>Dr Antje Behring</b> , Head of Pharmaceuticals Department, Federal Joint Committee (G-BA), Germany
Company perspective	<b>Dr Alicia Granados</b> , Head of Global HTA Strategy, Sanofi, France

<b>Transcontinental initiatives on scientific advice and interactions during development - what new opportunities have been identified and how could these be applied more widely?</b> NICE/CADTH partnership	<b>Jeanette Kusel</b> , Director of NICE Scientific Advice, NICE, UK <b>Dr Michelle Mujoondar</b> , Director, Scientific Affairs, CADTH
<b>Session 3: Focus on regulatory-HTA interaction and collaborations – does this provide aligned thinking to improve regulatory and HTA outcomes and patient access?</b>	
<b>Session Chair introduction</b>	<b>Prof Hans-Georg Eichler</b> , Senior Medical Officer, European Medicines Agency (EMA)
<b>HTA/Regulatory collaborative activities in Europe- what has been successful, what needs to be improved and how is success being measured?</b>	
<b>Prime - Is this a model for prioritisation of medicines of unmet need, which aligns the needs of companies, regulatory and HTA agencies?</b>	<b>Wendy Palframan</b> , Senior Director & Team Leader – Oncology, Global Regulatory Affairs, GlaxoSmithKline (GSK), UK
<b>EMA-HTA cooperation on products and methodologies - what has been achieved?</b>	<b>Dr Michael Berntgen</b> , Head of the Evidence Generation Department, EMA
<b>Collaboration during the review process – is this decreasing the delay between the regulatory and HTA decision making?</b>	<b>Dr Ly Tran</b> , ZIN, The Netherlands <b>Kevin Liebrand</b> , MEB, The Netherlands
<b>Jurisdictional joint HTA/Regulatory collaborations and activities initiatives – what are the hopes and can these ensure sustainable patient access to innovative medicines?</b>	
<b>UK Innovative Licensing and Access Pathway – what are the aspirations and measures of success?</b>	<b>Dr Nick Crabb</b> , Programme Director, Scientific Affairs, NICE, UK <b>Dr Daniel O'Connor</b> , Medical Assessor, MHRA, UK
<b>Regulatory/HTA post approval collaboration: the need to optimise the use of RWE for decision making</b>	<b>Dr Craig Simon</b> , Acting Director, Health Products Surveillance and Epidemiology Bureau, Marketed Health Products Directorate, Health Products & Food Branch, Health Canada
<b>Session 4: Focus on payer interactions with regulators and HTA – what are the challenges, opportunities and future developments across stakeholders?</b>	
<b>CIRS welcome and introduction to Day 2</b>	<b>Dr Neil McAuslane</b> , Director, CIRS
<b>Session Chair introduction</b>	<b>Dr Brian O'Rourke</b> , Chair, HTA Steering Committee, CIRS
<b>Early involvement of payers today – who should they be interacting with and when - what is the business case?</b>	
<b>Payer perspective</b>	<b>Evert Jan van Lente</b> , Director, EU-Affairs, Allgemeine Ortskrankenkassen (AOK)-Bundesverband, Germany
<b>Company perspective</b>	<b>Dr Vanessa Schaub</b> , Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, Roche, Switzerland
<b>Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?</b>	

<b>Company perspective</b>	<b>Shane Kavanagh, Vice President Health Economics &amp; Real World Evidence, Janssen, Belgium</b>
<b>Regulator perspective</b>	<b>Bruce Randall, Senior Executive Director, Therapeutic Products Directorate, Health Canada</b>
<b>HTA perspective</b>	<b>Andrew Mitchell, Strategic Adviser, Evaluation, Department of Health, Australia</b>
<b>Payer perspective</b>	<b>Dr Michael Ermisch, Specialist, GKV-Spitzenverband, National Association of Statutory Health Insurance Funds, Germany</b>
<b>Session 5: Breakout Discussions</b>	
<b>Introduction to breakout discussions</b>	<b>Dr Neil McAuslane, Director, CIRS</b>
<b>Breakout A: Effective models of engagement: What are the characteristics that facilitate better evidence generation in the development space? What is working, could improve or hasn't been tried yet?</b>	<b>Chair: Prof Adrian Towse, Emeritus Director and Senior Research Fellow, Office of Health Economics, UK</b>  <b>Rapporteur: Dr Charlie Mortazavi, Senior Manager – Global Regulatory Science &amp; Policy, Sanofi R&amp;D, France</b>
<b>Breakout B: Convergence through collaboration – are stakeholder interactions/collaborations improving the probability of regulatory and reimbursement success and patient access? Does this differ by product characteristic?</b>	<b>Chair: Dr Claus Bolte, Head of Sector Marketing Authorisation, Swissmedic</b>  <b>Rapporteur: Dr Gracy Crane, International Policy Lead, Roche, UK</b>
<b>Breakout C: Focus on 2030 and what would an ideal ecosystem be for interactions and collaboration - jurisdictional, regional, transcontinental: What should be considered as the key building blocks to ensure each of the interactions provides value to the stakeholders and improved outcomes for patient access?</b>	<b>Chair: Prof Hubert Leufkens, Professor, Utrecht University, The Netherlands</b>  <b>Rapporteur: Dr Melinda Goodall, Director, HTA Policy Research, MSD, UK</b>
<b>Breakout D: Ensuring interactions and collaborations between different stakeholders are adding value - How can success be measured and what processes should be put in place to ensure iterative improvements as the landscape evolves?</b>	<b>Chair: Dr Mark MacGregor, Chair, Scottish Medicines Consortium (SMC)</b>  <b>Rapporteur: Dr Álmuth Spooner, Director Regulatory Policy and Intelligence, AbbVie, Ireland</b>

## Key points from presentations

*Please note, affiliations are stated as they were at the time of the meeting (10-11<sup>th</sup> March 2021).*

### Session 1: Interactions and cross-regulatory jurisdiction collaborations – enabling efficient and effective development

**Lenita Lindström-Gommers**, *European Commission Directorate General for Health and Food Safety (SANTE) and Chair of the ICH Assembly*, explained that the purpose of ICH is harmonisation of requirements, rather than regulatory convergence. However, the increased uptake of ICH guidelines by regulators worldwide contributes to and complements efforts relating to regulatory convergence. Surveys carried out for ICH by CIRS in 2019 have identified different interpretations of the concept of 'adequate' guideline implementation; although these issues have been addressed, ICH is increasingly focusing on training activities particularly for its regulatory members on guideline implementation.

**Sharon Gorman**, *Director, Regulatory Intelligence and Analysis, Pfizer, UK*, described how the use of EU regulatory scientific advice is established and its value (in terms of regulatory approval) well recognised. Although there has been progress in recent years, new integrated and flexible models of collaboration that go beyond parallel regulatory/HTA advice are needed to optimise the efficiency of medicines development. These may be informed by the learnings and experiences of the COVID-19 pandemic.

**Michael Shum**, *Director, Application and Advisory Management, Prescription Medicines Authorisation Branch, Therapeutic Goods Administration (TGA), Australia* gave an overview of Project Orbis, a global collaborative review programme that was initiated by the US Food and Drug Administration to provide a framework for concurrent submission and review of oncology products among international partners including TGA. Benefits for both industry and regulators are being observed from the pilots undertaken so far, such as faster market access for new products and improved regulatory efficiency. Nevertheless, regulators and applicants need to be agile to participate in Project Orbis, as there are resource implications for evaluation and coordination aspects.

**Tina Wang**, *Manager, HTA Programme, CIRS*, presented the results of the pre-workshop survey, which explored company and agency perceptions and experiences of multi-stakeholder interactions and collaborations. Almost all respondents indicated that multi-stakeholder interactions/collaborations were a priority in their organisational strategic plan. Respondents also believed that an ideal interactions ecosystem should facilitate separate remits for stakeholders; converged requirements; aligned process; and increased transparency and trust.

### Session 2: Focus on HTA-HTA interactions and collaborations – is this supporting future convergence and work-sharing across HTA agencies?

**Professor Tracy Merlin**, *Chair of INAHTA, Director of Adelaide Health Technology Assessment and Head of School of Public Health, University of Adelaide, Australia*, described how INAHTA has facilitated HTA-HTA knowledge sharing, developed consensus on HTA and helped to converge HTA methods. While HTA agencies and networks like INAHTA are creating opportunities for harmonisation wherever possible, local health systems and local HTA requirements will always be a limiting factor to HTA harmonisation efforts.

**Dr Indranil Bagchi**, *Senior Vice President and Head, Global Value & Access, Novartis, USA*, spoke about opportunities for HTA harmonisation that may help align and build evidence convergence and improve efficiency, ultimately expediting patient access. To move forward with HTA harmonisation, multi-stakeholder collaborations should look to establish principles of good HTA practice; provide joint HTA

advice; dedicate resources for the EUnetHTA early decision and loosen HTA participation rules for EUnetHTA; encourage collaboration on joint clinical assessment with patients such as parallel EMA/EUnetHTA advice; and ensure appropriate uptake of supra-national assessment at the national level.

**Dr Antje Behring**, *Head of Pharmaceuticals Department, G-BA, Germany*, gave an overview of the impact of EUnetHTA early dialogues in facilitating learning and trust building amongst HTA agencies as well as the integration of HTA needs into development plans. Although there is currently a lack of experience in transferring the results of multi-HTA consultations to the final joint assessment, multi-HTA consultations have helped to provide clarity on common HTA expectations and shown that there is a high level of agreement on key aspects of study design.

**Dr Alicia Granados**, *Head of Global HTA strategy, Sanofi, Spain*, described how early scientific dialogues are opportunities for companies to align internal strategies on evidence generation and to test that proposed evidence generation plans are relevant for different health authorities and patients. To get the most value from early scientific dialogues involving HTA agencies, companies need to leverage HTA competencies and have a high level of scientific and coordination expertise. Future considerations for early scientific dialogue include involving patients and healthcare professionals, improving report deliverables, and facilitating continuous dialogue with HTA agencies.

**Jeanette Kusel**, *Director for NICE Scientific Advice, NICE, UK*, and **Dr Michelle Mujoomdar**, *Director, Scientific Affairs, CADTH, Canada*, spoke about how NICE and CADTH came together in 2018 to offer joint scientific advice. For the five joint projects completed so far, the experience has been positive, however, the collaboration is limited to the topics that are brought by companies. There may be new opportunities for HTA agencies to collaborate e.g. in horizon scanning, joint effectiveness reviews. For successful collaboration, there must be clear objectives for all participating, defined terminology and common understanding of different ways of working.

### **Session 3: Focus on regulatory-HTA interaction and collaborations – does this provide aligned thinking to improve regulatory and HTA outcomes and patient access?**

**Wendy Palframan**, *Senior Director Oncology, Global Regulatory Affairs, GSK, UK*, spoke about the impact of the EMA Priority Medicines (PRIME) scheme and GSK's experience of using the scheme. While PRIME appears to be having a positive impact on approval timelines, it is too early to say whether it is facilitating earlier patient access. PRIME facilitates expedited development in line with CHMP expectations and its iterative, data-driven scientific advice aligns the needs of regulators and industry, however, it does not currently address the gap between regulatory and HTA evidence requirements.

**Michael Berntgen**, *Head of the Evidence Generation Department, EMA*, described how regulators and HTA agencies are increasingly exchanging information on their respective product assessments and initiating collaborations on methodologies. Alignment on methodologies and types of evidence would support the possibility to have evidence generation plans that are universal by serving different types of decision making. Discussions across decision-makers are crucial to better guide on evidence requirements throughout a medicine's lifecycle, including post-authorisation evidence.

**Dr Ly Tran**, *Advisor, Deputy Secretary of the Scientific Advisory Board for Medicines, ZIN, The Netherlands*, and **Kevin Liebrand**, *Regulatory Project Leader, MEB, The Netherlands*, spoke about the MEB-ZIN parallel procedure, which increased efficiency and reduced the total time for registration and reimbursement by approximately 90 days. The pilot showed that early multi-stakeholder dialogue enables a more constructive approach towards reimbursement but there must be transparency on price to facilitate this dialogue. Although only two products have completed the

MEB-ZIN parallel procedure, the experience has been positive and has led to the commitment to implement the parallel procedure as one of the routes for reimbursement in the Netherlands.

**Dr Daniel O'Connor**, *Medical Assessor, MHRA, UK*, and **Dr Nick Crabb**, *Programme Director, Scientific Affairs, NICE, UK*, gave an overview of the UK Innovative Licensing and Access Pathway (ILAP), which promotes system alignment between MHRA, NICE, SMC and other partners as well as early engagement with companies. Through ILAP, innovative methods and tools have been developed that accelerate availability of robust data including the development of a specific roadmap tailored to the needs of each innovative product. So far, four pilots have taken place to test the roadmap and companies and partners have reported positive experiences; lessons learned are currently being incorporated.

**Dr Craig Simon**, *Acting Director, Health Products Surveillance and Epidemiology Bureau, Marketed Health Products Directorate, Health Products & Food Branch, Health Canada*, described how Health Canada collaborates with a variety of domestic and international partners to align use of Real World Evidence (RWE) across the product life cycle and jurisdictions. While RWE can be leveraged to support decision-making, it should not be seen as a ‘magic bullet’. Timely availability of high-quality data remains key to the optimal use of RWE and will continue to be integral for the appropriate use of RWE in the future.

#### **Session 4: Focus on payer interactions with regulators and HTA – what are the challenges, opportunities and future developments across stakeholders?**

**Evert Jan van Lente**, *Director of EU-Affairs, AOK-Bundesverband, Germany, and Chair of Medical Evaluation Committee (MEDEV), Belgium*, described how multi-stakeholder cooperation is needed to tackle the challenges payers face with new technologies i.e. uncertainty and pricing challenges. While payers must create legal options for reassessments and renegotiations on the price when there is an evidence gap, the resources invested by payers for early dialogues, evidence generation and the implementation of new payment models must also pay off through ‘realistic’ prices.

**Dr Vanessa Elisabeth Schaub**, *Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, Roche, Switzerland*, spoke about the importance of early stakeholder involvement in drug development, which needs to be complemented by continuous stakeholder engagement for post-licensing evidence generation. In relation to the post-licensing phase and the complementary RWE required, there is a need for alignment and clarification in terms of different jurisdictional levels, different data collection requirements and the different use cases for the collected data.

**Shane Kavanagh**, *Vice President Health Economics & Real World Evidence, Janssen, Belgium*, gave a company perspective on the future landscape for company, regulator, HTA and payer interactions. Although future methodological advances and further understanding of technical requirements are likely to address current issues around trials designs and RWE, new questions on new data sources and surrogate endpoints may arise. The need for interactions and collaborations on population definitions, evidence packages etc will continue and role clarity will remain relevant.

**Bruce Randall**, *Senior Executive Director, Therapeutic Products Directorate, Health Canada*, gave a regulatory perspective on the future landscape for company, regulator, HTA and payer interactions. There is a need for continued collaboration and alignment to create efficiencies and maximise patient outcomes, while maintaining a balance and ensuring recognition of the independent and complementary roles of various organisations.

**Andrew Mitchell**, *Strategic Adviser, Evaluation, Office of Health Technology Assessment, Australian Government Department of Health*, gave an HTA perspective on the future landscape for company,

regulator, HTA and payer interactions. HTA agencies should continue to have collaborative interactions with payers, other HTA agencies, regulators and companies. However, the interactions with companies should be kept separate, to acknowledge differences in objectives, and interactions with payers and other HTA agencies should be aligned and harmonised, respectively.

**Dr Michael Ermisch, Specialist, GKV-Spitzenverband, National Association of Statutory Health Insurance Funds, Germany**, gave a payer perspective on the future landscape for company, regulator, HTA and payer interactions. While there are cooperation initiatives happening that include payers, there is a need for more alignment and recognition of different stakeholder responsibilities. This is now even more important given that the COVID-19 pandemic has intensified expectations around access to medicines; the time has come to further develop cooperation with selected products in concrete projects.

### Session 5: Breakout discussions

**Breakout A** was asked to assess current stakeholder experiences of interactions and collaborations. The EUnetHTA regulatory/HTA parallel consultation was suggested as a good example of an interaction model, as it has promoted cross-function collaboration within companies and among agencies. Areas for future improvement during early stakeholder interactions included reaching consensus among regulatory and HTA agencies on the evidentiary requirements at both pre-launch and post-launch stages; further alignment among HTA agencies; balancing early access for new medicines and long-term follow up of health outcomes; and addressing wider value aspects. The group also identified characteristics of an effective engagement model, which included clear definitions of 'early' interactions from both regulatory and HTA perspectives; engagement with multiple stakeholders but with a focus on key HTA agencies; identifying and understanding uncertainty as well as trade-offs between global and jurisdictional needs; and managing both scientific and commercial risks.

**Breakout B** examined the characteristics of interactions that enable convergence amongst stakeholders as well as potential opportunities, barriers and solutions. Appropriate clinical evidence and methodology, alignment on definition of unmet need, understanding of innovative study designs and early HTA input were identified as key characteristics for interactions focused on supporting evidence generation during development. Issues that were highlighted by the group included how to measure success and manage uncertainty, while early dialogue was thought to be a potential solution.

**Breakout C** were asked to focus on 2030 and discuss what an ideal ecosystem for interactions and collaboration would look like. Shared language/definitions, early stakeholder engagement and collaborative networks were identified as important for interactions on evidence generation for licensing, while technical guidance and clear requirements and standards were needed for the post-licensing space. Key building blocks or success factors for the ideal 2030 ecosystem included patient centricity, best practices, flexibility, common objectives and a stable platform for dialogue.

**Breakout D** examined how the success of interactions and collaborations can be measured. Suggested success indicators were speed (time to patient access), 'correct-ness' of decisions, patient relevance of the evidence generated and equity of access. The group agreed that while there is value in multi-stakeholder interactions, these interactions occur at different levels and expectations of value can differ. To ensure iterative improvements in interactions and collaborations, the group suggested that stakeholder surveys be conducted, for example, on the value of interactions, and information/data sharing be promoted to build trust and improve transparency.

## Section 2: Presentations

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### **ICH at 30 years: driving convergence of technical standards for global regulatory acceptance – has this decreased divergence of requirements across agencies?**

**Lenita Lindström-Gommers, European Commission Directorate General for Health and Food Safety (SANTE) and Chair of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Assembly**

ICH is a unique harmonisation project bringing together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of drug registration. The overall objectives of ICH are to improve efficiency of new drug development and registration and to promote public health, prevent duplication of clinical trials and minimise the use of animal testing without compromising safety and effectiveness.

#### **Harmonised regulatory guidelines and standards**

A key activity of ICH is the development and implementation of harmonised regulatory guidelines and standards. Since its initiation in 1990, ICH has developed approximately 70 guidelines and established Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B), the Common Technical Document (CTD) and electronic CTD, and the Medical Dictionary for Regulatory Activities Terminology (MedDRA). Key to ICH's success over the last 30 years is its science-based approach, with involvement of regulators and industry in the scientific development phase (with regulators deciding on the adoption of the guidelines); well managed and clear processes supported by a permanent secretariat; use of highly qualified experts appointed by members and observers; and the commitment of its regulatory members to implement products of harmonisation.

In 2015, ICH underwent fundamental reform to facilitate harmonisation efforts beyond the founding regions of USA, Europe and Japan. The focus of these reforms were around governance, to strengthen the decision-making role of regulators vs regulated industry in the guideline adoption process; transparency, to improve openness of ICH and its processes; international outreach, to increase the involvement of regulators as well as other stakeholder affected by ICH guidelines; legal construct, to set up ICH as an independent legal entity (non-profit association under Swiss law); and funding, to develop a sustainable funding model through membership fees. Since the introduction of these reforms, ICH members have grown in number and diversity, with a total of 17 members and 32 observers as of March 2021.

The purpose of ICH guidelines is harmonisation of requirements, rather than regulatory convergence. However, the increased uptake of ICH guidelines by regulatory authorities worldwide contributes to and complements efforts relating to regulatory convergence in terms of scientific and technical requirements. The International Pharmaceutical Regulators Programme (IPRP) also has an important role in promoting regulatory convergence, information sharing and best practices amongst regulators.

## Implementation of ICH guidelines

In accordance with the ICH Articles of Association, regulatory members of ICH are expected to implement ICH guidelines. ICH has introduced independent surveys to assess regulatory agencies' and companies' perspectives on the implementation and adherence to ICH guidelines. These surveys not only give an indication of the state and adequacy of guideline implementation but also help to inform ICH Assembly decisions on new membership applications as well as identifying training needs. CIRS conducted the first survey in 2019 and is currently working on the next one.

The 2019 survey indicated some different interpretations of the concept 'adequate implementation' (the 2019 survey report is available on the [ICH website](#)). These issues have been addressed and ICH is increasingly focusing on training activities particularly for its regulatory members on guideline implementation.

## Future challenges

ICH faces challenges due to its growth in membership and guidelines. ICH may need to review the future format of its meetings and hopes in the future to have other stakeholders impacted by ICH guidelines, such as international patient organisations, join ICH as observers. ICH may also consider going forward the possibility to regroup existing guidelines within given topic areas and will continue its efforts to ensure coherent implementation of guidelines across ICH regions. However, challenges remain in relation to ensuring that new and existing ICH guidelines remain up to date with emerging and rapidly evolving topics.



## Decreased divergence of requirements?

ICH issues guidelines on **scientific and technical requirements** with a view to reach harmonisation

The purpose is not regulatory convergence but harmonisation of requirements, however the increased uptake of ICH guidelines by regulatory authorities worldwide **contributes to regulatory convergence in terms of scientific and technical requirements**

Important role of **IPRP** (International Pharmaceutical Regulators Programme) which is working on regulatory convergence, information-sharing and sharing of best -practices amongst regulators

7



## Jurisdictional regulatory early scientific advice – does this enable more effective and efficient medicines development?

**Sharon Gorman, Director, Regulatory Intelligence and Analysis, Pfizer, UK**

Integrated scientific dialogue along the development continuum with engagement and alignment of relevant stakeholders is considered a priority for developers and regulators. The EMA has recognised this need in its Regulatory Science Strategy 2025, and it is also reflected in the European Medicines Regulatory Network (EMRN) strategy. Learnings from COVID accelerated scientific advice can be viewed as many of the principles in action.

Several types of regulatory scientific advice procedures are available in the EU, some of which aid regulatory planning only and others which aid both regulatory and reimbursement planning. They all serve different purposes and have their own distinct advantages and limitations. Although development plans are on a global scale, national scientific advice still has value in giving insights on EU member state views and can be useful to complement CHMP advice.

### **Value of scientific advice**

Companies are increasingly using regulatory scientific advice procedures, which supports their value in enabling efficient and effective medicines development towards regulatory approval. However, questions remain over whether advice procedures truly aid the ultimate goal of patient access. Multi-stakeholder or collaborative scientific advice is still relatively underused by industry, suggesting that the value of these procedures has not yet been clearly demonstrated. Pfizer's experience of parallel regulatory-HTA scientific advice, although relatively limited, has been generally positive and led to tangible impacts on clinical development plans.

### **New collaborative models**

Efficient and effective medicines development requires a collaborative approach to patient access, which is the ultimate goal. Although there has been progress in recent years, new models of collaboration are needed beyond parallel scientific advice, and these may be informed by the learnings and experiences of the COVID-19 pandemic.

The recently launched UK Innovative Licensing and Access Pathway (ILAP) provides a single platform for sustained collaborative working between the Medicines and Healthcare Products Regulatory Authority (MHRA), National Institute of Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), other research partners and the medicine developer. ILAP partners have a common aim and combined responsibility to enable development to the point of patient access. There is flexibility to enter the scheme at any time, which is beneficial for developers, and the patient voice is integrated at every stage. While this sort of collaborative model may work well in the UK, scaling up something similar for the EU or other countries would have practical challenges.

### **Challenges to overcome**

To build better collaborative models, several challenges need to be addressed such as balancing early access and value-based prices with evidence commitments, adapting payer and HTA methods and incentives, creating efficient processes in industry, catalysing existing collaborations, collecting real-world outcomes and building trust through process and pilots. Potential solutions to negotiation conflicts include using precision medicine and lifecycle indication expansion (connecting science to financial

consequences), collaborating with stakeholders, connecting internal decisions to external responses, and finding ways to use resources more efficiently.

## In Summary



- Use of EU regulatory scientific advice established; value (in terms of regulatory approval) well recognised.
  - More ‘efficient/ effective’ medicines development requires a collaborative approach to ‘patient access’ which is the ultimate goal
    - Some progress (e.g Parallel Scientific Advice) but potential not fully optimised
  - ‘Deeper’ (more **integrated** and **flexible**) and ‘wider’ (include but go beyond parallel scientific advice/ initial approval) collaboration models are needed to optimise the efficiency of medicines development
    - Pilots (national, regional and global) and innovative approaches are needed (eg ILAP, ORBIS etc).



## Project Orbis – a new model of regulatory cooperation

**Michael Shum, Director, Application and Advisory Management, Prescription Medicines Authorisation Branch, Therapeutic Goods Administration (TGA), Australia**

TGA is expanding its work with international partners, with a key aim to participate in work sharing, information sharing and regulatory convergence activities. TGA works with regulators that have similar values and approaches to critical decision making through its Comparable Overseas Regulator (COR) pathway, the Australia-Canada-Singapore-Switzerland-United Kingdom (Access) work sharing consortium and Project Orbis.

### What is Project Orbis?

Project Orbis is a global collaborative review programme that was initiated by the FDA Oncology Center of Excellence (OCE) to provide a framework for concurrent submission and review of oncology products among international partners. Collaborative review of the dossier is facilitated through use of a common review document (the Assessment Aid) and by leveraging FDA resources and expertise. Project Orbis partners currently include TGA, Health Canada, MHRA (UK), HAS (Singapore), Swissmedic (Switzerland) and ANVISA (Brazil). Each partner retains its sovereign decision making in the process.

Project Orbis is primarily aimed at high-impact, clinically significant oncology products that are generally expected to meet the criteria for FDA priority review. Sponsors are required to meet administrative requirements such as submission of Assessment Aid documentation, availability of top-line clinical trial results, global submission plan and sponsor authorisation letters to facilitate information sharing.

### Process of Project Orbis

There are three types of review in Project Orbis, which are based around the level of alignment between submission to the FDA and to participating agencies. Type A allows for maximal collaboration and near simultaneous regulatory action, as it involves concurrent submission to participating regulators (within one month of submission to FDA). Type B is a modified route for applications where there is a submission delay of over three months, whereas Type C is where the FDA has already approved an application and makes reports available to Project Orbis partners. While TGA has found that timelines are generally reduced with Type A Project Orbis, they are not always reduced with type B and C.

FDA is the primary coordinator that identifies applications and puts them forward to the Project Orbis partners, who can either accept or decline to participate in the evaluation. After a kick-off meeting to discuss application logistics, all partners conduct their own review of the dossier and work directly with the local applicant. Collaboration usually takes the form of sharing Requests For Information, where all questions and answers are shared on a rolling basis amongst partners to avoid duplication. During Type A and B reviews, the FDA also coordinates collaborative teleconferences for reviewers to discuss various sections of the Assessment Aid and may also invite partners' reviewers to sit in on its own internal meetings.

### Impact of Project Orbis

During 2020, Project Orbis completed 49 submissions, 17 of which were New Chemical Entities (NCE) or New Biological Entities (NCB) and 32 new indications. The median submission gap between FDA and Orbis partners was 0.6 months with a range of -0.8 to 9 months [1]. Although Project Orbis is relatively new, benefits for both industry and regulators are being observed, such as faster market access for new products and improved regulatory efficiency (see below).

## TGA's experience of Project Orbis

TGA completed 13 submissions through Project Orbis in 2020, 5 of which were NCE/NCB and 8 new indications. Evaluation timeframes were reduced for several NCEs, including acalabrutinib, which was approved via TGA's provisional approval pathway within 35 working days and tucatinib which was approved under priority review within 113 working days. From TGA's perspective, Project Orbis is achieving its objective of encouraging earlier submissions in Australia.

As Project Orbis has been operating as a pilot so far, this has allowed learnings to be implemented continuously (such as the tiering of applications into types A, B and C) and collaborative opportunities to be maximised. Transparency across all Project Orbis partners has also facilitated learning and given valuable insight into FDA processes as well as access to FDA resources. Nevertheless, regulators and applicants need to be agile to participate in Project Orbis, as there are resource implications for evaluation and coordination aspects. Although applicants have reported challenges related to operational processes, setting up local entities and the intensity of rolling applications, experiences have generally been positive, and there is excitement about the future of Project Orbis.



## Project Orbis benefits

Industry	TGA
<ul style="list-style-type: none"><li>• Faster market access for new products</li><li>• Decreased workload through reduced set of Request For Information (RFI)</li><li>• Utilisation of common dossiers</li></ul>	<ul style="list-style-type: none"><li>• Improved efficiency with potential to reduce regulatory effort</li><li>• Best of both worlds – sovereign decisions and potential for greater international harmonisation</li><li>• Collaborative approach to decision making leading to more robust decisions</li><li>• Better access to medicines for the Australian community</li></ul>

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## Stakeholder perceptions of regulatory, HTA and payer interactions and collaborations: results of the CIRS pre-workshop surveys

Tina Wang, Manager, HTA Programme, CIRS

Prior to the workshop, CIRS conducted a focus study to explore current interactions and collaborations between companies, regulatory and HTA agencies, and determine each stakeholder's perception of the value that these interactions bring. An 'interaction' was defined as a situation where two or more stakeholders communicate with or react to each other, whereas a collaboration was defined as a situation of two or more stakeholders working together to create or achieve the same goal.

Surveys were distributed to companies and agencies (regulatory and HTA agencies) with the following objectives:

Agency survey objectives	Company survey objectives
1) Identify the current landscape of interactions and collaborations within and across regulatory and HTA agencies, and what stakeholders believe are effective models of engagement.	1) Identify current experiences from companies on stakeholder engagement and what they believe to be effective models of engagement.
2) Assess the added value of these interactions in improving decision making, increasing process predictability, enabling early access and mitigating uncertainty during development and jurisdictional roll-out.	2) Assess how companies measure the success of participating in multi-stakeholder interactions, at the product level, therapeutic level and policy level.
3) Explore what the future ecosystem could be for interactions and collaboration across stakeholders by determining where the key barriers and enablers are, and what the building blocks are to ensure each of the interactions provides value to the stakeholders and improved outcomes for patient access.	

Responses were received from nine international companies, seven regulatory agencies and six HTA agencies. The agencies represented jurisdictions in North America, Europe and Asia.

### Current multi-stakeholder collaborations and interactions

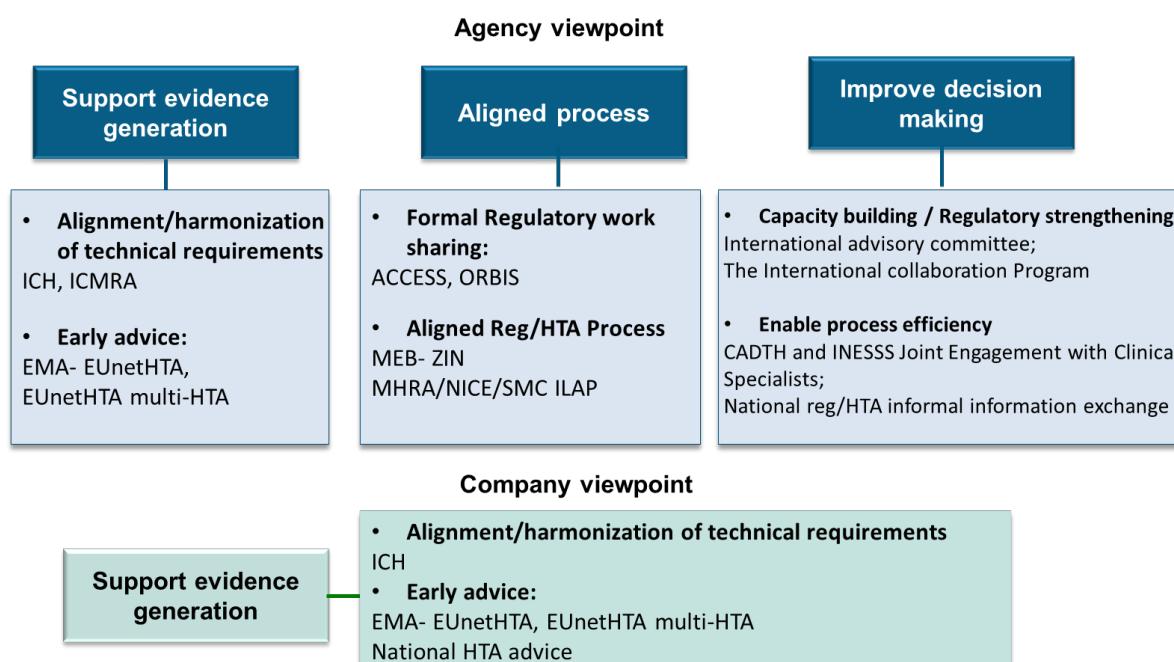
All seven regulatory and six HTA agencies indicated they have interactions with their peer agencies, as well as between regulatory and HTA agencies. For regulatory-regulatory interactions, the top areas of interaction were formal work sharing during review (86% positive response), regulatory strengthening through workshops and training (86%) and informal exchange of knowledge and information (76%). For HTA-HTA interactions, the top areas of interaction were HTA methodology/framework (83%), HTA capacity building (67%) and informal exchange of knowledge and information (67%). Other areas of interaction reported by regulatory and/or HTA agencies included regulatory reliance, joint HTA assessment, joint regulatory scientific advice, multi-HTA scientific advice and post-licensing evidence generation (PLEG).

For cross-stakeholder interactions, the top areas of regulatory-HTA interaction were exchange of knowledge and information during regulatory and HTA review (85%) and PLEG (46%). Only 15% agencies reported cross-stakeholder interactions relating to alignment/harmonisation of evidence requirements. Both stakeholder groups (regulators and HTA agencies) reported having interactions with payers to facilitate informal exchange of knowledge and information. HTA-payer interactions also tended

to focus on the implementation of HTA recommendations, discussion on pricing and budget impact and conditional reimbursement/managed entry schemes.

89% companies reported having interactions/collaborations for early scientific advice with a regulator, an HTA agency or through parallel regulatory-HTA advice. 56% had experience with multi-HTA joint advice and 44% with joint multi-regulator advice. Company interactions on PLEG plans tended to be more common with regulators than with HTA agencies (56% vs 22%).

Both companies and agencies were asked to provide examples of what they believed to be effective models of collaboration/interaction (Figure 1). These could be grouped according to the purpose of the collaboration/interaction, for example, to support evidence generation, aligning processes and improving decision making. Both companies and agencies agreed that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the European Network for HTA (EUnetHTA) were effective collaboration models to support evidence generation.



**Figure 1: Effective models of collaboration/interaction as perceived by regulatory and HTA agencies and companies**

### Value-add of multi-stakeholder interactions

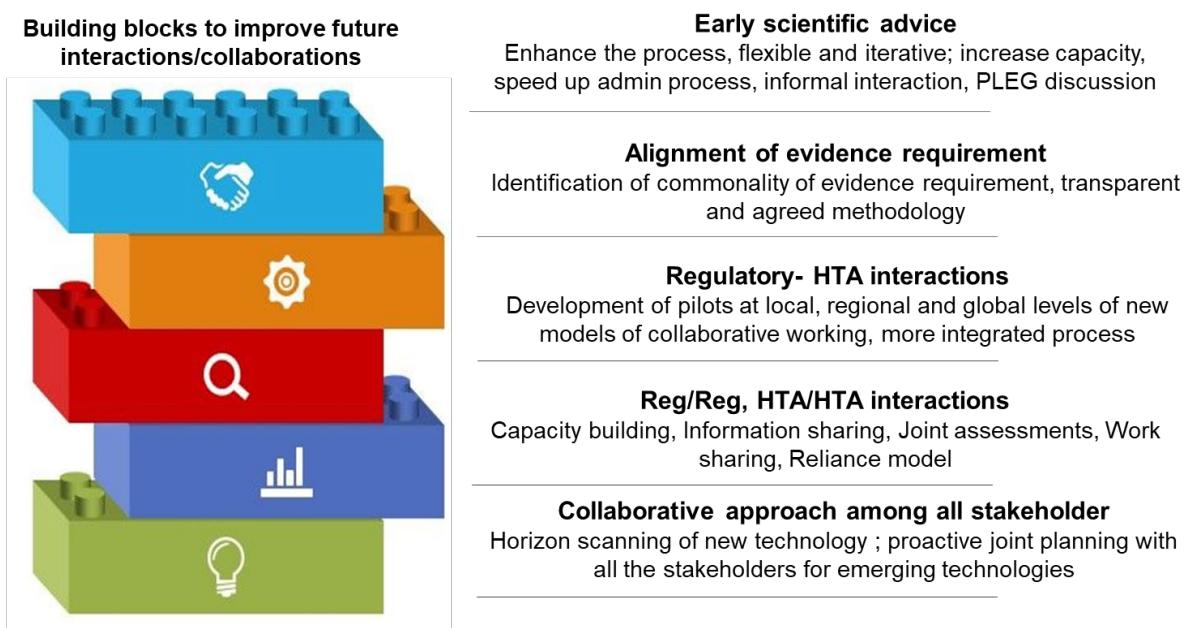
70% companies indicated that the “success of interaction is measured subjectively” with a partially developed set of indicators. At the product level, all companies viewed faster patient access as a key area in which to build success indicators. Value framework/evidence standard for disease was the most suggested area in which to build a success indicator at the therapeutic level, (67% positive response rate), while input into guideline development was the most suggested area at the policy level (89%).

When asked about the added value of stakeholder interactions/collaborations, agencies reported a wide range of benefits, which varied according to whether the interaction was regulatory-regulatory, HTA-HTA and regulatory-HTA. However, there was agreement that all three types of interactions improved understanding of the divergences across evidentiary requirements and provided a learning opportunity about the complexity of multiple system interactions. Regulatory-regulatory and HTA-HTA interactions

also helped to validate internal thinking within respondents' agencies. Regulatory-HTA interactions were seen to have fewer practical benefits than regulatory-regulatory and HTA-HTA interactions, such as in reducing duplication of work or providing an opportunity for capacity building/strengthening, which may suggest areas for improvement.

### Future ecosystem for multi-stakeholder interactions

92% of agency and 100% of company respondents indicated that multi-stakeholder interactions/collaborations were a priority in their organisational strategic plan. Suggested building blocks to improve future interactions/collaborations included early scientific advice; alignment of evidence requirement; regulatory-HTA interactions; regulatory-regulatory and HTA-HTA interactions; and a collaborative approach among all stakeholders (Figure 2).



**Figure 2: Company and agency perspectives of potential building blocks to enable the evolution of interactions/collaborations**

When asked about the ideal ecosystem for multi-stakeholder interactions and collaborations, both company and agency respondents highlighted the importance of having separate remits, functions and principles between stakeholders; converged evidence requirements; aligned process and reliance where appropriate; and increased transparency and trust (Figure 3). In addition, at the jurisdictional level, respondents indicated that there should be collaborative approaches on horizon scanning, to support innovation and to facilitate patient access.



**Figure 3: Ideal future ecosystem for multi-stakeholder interactions to support the development, review and access of new medicines**

## HTA global collaboration – international collaborations on policy and technical issues – what outcome would be of value and most benefit to patients?

### International Network of Agencies for Health Technology Assessment (INAHTA) perspective

**Professor Tracy Merlin, Chair of INAHTA, Director of Adelaide Health Technology Assessment (AHTA) and Head of School of Public Health, University of Adelaide, Australia**

INAHTA is a global network of 50 HTA agencies that support health system decision making affecting over one billion people in 31 countries. Membership includes 31 HTA agencies from Europe, five from Latin America, five from USA and Canada, five from Asia, three from Australia and New Zealand and one from Africa. INAHTA also works with other organisations, societies, and networks such as the World Health Organisation (WHO), HTA international (HTAi), European Network for Health Technology Assessment (EUnetHTA), HTAsiaLink and Health Technology Assessment Network of the Americas (RedETSA). INAHTA's objectives are to:

- Bring agency **leadership and expertise** to the global HTA community to advance the science and practice of HTA.
- Demonstrate the **value of HTA** agencies as key components of modern health systems to support robust decision-making based on the best available scientific evidence.
- Support **best practice** and innovation for building and maintaining thriving HTA agencies.
- Enable continuous **exchange of knowledge** and learning among member agencies.

### Feasibility of HTA harmonisation

HTA processes vary internationally in terms of the objective of each process; whether there is a direct or indirect impact on policy; the trigger for appraisal (proactive vs reactive); the scope of policy impact (local vs regional vs national); maturity of health system and HTA processes; methodologies (secondary vs primary research, type of research considered); components of the HTA (safety, clinical effectiveness, cost, social, ethical, legal etc); transparency of process; and funding mechanisms. This variation is driven by the health systems in which the HTA is conducted, so convergence may only be feasible for HTA agencies with similar health systems.

HTA agencies work by initially 'globalising' the evidence, for example by looking at regulatory guidance on trial design, conduct and reporting as well as international published and unpublished evidence. The next step is to 'localise' the decision, by considering factors that impact how the HTA is done and appraised, such as variations in clinical practice (and thus selection of a relevant comparator); cost-effectiveness of the technology in the local health system and willingness-to-pay; ethical issues; access issues; consumer and patient preferences; workforce planning; and training users of the technology. While harmonisation of HTA processes is occurring to some extent at the global evidence level, it is challenging to harmonise at the local decision level because of the variety of contextual factors that HTA agencies need to consider.

### HTA-HTA knowledge sharing

INAHTA promotes knowledge sharing among HTA agencies through its annual congress, electronic mailing list, surveys, learning groups, webinars, task groups and international HTA database. The HTA database is publicly available and provides a single point of access to bibliographic information about ongoing and published HTAs that have been commissioned or undertaken by HTA agencies internationally.

## Developing consensus on HTA

INAHTA is helping to promote consensus and principles of HTA through its HTA Glossary, which is available in six languages (English, French, German, Spanish, Portuguese and Russian). It also had a key role in developing consensus on the definition of HTA by working with HTAi and other partners [1]. This work took two years to complete, thus highlighting the difficulty in harmonising HTA. INAHTA has recently started developing position statements on different principles of HTA, which undergo a rigorous process requiring at least 70% consensus from INAHTA members.

## Convergence of methods and work sharing

A survey carried out by INAHTA showed that approximately half of HTA agencies' reports are adapted from HTA products produced by other agencies [2]. For this reason, the INAHTA HTA database is an important resource for updating and adapting HTAs from other jurisdictions to local circumstances. There are also collaborations or work sharing between agencies with the same language, similar methods and/or similar health systems.

## Final thoughts

In summary, HTA agencies and networks like INAHTA are creating opportunities for harmonisation wherever possible. However, the local health systems and local HTA requirements will always be a limiting factor to HTA harmonisation efforts.

## INTERNATIONAL VARIATION IN HTA PROCESSES

- **Objective of HTA process**
- **Direct vs indirect impact on policy**
- **Trigger for appraisal - proactive vs reactive**
- **Scope of policy impact- local vs regional vs national**
- **Maturity of health system and HTA processes**
- **Methods – secondary vs primary research, type of research considered**
- **Content – safety, clinical effectiveness, costeffectiveness, social, ethical, legal**
- **Transparency of process**
- **Funding mechanisms**

HTA models and uses differ according to the health systems in which they work



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## Reimagining HTA: Wouldn't it be nice if we had HTA harmony?

**HTA global collaboration – international collaborations on policy and technical issues – what outcome would be of value and most benefit to patients?**

### Company perspective

**Dr Indranil Bagchi, Senior Vice President and Head, Global Value & Access, Novartis, USA**

Despite globalisation of therapies and new technologies, patients face global disparities in time to access and product availability. HTA median approval times vary across jurisdictions and it can take a considerable amount of time for patients to access a drug after regulatory approval [1,2]. HTA agencies often consider different variables and weightings, resulting in different value assessments [3]. HTA harmonisation may help align and build evidence convergence and improve efficiency, which may ultimately expedite patient access.

### Opportunities for HTA harmonisation

There may be opportunities for harmonisation between HTA agencies, as well as between regulatory and HTA agencies, in the areas of safety and efficacy, as each agency assesses these areas in their reviews. There may also be opportunities for HTA agencies to learn from the regulatory community in relation to collaborations and work sharing; international regulatory partnerships like Project Orbis and the Access Consortium have shown that global collaborations lead to faster access and improved efficiency.

### Joint HTA assessments

The European Network for HTA (EUnetHTA) Rapid Relative Effectiveness Assessment (REA) is a joint HTA assessment conducted by at least four EUnetHTA partners from different European countries. The REA consists of four domains that are both important and transferable between countries: health problem and current use of the technology; description and technical characteristics of the technology; safety; and clinical effectiveness.

EUnetHTA has shown that using EUnetHTA joint HTA assessments can reduce the amount of time required to carry out agency assessment work such as data extraction and critical appraisal of clinical studies; improve the quality of national reports; strengthen the basis for agency findings about the data in industry submissions and agency recommendations to decision makers; and may enable agencies to negotiate earlier application for reimbursement and as a consequence, this can lead to earlier decision making about use of a health technology [4]. However, there is still variability in the adoption of the EUnetHTA REA report across EU countries. Challenges to its adoption include differences in HTA scope and process; need for local language translations; lack of alignment between the REA report structure and the country-specific report; issues with timing of the availability of the REA; and variations in HTA evidence requirements.

### Looking ahead

The COVID-19 pandemic has demonstrated that regulators, industry, HTA/payers and patients can together address multi-faceted issues while fostering trust and transparency. Incremental innovation to harmonise HTA may be better received by HTA agencies than aggressive innovation. HTA agencies reflect competing country priorities so there must be mutual understanding between stakeholders that HTA agencies' perception of value depends on their country (or even regional) culture.

To move forward with HTA harmonisation, multi-stakeholder collaborations should look to establish principles of good HTA practice; provide joint HTA advice; dedicate resources for EUnetHTA early decision and loosen HTA participation rules for EUnetHTA; encourage collaboration on joint clinical assessment with patients such as parallel EMA/EUnetHTA advice; and ensure appropriate uptake of supra-national assessment at the national level.

## Seeking HTA harmonisation



CIRS HTA Global Collaboration | March 2021

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## European multi HTA early dialogues

**Are these enabling improved evidence generation, quality of submission and HTA assessment outcomes at the time of HTA assessment over single HTA early advice?**

### HTA agency perspective

**Dr Antje Behring, Head of Pharmaceuticals Department, Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), Germany**

G-BA is the highest decision-making body of the joint self-governing system of physicians, dentists, hospitals, and health insurance funds in Germany. It issues directives for the benefit catalogue of the statutory health insurance funds and thus specifies which services in medical care are reimbursed (but not how much is paid). G-BA is mandated to conduct early benefit assessments of all new drugs that come onto the market in Germany and to offer companies consultations for scientific advice. The demand for G-BA consultations is increasing, with over 300 meetings taking place in 2020 compared to less than 50 meetings in 2011.

### EUnetHTA early dialogues

G-BA is a member of the European Network for HTA (EUnetHTA) and co-leads the work package on early dialogues. Between May 2017 and March 2021, EUnetHTA received 119 letters of intent that led to a total of 38 early dialogue meetings. Six of these were multi-HTA consultations, 31 parallel (regulatory-HTA) and one medical device consultation. The high demand for parallel consultations over multi-HTA may reflect that sometimes companies need to seek alignment internally i.e. between regulatory and market access teams. The EUnetHTA early dialogues not only allowed participating HTA agencies to learn from each other but also built trust between the agencies.

A qualitative analysis of EUnetHTA early dialogue documents examined the level of alignment between participating HTA agencies. This showed that there were commonalities in approaches, such as a preference for dose finding studies before phase III; requirement to demonstrate validity and patient relevance of surrogate endpoints; preference for overall survival data in oncology and some other indications; and quality of life data being viewed as very relevant and important. Patient input was also regularly requested and included in the final written recommendations, though individual agency approaches sometimes differed. Topics with divergent approaches that were mainly due to differences in national systems/modelling were economics, companion diagnostics, statistical analysis, outcomes/endpoints, progression-free survival in oncology, patient-reported outcomes (PROs), and quality of life measures.

16 out of 23 companies (69%; two multi-HTA and 14 parallel consultations) reported making changes to their development plans following EUnetHTA early dialogues. These changes related to endpoints, clinical trial design, populations, economic models and/or comparators. A new topic that is arising in early dialogue consultations is post-licensing evidence generation. This is especially important for orphan products, which may require multi-stakeholder collaboration with regard to registries.

### Multi vs single HTA advice

Multi-HTA and single HTA advice varies in terms of transparency, clarity, specificity, patient involvement, accountability and workload (see below). For example, sometimes the context of single HTA advice is not always clear from meeting minutes, whereas multi-HTA advice procedures are often more transparent and give a better understanding of HTA requirements. Nevertheless, multi-HTA advice has a higher

workload, and the provided advice may be more general than single HTA advice, which is targeted at the national assessment procedure.

## Conclusion

Multi-HTA consultation is currently hampered by lack of experience in transferring the results of multi-HTA consultations to the final joint assessment. However, there is clarity on common HTA expectations and a high level of agreement in key aspects of study design. Multi-HTA advice has also increased understanding of the needs of HTA bodies, which has been reflected in better quality of data collection, such as QoL data; clearer definition of endpoints; and selection of study population.

## Multi HTA vs. Single HTA Advice

	Multi HTA	Single HTA
Transparency	Positions from other HTAbodies are shared and can be discussed	Advice from other HTA bodies only available, if company shared advice, context sometimes unclear
Clarity	If agreement, clear position of HTA body	Only opinion of one single HTAbody
specificity	general advice	Explicitly targeted at the national assessment procedure
Patient involvement	Rather regularly	depending on national requirements
Accountability	Not binding	Not binding
workload	higher	lower



## European multi HTA early dialogues

**Are these enabling improved evidence generation, quality of submission and HTA assessment outcomes at the time of HTA assessment over single HTA early advice?**

### Company perspective

**Dr Alicia Granados, Head of Global HTA strategy, Sanofi, Spain**

Companies are faced with increasing uncertainty on what evidence matters to whom as well as inefficiencies in R&D processes. Early scientific dialogue is an important step for companies to enable more effective investment decisions during development and minimise delays in patient access.

### How early is 'early'?

There are opportunities for stakeholder dialogue throughout the entire medicine lifecycle. Even before a technology is developed, stakeholder dialogues help to identify needs and define priorities in a therapeutic area. Early dialogues with HTA agencies specifically can facilitate the integration of HTA requirements into development plans before phase III trials are decided. A key time point for multi-stakeholder dialogue is when additional data collection for Real World Evidence (RWE) is being considered, which may be at the time of marketing authorisation and/or HTA assessment.

### Impact of early dialogues

Feedback from eight companies that used European Network for HTA (EUnetHTA) early dialogues showed that 75% made changes to their development plans as a result of the advice [1]. These changes were often focused on the treatment population, closely followed by endpoints and clinical trial design. A study of parallel EMA-HTA scientific advice procedures between 2010 and 2015 highlighted that companies tend to implement changes to the development programme based on both regulatory and HTA advice with regards to the choice of primary endpoint and comparator [2].

Early scientific dialogues may increase companies' chances of obtaining regulatory and reimbursement positive recommendations [3]. A study performed by Haute Autorité de Santé (HAS) showed that of the 84 early dialogues it had conducted by the end of 2018, only eight medicinal products were appraised by HAS for reimbursement, but all of these products obtained a clinical added value score [4]. Similarly, 100% (23 out of 23) products that received scientific advice from the National Institute for Health and Care Excellence (NICE) were recommended for reimbursement [5].

### Lessons learned

Early scientific dialogue is an opportunity for companies to align internal strategies on evidence generation and to test that proposed evidence generation plans are relevant for different health authorities and patients. It also allows companies to have a transparent and constructive discussion with stakeholders on target value proposition, which informs internal 'go/no-go' decision making. The selection of multi vs single HTA advice is dependent on internal therapeutic area strategies and external circumstances. However, it would be more desirable to have less diversity and more alignment in HTA feedback related to patient-intervention-comparison-outcome-study design (PICOS).

To get the most value from early scientific dialogues involving HTA agencies, companies need to leverage HTA competencies and have a high level of scientific and coordination expertise. Future considerations for early scientific dialogues are to involve patient representatives and expert health care

professionals throughout the process and to improve report deliverables so that they contain systematic reasoning for convergences and specificities by country. While follow-up with HTA agencies (continuous dialogue) is desirable, questions remain around how this would work in practice.

### Industry Perspective on Early Scientific Dialogue - Lessons Learnt

- ✓ An opportunity to align internal strategies on the evidence generation.
  - ✓ Test whether our proposed evidence generation plans are relevant for different health authorities and patients.
  - ✓ A transparent & constructive discussion with stakeholders on target value proposition
  - ✓ A factor into internal Go / No Go decision making process.
  - ✓ European or single country HTA? It depends on internal therapeutic area strategies and external circumstances.
- ... But it would be desirable for less HTA diversity of feedback in early scientific dialogue related to patient-intervention-comparison - outcome-study design (PICOS).



| 12

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## Transcontinental initiatives on scientific advice and interactions during development – what new opportunities have been identified and how could these be applied more widely?

**Jeanette Kusel**, Director for NICE Scientific Advice, NICE, UK

**Dr Michelle Muroomdar**, Director, Scientific Affairs, CADTH, Canada

### NICE-CADTH scientific advice

NICE and CADTH share commonalities in terms of their scientific advice processes and the methods they use to evaluate new treatments, which are based on quality-adjusted life years (QALY). In recognition of the importance of a strong combined HTA voice, NICE and CADTH launched parallel scientific advice in 2018.

The process for NICE-CADTH scientific advice involves submission of a single briefing book and the opportunity to direct specific questions to NICE and/or CADTH. The NICE and CADTH teams will share and discuss issues in preparation for a virtual meeting with the applicant, which also includes English and Canadian experts, such as clinicians, HTA experts, health economists and patient representatives. The meeting will usually focus on study population and subgroups, relevance of comparators, acceptability of endpoints, relevant patient-reported outcomes, resource use and cost data, economic modelling approach and other sources of data such as registries. The advice is documented in a single joint report, which includes a summary of advice highlighting areas where NICE and CADTH align, as well as each agency's responses to questions.

For the five NICE-CADTH advice projects completed so far, the experience has been positive for both agencies and companies. Discussion topics have included clinical trial design, indirect comparisons, economic modelling and patient preference studies. For NICE and CADTH, the benefits of the joint advice process are the opportunity to share and discuss issues, for example, in new areas such as patient preference studies, and to identify areas where further methods work might be needed in both markets. However, the collaboration has come at a cost in that additional steps had to be added to the process and the joint advice summary takes longer to prepare. In addition, the extent of the collaboration is limited to the topics that are brought by companies. From a company perspective, a key benefit of NICE-CADTH advice is efficiency, as advice is received from two major markets in a single streamlined process.

### New opportunities for collaboration

HTA-HTA collaborations can take the form of informal networking, which may be discussions between single agencies; multi-HTA discussions, which are important for sharing knowledge during public health emergencies such as COVID-19, as well as on process-related or policy topics; or formal collaborations, such as scientific advice and methods projects.

There may be other opportunities in which HTA agencies can collaborate, for example, in horizon scanning, joint effectiveness reviews and post-review data collection. The HTA community could also potentially learn from regulatory colleagues on work-sharing collaborations such as the Access Consortium between Australia, Canada, Singapore, Switzerland and UK.

### Lessons learned from collaborations

For successful collaboration, there must be clear objectives for all participating, defined terminology and common understanding of different ways of working. Questions that need to be considered for future

collaborations include: will further collaboration bring benefits to HTA agencies; are joint effectiveness reviews feasible and useful; and will industry welcome further collaboration, such as joint submissions across HTA agencies?

## Lessons learned / reflections from other collaborations



- Clear objectives for all participating
- Terminology (e.g., parallel, joint, aligned, etc) matters
- Understanding of different ways of working → collaborative model may be new or different

## **PRIME – is this a model for prioritisation of medicines of unmet need, which aligns the needs of companies, regulatory and HTA agencies?**

**Wendy Palframan, Senior Director Oncology, Global Regulatory Affairs, GSK, UK**

The EMA Priority Medicines (PRIME) scheme targets products with potential to be a major therapeutic advantage for conditions where there is unmet medical need. The scheme enhances dialogue with EMA stakeholders such as the Committee for Orphan Medicinal Products (COMP) and the Paediatric Committee (PDCO) and promotes early and iterative building of product knowledge. Since its launch in 2016, PRIME has been refined following multi-stakeholder consultations; for example, in 2018 it was extended to include medicines in pivotal trial(s) and/or that had received scientific advice.

### **Impact of PRIME on approval times and patient access**

13 PRIME products were approved between 2018-2020, and these were approved more quickly than non-PRIME products (see below). In relation to Advanced Therapeutic Medicinal Products (ATMPs) and conditional marketing authorisations, PRIME reduced median approval timelines by three months and two months, respectively. However, for products approved under accelerated assessment, PRIME did not seem to reduce approval timelines. Furthermore, although PRIME products were more likely to be granted accelerated assessment than non-PRIME products, maintaining this status was not guaranteed. The majority of PRIME products were granted conditional marketing authorisations, which may reflect the specific criteria of PRIME and that many of the products were ATMPs.

While PRIME appears to be having a positive impact on approval timelines, it is too early to say whether it is facilitating earlier patient access. Only three PRIME products received first HTA recommendations from England, France, Germany, Scotland and Sweden between 2018-2020 [1]. With the exception of Germany, access to these products is limited and variable across these jurisdictions, often involving a managed entry or access agreement.

### **Experience of PRIME - Blenrep case study**

Multiple myeloma drug, Blenrep, was granted PRIME designation in October 2017 and underwent five scientific advice meetings before being granted accelerated assessment in November 2019. The PRIME kick-off meeting was valuable in facilitating early and open dialogue with relevant EMA stakeholders; providing useful feedback on potential topics for scientific advice; and initiating building product knowledge and relationships with the Rapporteur and their assessment team. However, scheduling of the kick-off meeting was challenging, and some discussions were high-level due to limited data. There was also strong encouragement to apply for joint Committee for Medicinal Products for Human Use (CHMP)/HTA advice, which took longer than EMA's standard advice. A potential solution would be to allow HTA participation in the kick-off meeting to understand regulatory perspectives and provide initial high-level feedback.

During the development of Blenrep, the EMA/CHMP partnership strongly encouraged iterative data-driven scientific advice and allowed the Rapporteur's agency to build good product knowledge in the absence of local clinical trials. In addition, annual updates ensured EMA was kept well informed, and that the momentum from the kick-off meeting was maintained. While the joint CHMP/HTA advice confirmed known gaps for some HTA agencies, it was not found to be helpful as it prolonged timelines and did not facilitate multi-stakeholder interactions very well. In addition, regulatory flexibility for the conditional marketing authorisation evidence dossier was not consistent with some HTA needs and increased internal resource was required for multiple advice procedures. To address these challenges, there needs to be a flexible and innovative HTA review process for PRIME-designated medicines e.g. prioritised

assessments, parallel review. For medicines applying for conditional marketing authorisation, stakeholders need to come together to enable patient access based on the regulatory package whilst further data is generated.

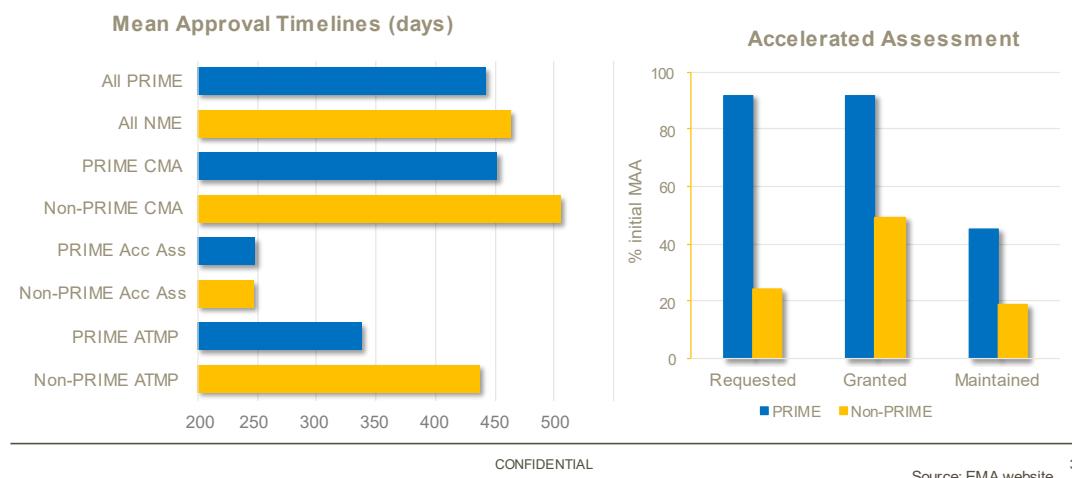
The pre-submission alignment meeting with the Rapporteur and new EMA contacts focused on compliance with scientific advice, which was very helpful. While the Rapporteur demonstrated detailed product knowledge during the marketing authorisation application review, updating the Co-Rapporteur on the extensive regulatory history was challenging. The maintenance of Orphan Drug Designation also added complexity and meant additional criteria needed to be met. Possible solutions to these challenges would be to appoint the Co-Rapporteur earlier e.g. in time for pivotal trial advice or the pre-submission meeting, and for PRIME-designated medicines, consider expedited HTA reviews and innovative patient access strategies (e.g. NICE's Cancer Drug Fund) until additional data is available.

## Summary

PRIME facilitates expedited development in line with CHMP expectations and its iterative, data-driven scientific advice aligns the needs of regulators and industry. However, PRIME does not currently address the gap between regulatory and HTA evidence requirements. Questions that need consideration are: would including HTAs in PRIME designation decision-making facilitate better alignment? Could PRIME designated medicines have a specific access/HTA track with innovative patient access strategies to share the risk? In addition, there is a need to better understand the impact of PRIME on patient access by conducting focused analyses and earlier involvement of the Co-Rapporteur and the Chemistry Manufacturing and Control (CMC) toolbox should be explored.

## Does PRIME result in faster regulatory approval?

Marketing Authorisation Applications 2018 -2020; 13 PRIME, 102 Non -PRIME



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Source: EMA website 3

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- [1] CIRS HTADock database, courtesy of Tina Wang, data extracted February 2021.

## EMA-HTA cooperation on products and methodologies - what has been achieved?

**Dr Michael Berntgen, Head of the Evidence Generation Department, EMA**

The aim of cooperation across decision makers is the alignment of thinking to facilitate patient access. To better align on evidence requirements, regulators and HTA agencies are increasingly exchanging information on their respective product assessments and initiating collaborations on methodologies.

### Product-specific engagement

In 2017, EMA and the European Network for HTA (EUnetHTA) came together to enhance information exchange on products and better connect the regulatory benefit-risk opinion to the relative effectiveness assessment (REA) by supporting joint REA production. This led to an increase in uptake of joint REA production by EUnetHTA, establishment of the EUnetHTA Prioritisation List and joint identification of products for exchange outside REA production. Based on initial experiences, the operational framework agreed between EMA and EUnetHTA was fine-tuned in 2019.

12 products have been subject to REA-related exchange, half of which were orphan medicinal products and 42% were oncology related. The format of the information exchange is a webinar between regulatory assessors and HTA authors based on the final regulatory output. Feedback on the product-specific discussion in the webinar has demonstrated increased mutual understanding, clarity about regulatory outcomes (for HTA agencies) and aspects for assessment report improvement (for regulators). Typical discussions and questions received from HTA agencies focused on the strength of evidence in different (sub-)populations as well as the need for additional evidence to address remaining uncertainties. Therefore, the earlier discussions on post-licensing planning that these webinars helped to stimulate was found to be valuable.

A recent study looking into regulatory-HTA information exchange on evidence needs highlighted multiple areas where information in the electronic Public Assessment Report (ePAR) is beneficial for REA. Opportunities to further enhance this exchange were also identified, such as increasing upstream working on evidence planning [1].

Other initiatives to ‘bridge the gap’ between regulators and HTA agencies include parallel procedures. For example, the Dutch regulator and HTA agency, MEB and ZIN, respectively, came together in 2019 to pilot a parallel procedure. Canada also has a parallel regulatory-HTA procedure, which was developed following a pilot focused on oncology products.

An area still in need of regulatory-HTA alignment is conditional marketing authorisations. Conditional marketing authorisation is a framework to facilitate approval of medicines addressing unmet medical need, subject to conditions for post-licensing data generation. CIRS work has shown that conditionally approved New Active Substances (NAS) have variable HTA outcomes, highlighting the need to better understand factors and uncertainties underlying HTA recommendations [2].

### Cooperation on methodologies

In addition to product-specific engagement, EMA and EUnetHTA are working together under the EMA-EUnetHTA 2017-2021 work plan to share methodologies to assess evidence and practices to facilitate alignment. A collaborative review between EMA, EUnetHTA members and industry on post-licensing evidence generation (PLEG) highlighted the need for advice involving different decision makers to optimise PLEG plans to address remaining uncertainties after licensing and launch [3]. EMA and HTA

agencies are also collaborating on approaches to extrapolation (or evidence transfer, for HTA agencies) by discussing different use cases and sharing draft guidance documents.

## Summary

With increasing exchange between regulators and HTA agencies, there is an opportunity to perform comparisons of views on (the same) evidence and to inform better prospective planning. Alignment on methodologies and types of evidence would support the possibility to have evidence generation plans that are universal by serving different types of decision making. Discussions across decision-makers are crucial to better guide on evidence requirements throughout a medicine's lifecycle, including post-authorisation evidence.



## EMA-HTA cooperation on products and methodologies

- Increasing experience with **exchange of information** between regulators and HTAs on their respective assessments
  - Opportunity to perform comparisons of views on (the same) evidence across decision makers and to inform better prospective planning
- Initiation of more collaboration on **methodologies** and types of evidence
  - Alignment would support the possibility to have evidence generation plans that are universal by serving different types of decision making
- Discussions across decision-makers are crucial to better guide on **evidence requirements** throughout the medicine's lifecycle, including post-authorisation evidence

14 EMA-HTA cooperation on products and methodologies - What has been achieved?  
Classified as public by the European Medicines Agency

10 March 2021

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## MEB-ZIN parallel procedure

### Collaboration during the review process – Is this decreasing the delay between the regulatory and HTA decision making?

**Dr Ly Tran, Advisor, Deputy Secretary of the Scientific Advisory Board for Medicines, National Health Care Institute (ZIN), The Netherlands**

**Kevin Liebrand, Regulatory Project Leader, Medicines Evaluation Board (MEB), The Netherlands**

In the Netherlands, the average lag time between marketing authorisation and market access is approximately 200 days. Although new forms of access have been introduced such as conditional approvals and compassionate programmes, it is only possible for companies to submit their reimbursement dossiers after receiving marketing authorisation. To streamline this process with the aim to increase patient accessibility to new medicines, ZIN and MEB came together to pilot a parallel procedure.

#### Piloting the parallel procedure

The two-year pilot started in April 2019, with the first year being focused on developing the parallel procedure concept, increasing publicity and creating an industry workgroup, and the second year focused on testing, optimising and fine-tuning the procedure. The parallel procedure that was agreed involves reimbursement processes starting at Day 181 (if there are no major objections from the Committee for Human Medicinal Products), with the goal to publish the advice on reimbursement one week after the European Public Assessment Report (EPAR) is published. This increase in efficiency has led to a reduction in the total time for registration and reimbursement by approximately 90 days. As of March 2021, two products had completed the parallel procedure and two were pending marketing authorisation assessment, with expected completion by Q3 2021.

#### Learnings and challenges

The pilot has shown that early multi-stakeholder dialogue enables a more constructive approach towards reimbursement and that it is necessary to be transparent and open to facilitate this dialogue. The increased interactions between MEB and ZIN were beneficial; the agencies found that sharing knowledge in writing e.g. via the EPAR had limitations therefore discussion meetings were often more useful. Other learnings included the need for flexibility and to not 'reinvent the wheel' with a completely new procedure; it is important to have some similarities with the sequential procedure so that companies are familiar with them.

A key challenge that arose during the pilot was around transparency; there needed to be transparency on price before marketing authorisation so that reimbursement processes could begin. A constructive approach calls for more transparency on pending assessment for marketing authorisation. Another challenge was the dependency on the establishment of positive benefit-risk, as the parallel procedure could not commence when benefit-risk was uncertain.

#### Next steps

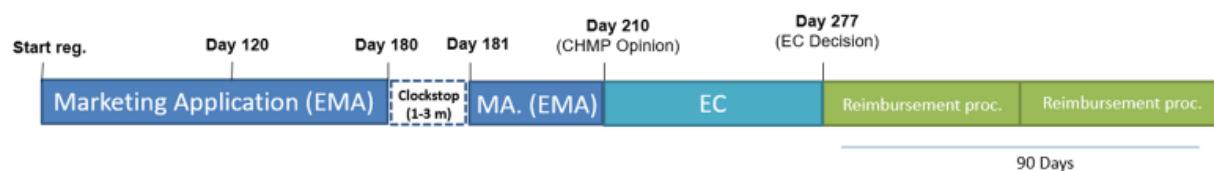
Although only two products have completed the MEB-ZIN parallel procedure, the experience has been positive and has led to the commitment to implement the parallel procedure as one of the routes for reimbursement in the Netherlands. As more products undergo parallel assessment, MEB and ZIN are

hoping to gain more hands-on experience on hospital medicines and advanced therapeutics such as gene therapies.

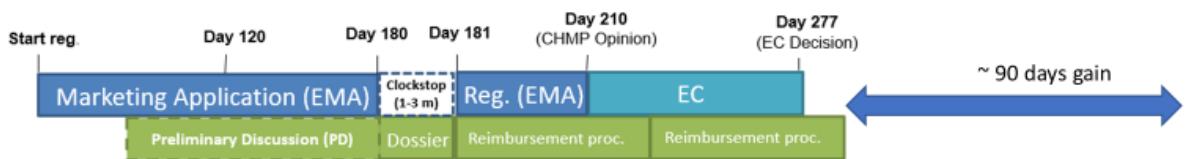


### Impact of the MEB-ZIN parallel procedure on access timelines

#### Sequential procedures



#### Parallel procedures



## UK Innovative Licensing and Access Pathway (ILAP) – what are the aspirations and measures of success?

**Dr Daniel O'Connor, Medical Assessor, MHRA, UK**

**Dr Nick Crabb, Programme Director, Scientific Affairs, NICE, UK**

The Innovative Licensing and Access Pathway (ILAP) was launched on 1<sup>st</sup> January 2021 with the aim to deliver safe, early and financially sustainable patient access to innovative medicines. The key components of ILAP are a new designation called the **Innovation Passport**; the **Target Development Profile (TDP)** roadmap; a **toolkit**; and an **integrated pathway** pulling together expertise from across the MHRA, NICE and Scottish Medicines Consortium (SMC) and partners in the wider healthcare system including the NHS in England and Scotland.

### **Innovation Passport**

The Innovation Passport enables access to ILAP and future activities in the TDP. It has built-in flexibility, with multiple entry points along the pathway and can be applied for with non-clinical data or clinical trial evidence, or by a commercial or non-commercial applicant. The principles of this new designation are:

- Broad and inclusive definition of innovation in order to capture a wide range of products, including drug repurposing
- Non-clinical entry point provides ambition for long-term interactions
- Thinking about the patient from the start
- Encourages structured engagement between the MHRA, HTA body and drug developer
- Joint decision making between MHRA, NICE and SMC.

Three criteria must be met for a positive opinion on the Innovation Passport. The first is to demonstrate that the condition is life-threatening or seriously debilitating, or that there is a significant patient or public health need. The second is to show that the medicine is either innovative; being developed in a clinically significant new indication; being developed for a rare disease and/or other special population; or being developed in line with objectives for public health priorities. The third is to demonstrate the potential benefit to patients; applicants are strongly encouraged to include the views from patients or patient organisations in their evidence.

### **Target Development Profile (TDP)**

The TDP defines key regulatory and development features, identifies potential pitfalls and creates a road map for delivering early patient access, using tools from the toolkit (described below). The TDP includes how the company can work together with other UK stakeholders for coordinated and efficient evidence generation and evaluation. The TDP step can only be accessed via the Innovation Passport and allows high-level consideration of a broad range of issues impacting product development, licensing and access allowing end to end planning.

### **ILAP toolkit**

A wide range of tools are available or are being developed under ILAP. These include adaptive inspections; novel clinical trial methodology and design support; Rapid Clinical Trial Dossier pre-

assessment service; enhanced patient engagement; new licensing procedures, such as rolling review and international options including the FDA Orbis Project and Access Consortium.

### Measures of success

Potential measures of success for ILAP are the number of applications over time, approval rate and timing for the conversion of the TDP roadmap to a licence and access. Other aspects that would be valuable to measure are the attractiveness and speed of ILAP compared to pathways in other jurisdictions and whether patient engagement and influence have been enhanced through ILAP.

### Activity to date

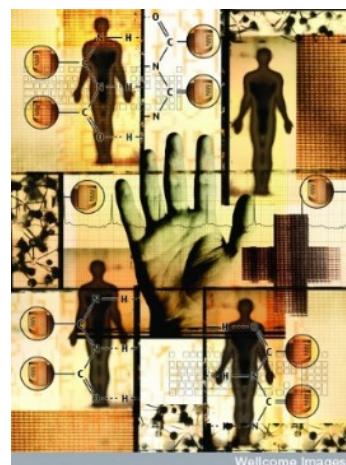
In the second half of 2020, four pilots were undertaken to test the TDP; positive experiences were reported by companies and partners and lessons learned are now being incorporated. Between January–February 2021, 12 Innovation Passport applications were received from companies of various sizes, including one from a spinout from a leading UK university. These applications included oncology products for FDA Orbis as well as products for rare and common diseases. The first Innovation Passport issued was for a treatment for adults with a rare disease called von Hippel Lindau disease.

### Summary

ILAP offers a radical, ambitious route to medicines approval and access. It recognises that innovative products require innovative approaches and promotes system alignment between MHRA, NICE and SMC as well as early engagement with companies. Through ILAP, innovative methods and tools have been developed that accelerate availability of robust data including the development of a specific TDP roadmap tailored to the needs of each innovative product. It is hoped that ILAP can facilitate earlier decision making in the drug development paradigm.

## What is the ILAP?

- Opportunity to think and practice differently after EU exit
- The ambition of the ILAP is to deliver safe, early and financially sustainable patient access to innovative medicines
- Key aspect of the ILAP is the partnership between the MHRA, NICE and Scottish Medicines Consortium (SMC)
- The NHS in England and Scotland are closely engaged, along with the Accelerated Access Collaborative and other UK health system partners



## Regulatory/HTA post-approval collaboration: the need to optimise the use of RWE for decision making

**Dr Craig Simon, Acting Director, Health Products Surveillance and Epidemiology Bureau, Marketed Health Products Directorate, Health Products & Food Branch, Health Canada**

Health Canada's Regulatory Review of Drugs and Devices (R2D2) was launched in 2017 to improve the agency's ability to assess and monitor the safety, efficacy and effectiveness of health products across their life cycle. Real World Evidence (RWE) projects for drugs and medical devices were included to provide insight into opportunities to optimise RWE use to support regulatory decision making. In some circumstances, routinely collected data relevant to health products can help regulatory decision making, hence the impetus to optimise the use of RWE through stakeholder engagement. Input from and collaboration with diverse stakeholders are essential to enhance current RWE use, identify new opportunities for RWE use, and develop guidance for optimal RWE use.

### Post-approval use of RWE for drugs

There are several opportunities for use of RWE across the drugs life cycle, for example, in the post-approval space to inform signal detection, pharmacovigilance, and risk management strategies. In 2019 Health Canada published information for stakeholders on how the agency aims to leverage and support RWE use, including guiding principles for study protocol development and considerations for data collection features to optimise RWD quality and a notice to industry reaffirming Health Canada's acceptance of RWE and articulating its approach to leveraging RWE [1,2].

Health Canada collaborates with a variety of domestic partners to leverage the use of RWE, including Canadian health technology assessment (HTA) agencies, CADTH and INESSS; Drug Safety and Effectiveness Network (DSEN); Canadian Institute for Health Information (CIHI); Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) project; patient group consultations; payers; and professional associations. These collaborations have led to ongoing projects and activities such as the Drug Core Action Team, which was formed between CADTH, INESSS, CIHI, industry and academia in October 2018 to inform RWE use across the drugs life cycle and to support key RWE activities. In addition, Health Canada has recently been working with CADTH and INESS to develop a Joint Strategic Plan to outline optimisation of RWE use across the drug life cycle.

At the international level, Health Canada participates in numerous collaborations in support of the use of RWE including cluster meetings to exchange information with other regulators; International Pharmaceutical Regulators Program (IPRP) Pharmacovigilance Working Group; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Pharmacoepidemiology Discussion Group; and the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 RWE and Observational Studies Working Group. The ICMRA COVID-19 RWE and Observational Studies Working Group consists of technical subgroups focused on pregnancy studies, building international cohorts and vaccine surveillance and vigilance. Each subgroup meets regularly, with representation from interested regulators, to enhance collaboration.

### Post-approval use of RWE for medical devices

Similar to drugs, post-approval use of RWE informs signal detection, vigilance, and risk management strategies for medical devices. Health Canada has published information for stakeholders on how the agency aims to leverage and support RWE use for medical devices [3-5]. Health Canada also has strong collaborations with key medical device stakeholders, which it maintains through regular stakeholder engagement and its partnership with the Canadian Medical Devices Sentinel Network (CMDsNet).

Collaborations have been leveraged for a number of ongoing activities including the Devices Core Action Team, which is under development; development of an RWE framework; development of guidance documents on RWE generation, analysis and appraisal; and the definition of implementation strategies to support RWE use across the medical device life cycle, based on the RWE framework and guidance documents.

### Considerations for the future of RWE

Health Canada remains committed to domestic and international collaborations to align use of RWD and RWE across the product life cycle and jurisdictions. While RWE can be leveraged to support decision-making, it is not a magic bullet. Timely availability of high-quality data remains key to the optimal use of RWE and will continue to be integral for the appropriate use of RWE in the future.

## Domestic RWE Collaborations

- Health Canada collaborates with a variety of domestic partners to leverage the use of RWE, e.g.:
  - Health Technology Assessment partners (e.g., CADTH, INESSS)
  - Drug Safety and Effectiveness Network (DSEN)
  - Canadian Institute for Health Information (CIHI)
  - CanREValue
  - Patient group consultations
  - Payers
  - Professional associations
- Ongoing Activities:
  - Drug Core Action Team: formed in October 2018
    - aims to inform RWE use across the drugs life cycle and to support key activities
    - collaboration with CADTH, INESSS, CIHI, industry and academia
  - Joint Strategic Plan (to be posted in 2021)
    - to outline optimization of RWE use across the drug life cycle
    - collaboration with CADTH and INESSS



DRUGS

HEALTH CANADA > 7

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## **Early involvement of payers today: who should they be interacting with and when – what is the business case study?**

### **Payer perspective**

**Evert Jan van Lente**, Director of EU-Affairs, Allgemeine Ortskrankenkassen (AOK), Germany, and Chair of Medical Evaluation Committee (MEDEV), Belgium

New technologies such as Advanced Therapeutic Medicinal Products (ATMPs) pose new challenges for payers, as there is uncertainty on the effectiveness and safety at the time of marketing authorisation and there is no algorithm for translating added patient benefit into an added price. Demanded prices are often too high and value propositions are unrealistic given the uncertainty for these technologies. As R&D costs are saved through expedited approvals, there is an obligation for manufacturers to be co-financers of post-authorisation studies, or prices must be reduced accordingly.

To tackle these challenges, there are potential areas for multi-stakeholder collaboration in the R&D space including discussion on unmet medical needs, which justifies accelerated approval procedures; horizon scanning to prepare for registries and special payment models; and discussion on pre- and post-marketing evidence generation, taking into account the evidence needs of payers and HTA agencies [1]. Once a product has been approved there needs to be multi-stakeholder cooperation on registries and post-marketing evidence generation; cooperation on new pricing models, such as Managed Entry Agreements with outcomes-based pricing; regional cooperation of payers to achieve a better negotiation position and more transparency; and transparency on R&D costs, including how much public funding was spent on R&D [1].

In summary, regulators, HTA agencies and payers share the same goal in facilitating patient access, and face common issues related to efficacy/effectiveness, standards for post-approval evidence generation and whether lower levels of evidence at approval are justified. While payers are willing to pay for effective and safe products that improve the lives of patients, they must create legal options for reassessments and re-negotiations on price, when there is an evidence gap. However, the resources invested by payers for early dialogues, evidence generation and the implementation of new payment models must pay off through ‘realistic’ prices. Best practices and case studies need to be identified to convince decision makers in payer organisations to invest in these additional resources and recognise the value in collaborating with other stakeholders, not just regulators, HTA agencies and industry, but also patients, healthcare professionals and national governments.

## Cooperation needed

#	Payer Action	Goal	Collaboration with
1.	Identifying unmet medical need (lack of adequate treatment options, disease severity, rarity)	Prioritisation of new technologies that might be eligible for expedited authorisations and special support from payers	EMA, manufacturers, health professionals and patient organisations
2.	Horizon scanning of technologies with potential major therapeutic advantages, assessing potential budget impact and expected costs	Anticipate emerging challenges and needs for pre - and post - launch actions to ensure patient access (especially for conditional marketing authorisations)	EMA, EUnetHTA International Horizon Scanning Initiative (IHSI)
3.	(Participation in) early dialogues on evidence generation	Ensure the highest level of evidence possible pre - and post - launch, identify current comparators, identify targeted patient (sub -)populations	EMA, EUnetHTA, MoCa (Mechanism of coordinated Access as a payer - manufacturer dialogue on access to medicines for orphan diseases)
4.	Assessment: Development of new methodologies to assess the added benefit of new technologies and how to use data from clinical practice	Methodologies for fundamentally new technologies and for evidence generation based on data from clinical daily practice	EUnetHTA, EMA
5.	Cost containment: financial Managed Entry Agreements (financial MEAs)	Budgets, price -volume contracts expenditure limits per patient.	Manufacturer
6.	Performance -based MEAs with data generation	Access with evidence generation and adaptive pricing; identifying patient (sub -)groups, outcome parameter, etc.	Manufacturer, HTA, EMA, Registry holders
7.	Information strategies with patients and doctors	Awareness of the uncertainty of products with conditional authorisation and/or conditional reimbursement and the possibility of withdrawing reimbursement from public systems	EMA, HTA, patient organisations, provider organisations
8.	Develop new pricing models and establish their legislative basis	Affordability and sustainability	National authorities, Governments and parliaments, European Institutions
9.	Cooperation with other EU -member states and creating new options in legislation for regional cooperations	Enhanced transparency on prices, improvement of negotiation position	National Governments and Parliaments of regional cooperations (Beneluxa , Valeletta - Visgrad- (V4) , FINOSE)



MEDEV "Reflection paper on national strategies for new medicines"

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## Early involvement of payers today: who should they be interacting with and when – what is the business case study?

### Company perspective

**Dr Vanessa Elisabeth Schaub, Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, Roche, Switzerland**

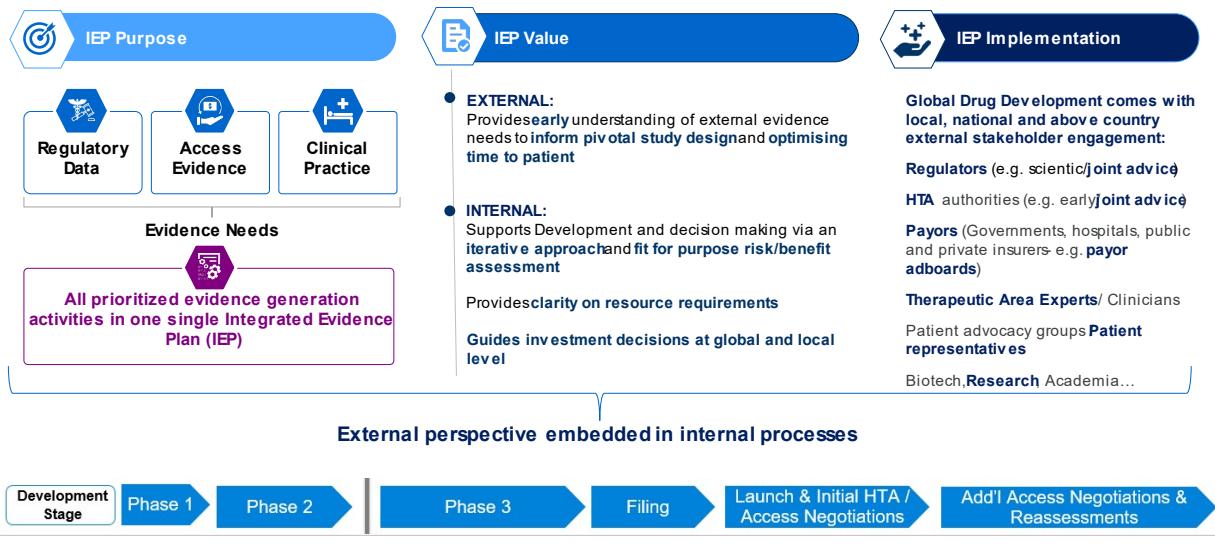
Companies engage with external stakeholders throughout drug development and the product life cycle and embed external perspectives in internal processes. Evidence generation activities for regulatory data, access evidence and clinical practice can be prioritised and brought together into a single integrated evidence plan. This provides early understanding of external evidence needs to inform pivotal study design and optimise time to patient access. In addition, the integrated evidence plan supports internal decision making via an iterative approach and fit-for-purpose benefit-risk assessment, provides clarity on resource requirements and guides investment decisions at the global and local level.

Global drug development comes with external stakeholder engagement at different jurisdictional levels. While engagement with regulators and/or health technology assessment (HTA) agencies tends to be at the national and above-country level, for example through the early EMA/EUnetHTA consultation programme and EU HTA regulation proposal, engagement with payers is more localised as the local economic framework needs to be considered.

Inclusive deliberation processes must be balanced with independent decision making. For example, HTA agencies need to be independent from reimbursement authorities to preserve objectivity, but also take an inclusive approach that balances the needs of all health stakeholders, sets priorities and informs trade-offs.

In summary, early stakeholder involvement in drug development is more important than ever given the transformative nature of biomedical innovation. This needs to be complemented by continuous stakeholder engagement for post-licensing evidence generation (PLEG), particularly for rare disease innovations that have more limited information at marketing authorisation and come with a lifecycle approach to medicine development. Various steps of patient access (early dialogue, regulation, HTA assessments, reimbursement decision, PLEG) may require involvement of different stakeholders at the local, national, or above-country level. In relation to the post-licensing phase and the complementary real-world evidence required, there is a need for alignment and clarification in terms of different jurisdictional levels, different data collection requirements and the different use cases for the collected data.

## Engagement with External Stakeholders throughout Drug Development and Product Life Cycle



3

## Development and access landscape of the future

**Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?**

### Company perspective

**Shane Kavanagh, Vice President Health Economics & Real World Evidence, Janssen, Belgium**

Advice procedures facilitate valuable interactions that improve companies' understanding of HTA agencies' perspectives on evidence generation. Between 2010-2015, Janssen completed 28 advice procedures for pharmaceuticals, which rose to 49 between 2015-2020. This included HTA advice from multiple advice mechanisms including multi-stakeholder advice procedures. HTA advice was orientated to the overall evidence package, with focus on clinical development programmes, and approximately two thirds of advice were in procedures with a relative effectiveness focus. Janssen's experience with HTA advice has led to learnings across different disease areas with evolution of questions, company positions and earlier timings of advice, and has also highlighted the importance of strong cross-organisational collaboration.

Available scientific advice procedures and pathways vary in their approach to prioritisation but focus of efforts on unmet need and novel treatment approaches are common. Advice procedures involving multiple agencies tend to have more criteria than those involving a single agency. For example, the new UK Innovative Licensing and Access Pathway (ILAP), which involves MHRA, NICE, Scottish Medicines Consortium and other partners, specifies criteria relating to new mechanism of action; unmet need; life-threatening or severely debilitating disease; development for a clinically significant new indication or special population; and alignment with policy initiatives.

Modelling is one aspect of the localisation of decision making, with both local healthcare context and local determination of value being key. Submission requirements across agencies are somewhat similar with some technical differences, for example, in utilities and sensitivity analyses. Local differences also relate to the presentation of results as well as willingness to pay thresholds. HTA model questions often focus on bridging global programmes to national/local decisions through additional local data on clinical practice and pathways, resource use patterns, costs, and patient outcomes and utilities. Advice requests are likely to be on individual local interactions with exceptions for new disease areas or novel 'curative' or 'disease modifying' treatments, where advice from multiple stakeholders could be beneficial to understanding the best approach for modelling disease progression and defining model structure.

In summary, the development and access landscape will continue to feature innovative treatments for high unmet needs that warrant accelerated or conditional approval. Methodological advances and further common understanding of technical requirements for trial designs, endpoints, real world evidence and modelling are likely, however, new questions will arise from further innovation in trial design, new (digital) data sources, advances in population biomarkers and surrogate endpoints, and dynamically changing disease areas. The need for interactions and collaborations on population definitions, evidence packages etc will continue and role clarity will remain relevant. While future interactions must inform relevant global development programmes, the local healthcare context and local determination of value for HTA must continue to be considered.

## Perspectives on the world in 2030...?

- Innovative treatments for areas of high unmet needs that warrant accelerated or conditional approvals<sup>1</sup> will continue
- Methodological advances and further common understanding of technical requirements for trial designs, endpoints, RWE <sup>2</sup>, and modeling are likely for the challenges we face today
- But new questions will arise... from further innovation in trial design, new data sources (digital...) <sup>3</sup>, advances in population biomarkers & surrogate endpoints, and dynamically changing disease areas as more treatments become available
- The need for interactions and collaborations on population definitions, evidence packages, etc., will continue
- For interactions role clarity will remain relevant... "each participating body should adhere to the roles and responsibilities under their respective remit." <sup>4</sup>
- Inform relevant global development programs, but considering the local healthcare context and local determination of value <sup>5</sup> for HTA

1. EMA <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation/criteria-and-conditions-section>; accessed 08 Mar 2021 FDA <https://www.fda.gov/patients/accelerated-approval-therapy-accelerated-approval-priority-review/accelerated-approval>; accessed 09 Mar 2021 ; FDA (2014) Expedited Programs for serious conditions <https://www.fda.gov/media/86377/download> accessed 09 March 2021

2. <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>  
3. <https://www.janssen.com/clinical-trials/innovation>  
4. <https://eunethta.eu/wp-content/uploads/2018/01/Guidance-on-Parallel-Consultation.pdf>  
5. <https://www.janssen.com/about/accesprinciples>



6

## Alignment in Canada's Prescription Drug Chain

**Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?**

### Regulator perspective

**Bruce Randall, Senior Executive Director, Therapeutic Products Directorate, Health Canada**

In 2018, Canadian regulatory and HTA agencies made collaborative efforts to improve patient access whilst maintaining each agency's independence. Previously, drug funding decisions were made up to 200 days after marketing authorisation by Health Canada, review processes were largely sequential, and interactions were informal and ad hoc. The implementation of concurrent reviews and formalised information sharing (with industry consent) reduced the average time between Notice of Compliance issuance and HTA recommendations by 68% (to approximately 60-70 days). As of January 2021, 59 aligned reviews had been completed and 15 were ongoing. While these regulatory-HTA alignment efforts have been positive in improving access, it is important that regulatory and HTA agencies keep monitoring changes in their health systems and prepare for future challenges together.

Increasingly complex and personalised products, such as artificial intelligence and cell/gene therapies, are challenging the sustainability of health systems around the world. While new innovative products offer hope and may improve health outcomes, they often come with high price tags. Demands for such treatment options create regulatory and health system challenges that need to be addressed with new agile approaches.

Health Canada has developed a Regulatory Innovation Agenda to respond to these issues and provide more regulatory flexibility to support innovative research and health product development (see below). This is made up of five key pillars: modernising clinical trial regulations; enabling advanced therapeutic products; agile licensing for drugs; agile licensing for medical devices; and information to Canadians. To enable advanced therapeutic products, Health Canada will look to take a health system need approach that provides flexibility for innovative products that do not fit within the current system. Early engagement with HTA and payers will be key to ensuring uptake of such products. Health Canada will also look to leverage by using regulatory tools to gather more precise information to support downstream decisions i.e. by HTA agencies and payers.

In summary, regulatory-HTA alignment has demonstrated its value in improving patient access. However, there is a need for continued collaboration and alignment to create efficiencies and maximise patient outcomes, while maintaining a balance and ensuring recognition of the independent and complementary roles of various organisations.

## Looking Ahead: The Regulatory Innovation Agenda



### Modernizing clinical trial regulations



### Enabling advanced therapeutic products



### Agile licensing for drugs



### Agile Licensing for medical devices



### Information to Canadians: a mobile strategy

to have better, safer, and more trials in Canada

to ensure a flexible approach for innovative products that do not fit within the current system

to make sure regulations align with the nature and lifecycle of health products

to make sure there is appropriate oversight while enabling innovation

to help empower Canadians to maintain and improve their health

## **Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?**

### **HTA perspective**

**Andrew Mitchell, Strategic Adviser, Evaluation, Office of Health Technology Assessment, Australian Government Department of Health**

The **HTA-payer** relationship is mostly focused on the decision of reimbursement and pricing, though there may be increasing opportunities for greater collaboration between these stakeholders across a lifecycle approach to HTA. HTA advice needs to understand the policy controls available to the payer and seek to optimise the value proposition in ways that the payer can implement. For example, a pay-for-performance arrangement is not appropriate if the payer has a limited pricing lever. This is particularly important for new disruptive technologies, which represent a greater problem for payer-managed funding programmes than for HTA. Having a clear understanding of these issues ensures that HTA can better help manage the introduction of these technologies. In Australia, the HTA and payer relationship is relatively strong for medicines, perhaps because of their profile or their budget implications, but seems to be more variable across other types of health technology.

The **HTA-HTA** relationship is strongest within early scientific advice. The other main way HTA agencies learn how each other works is through monitoring each other's HTA advice outcomes, however, this is always after the advice has progressed significantly. Following years of consultation and several pilots, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia now has the ability to disclose the clinical evidence relied on in its decision making. This extends to all data analyses within, across and beyond clinical studies (without disclosing prices) and includes assumptions in place of study results. This increase in transparency opens a potential new arena of collaboration, where HTA agencies can share submitted clinical evidence and thus better understand each other's perspectives in interpreting this largely common evidence base before finalising their advice. In future this could potentially lead to the formation of an HTA-like Project Orbis.

**HTA-regulatory** interactions and collaborations are essential, though it is important that the different functions of each stakeholder are acknowledged. While it is against international treaty obligations for regulator decisions to be influenced by costs, HTA agencies are invariably influenced by costs. Yet regulators influence evidence generation and eligible populations for HTA. While the Australian HTA and regulator entities are fortunate enough to reside in the same Department, they could do more to collaborate; the reality is that there is some competition from the benefits that are being sought simultaneously through greater regulator to regulator collaboration.

**HTA-company** interactions are the most frequent of all HTA agency interactions. As with the relationship with regulators, it is important to recognise that HTA agencies and companies do not necessarily share the same objectives. Clarity of the value proposition is at least a semi-objective way to align these different objectives by seeking best value for money. Trust, whether real or perceived, is key to the HTA-company relationship. In Australia, HTA agency representatives and local company affiliates get to know each other very well and these interactions are typically cordial and professional. However, there is often a sense that these interactions are intermediary, with the final decision-makers i.e. the payer and company's global head office, behind the scenes.

In summary, HTA agencies should have collaborative interactions with payers, other HTA agencies, regulators and companies. However, the interactions with companies should be kept separate, to

acknowledge differences in objectives, and interactions with payers and other HTA agencies should be aligned and harmonised, respectively.



## Future of interactions

HTA – payers: collaborative and aligned

HTA – HTA: collaborative and harmonised

HTA – regulator: collaborative

HTA – company: collaborative but separate

6

## **Separate, aligned, converged, harmonised, collaborative, reliant – what is the stakeholder's expectation of the development and access landscape of the future for company, regulator, HTA and payer interactions?**

### **Payer perspective**

**Dr Michael Ermisch, Specialist, GKV-Spitzenverband, National Association of Statutory Health Insurance Funds, Germany**

Cooperation between developers, regulators, HTA agencies and payers is beneficial, as although they have differences in tasks, they depend on the same information. While regulation may contribute to high costs, there are ways in which regulators can contribute to keeping drug spending sustainable, such as by rapidly approving generics and biosimilars; ensuring that 'me-too' follow-on products continue to come on the market; encourage clinical trials that measure value; and facilitate collection of other kinds of data that are important to payers [1].

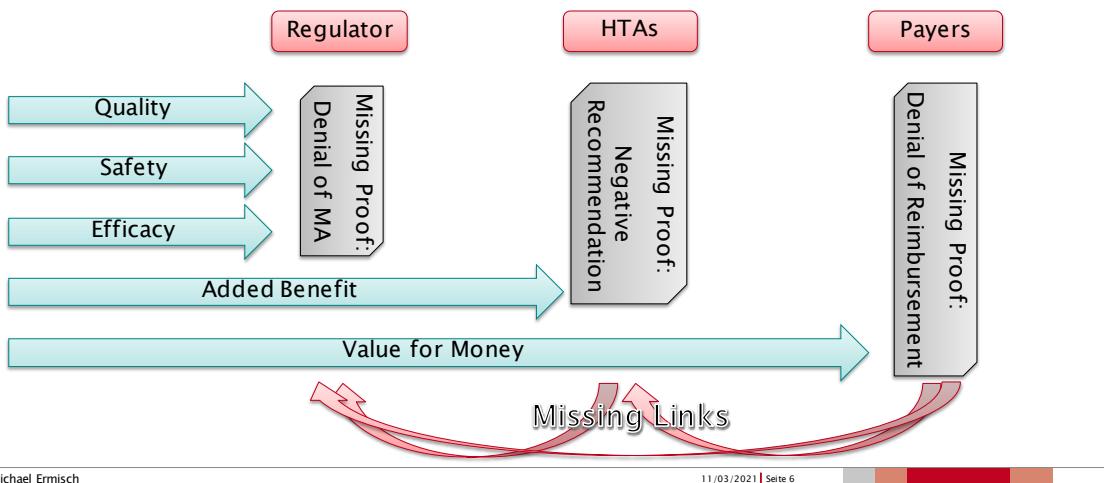
Joint advice may further individual stakeholder goals and increase the chance of successful development programmes. However, it has been shown that companies tend to prioritise regulatory advice over HTA advice following EU parallel regulatory-HTA scientific advice procedures [2].

While there are increasing opportunities for multi-stakeholder cooperation, it is important to recognise that cooperation faces limits. Each stakeholder decision is independent and there is a disconnect between upstream and downstream decisions. For example, the regulator determines which products receive marketing authorisation and are therefore assessed by the HTA agencies, but if evidence is missing on added benefit and a negative HTA decision is given, there is no feedback loop back to the regulator (see below). This limits the possibility for post-launch evidence commitments that are relevant to HTAs and payers at the time of regulatory approval.

Regulators, HTA agencies and payers share common problems with uncertainty but use different tools to mitigate it. For example, regulators can issue conditional marketing authorisations that require post-authorisation safety and efficacy studies. While it is not clear how far the fulfilment of the specific obligations helped to upgrade clinical knowledge and evidence [3], they can be relevant in relative efficacy assessments by HTA agencies if available [4]. Managed entry agreements are being used by payers to manage uncertainty, but increasingly evidence suggests that this is not an efficient solution as development costs are being shifted from pre- to post-launch and therefore to society [5]. HTA agencies need to be informative and point out any issues to payers, such as the need for reassessments.

While there are cooperation initiatives happening that include payers, there is a need for more alignment and recognition of different stakeholder responsibilities. This is now even more important given that the COVID-19 pandemic has intensified expectations around access to medicines. Thus, time has come to further develop cooperation with selected products in concrete projects.

## Why cooperation faces limits Different tasks and separate responsibility



Dr Michael Ermisch

11/03/2021 | Seite 6

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## Section 3: Breakout discussions

### Breakout A

**Effective models of engagement: what are the characteristics that facilitate better evidence generation in the development space? What is working, could improve or hasn't been tried yet?**

<b>Chair</b>	<b>Prof Adrian Towse, Emeritus Director and Senior Research Fellow, Office of Health Economics, UK</b>
<b>Rapporteur</b>	<b>Dr Charlie Mortazavi, Senior Manager, Global Regulatory Science &amp; Policy, Sanofi R&amp;D, France</b>

#### Background

CIRS's research agendas have focused on how to align or understand the divergences and/or synergies between regulatory agencies and HTA bodies, with the results of making recommendations on how to further improve evidentiary alignment. Multiple stakeholders play a significant role in the process of getting a medicine to patients; the interactions between the different stakeholders (regulatory, HTA, payer, patient and company) have been raised consistently as key components of building improved predictability into development and enabling more positive regulatory and access outcomes.

Over the last five years, regulatory and HTA interactions, as well multi-HTA and multi-regulatory interactions and collaborations, have evolved in thinking and mutual activities both at a product level as well as at a policy and cross jurisdictional level. This is not just around providing early scientific advice but also activities related to horizon scanning, ways to collaborate on registries and other forms of post-approval evidence generation to ensure work done by one agency can be reused by another.

The three key areas that interactions and collaboration are thought to enable are: 1) common direction for policy areas and health care priorities; 2) alignment of requirements and technical standards across stakeholders; 3) knowledge sharing and understanding of different stakeholders' uncertainties based on remits. The ultimate aim would be to ensure a sustainable cooperation model for all therapy areas for the future that enable improved outcomes for patients and access.

This breakout group was therefore asked to build on the workshop discussions and discuss effective models of engagement:

- **Assess the current experiences with the different stakeholders on interactions and collaborations** – what is working, could improve or hasn't been tried yet?
- **Identify the characteristics of an effective model** - what are the key components of interactions and collaborations that enable an effective outcome to support drug development?
- **Recommend an effective model for future interaction and collaboration** - what should be considered to support the evolution of current activities and what are the building blocks for the development for any future interactions?

## Discussion results

To facilitate the discussion, it was suggested that the interactions/collaboration process was assessed using the ***Input-Throughput-Output model***:

<b><i>Input of the process</i></b>	<b><i>Throughput of the process</i></b>	<b><i>Output of the process</i></b>
For example, preparation, administration, timing, resource allocation	For example, multi-stakeholder communication through the process, quality of interactions and collaboration, management of the process	For example, documentation of the interactions / collaborations, communication of the outcome, dissemination of the learnings

**Q1.** *What is an effective model of interactions from input, throughput and output perspectives? Please give examples of what has worked well in enabling an effective process.*

The EUnetHTA regulatory/HTA parallel consultation was suggested by the group as a good example of an interaction model, as it has promoted cross-function collaboration within companies and among agencies.

<b><i>Input of the process</i></b>	<b><i>Throughput of the process</i></b>	<b><i>Output of the process</i></b>
<ul style="list-style-type: none"> <li>Increasing internal interactions, but not reflected enough in external interactions/ collaborations</li> </ul>	<ul style="list-style-type: none"> <li>Consensus on sharing data between the regulator and HTA agency (sometimes there is resistance from the sponsor).</li> <li>Differences in data sharing in structured way HTA/Reg (Reg dossier vs HTA file/data).</li> </ul>	<ul style="list-style-type: none"> <li>Toolkit global vs local/national purpose (issues with time horizon and extrapolation)</li> <li>Usage differs according to data filing purpose</li> <li>Usage of a methodology for divergent assessment (Reg/HTA) – translation clinical data to cost</li> </ul>

**Q2.** *Discuss areas for improvement to further advance an effective process of stakeholder interactions and collaborations.*

- Consensus on pre-launch data generation – need internal alignment between regulatory and market access functions within companies.
- Data on long term follow-up (e.g. for ATMPs)
- Consensus on post-licensing data sharing between regulators and HTA agencies

- False assumption that not following advice will impact the review later - there is actually a firewall between advisor and reviewer.
- Issues with variations in HTA practices i.e. different evidence requirements and methodologies used by HTA bodies.
- Post launch evidence generation: multiplicity of data sources creates challenges

*Q3. Identify the characteristics of an effective model – what are the key components of interactions and collaborations that enable an effective outcome to support evidence generation?\**

<b>Aim of the interaction/collaboration</b>	<b>Key components of an effective model to support a value-added outcome</b>		
	<b>From whom?</b> The key stakeholders to be involved	<b>When?</b> What is the ideal timing for the interaction?	<b>How?</b> What areas need to be considered to ensure the interaction is fit for purpose?
<b>Support evidence generation during development</b>	Parallel consultation (all HTA bodies ideally, key HTA at least to participate in the consultation)	Engage early in the development process (clinical trial design, data for HTA, post-licensing evidence generation etc)	Manage commercial and scientific risk
<b>Support evidence generation post-approval</b>		Define the notion of “early” regulatory perspective vs HTA	
<b>Align/ harmonise evidence standards across stakeholders</b>			Extend collaboration above scientific & technical data sharing

\*Due to limited time, characteristics were not suggested for all the above areas so further development may be needed.

*Q4. Recommend future research projects for CIRS and other groups to undertake in this area – what should be considered to support or improve current activities?*

- Using the feedback from this workshop, CIRS could prepare a report consolidating the various lessons of all the early scientific options.
- Outputs from the workshop survey and meeting itself should be widely disseminated.
- When looking at alignment in evidence requirements, a good starting point is exploring advanced therapies. A potential research project could focus on relative efficacy assessment/patient-reported outcomes collected from the study, and a comparison with the approved label.

## Breakout discussion B

**Convergence through collaboration – are stakeholder interactions/collaborations improving the probability of regulatory and reimbursement success and patient access? Does this differ by product characteristic?**

Chair	<b>Dr Brian O'Rourke, Chair, CIRS HTA Steering Committee</b>
Rapporteur	<b>Dr Gracy Crane, International Policy Lead, Roche, UK</b>

### Background

Over the last five years, regulatory and HTA interactions, as well multi-HTA and multi-regulatory interactions and collaborations, have evolved in thinking and mutual activities both at a product level as well as at the policy and cross jurisdictional level. This is not just around collaborating to provide early scientific advice, but also on other activities such as registries and other forms of post-approval evidence generation to ensure work done by one agency can be reused or understood by another. At the global level (ICH, ICMRA, INHATA) there has been increased collaboration on both technical and policy issues. Within jurisdictions there is increasing cross agency collaboration and interaction at the product level e.g. NICE and MHRA, ZIN and MEB, CADTH and Health Canada.

In the regulatory space, where regulators have a long history of collaborations across jurisdictions, this has led to convergence and ultimately harmonisation in some areas. In Europe EUnetHTA has worked to align HTA with the questions of how multi-stakeholder interactions and collaborations are driving convergence and what are the product characteristics that stakeholders seek to maximise the opportunities for regulatory and access success? As regulators and HTA and payers have different remits, there is common ground where convergence or alignment can occur as well as rational divergences.

The key considerations for discussion from this breakout are at the product level:

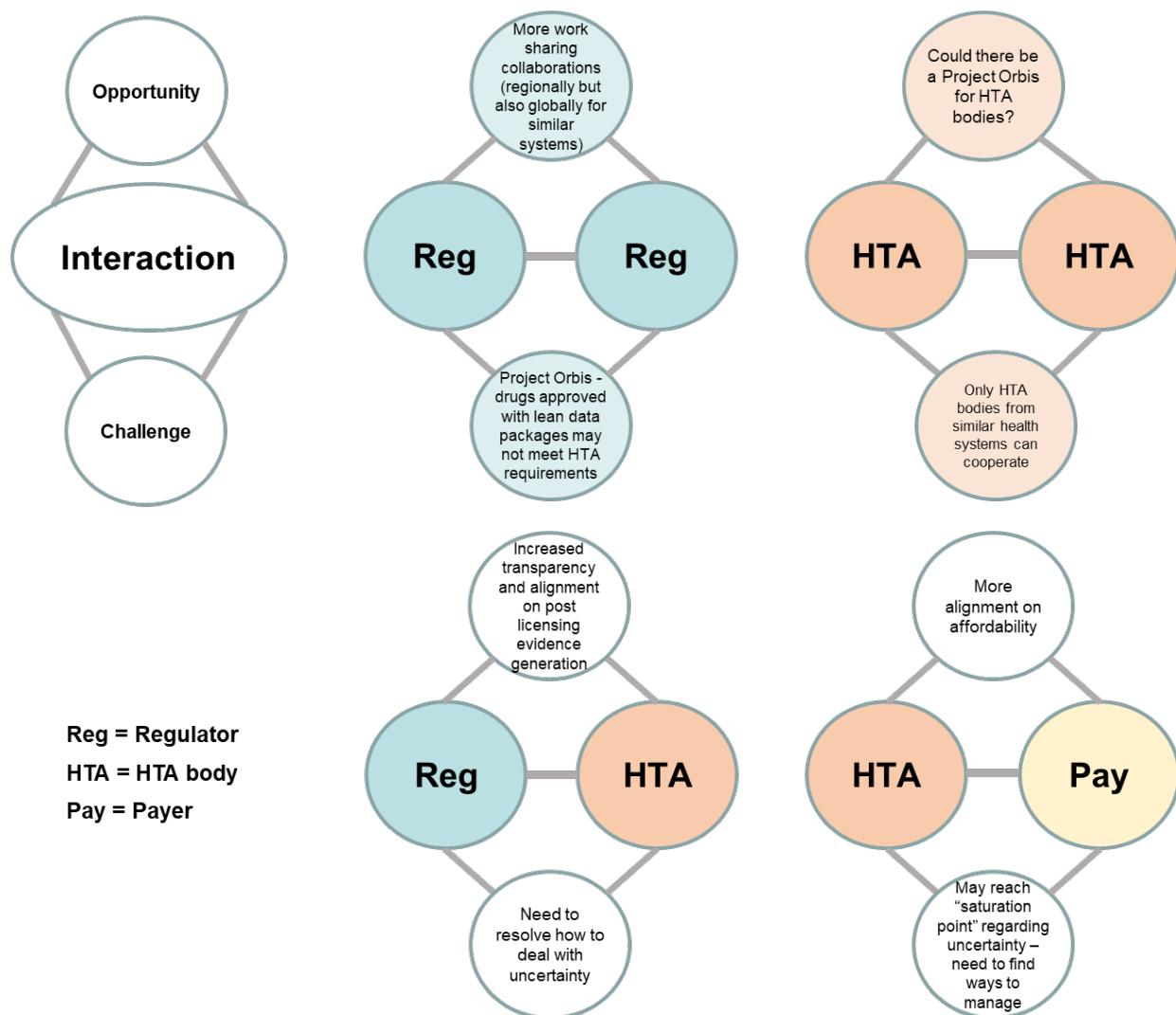
- **Are there types or product characteristics that make convergence more probable amongst stakeholders if so, what are they?**
- **What are the opportunities to enable more convergence or barriers to improve the probability of regulatory and reimbursement success?**
- **What solutions or policy changes are required and with which interactions that could lead to increased convergence?**

## Discussion results

*Q1. Are there product types or characteristics that make convergence on acceptability of evidence standards more probable amongst stakeholders? If so, what are they and does this change depending on the purpose of the interaction?*

Purpose of interaction	Characteristics that help to achieve convergence around evidence generation	Unresolved issues	Potential solutions	Considerations
Support evidence generation during development	<ul style="list-style-type: none"> <li>Appropriateness of the clinical evidence and methodology.</li> <li>Alignment on definition of unmet medical need.</li> <li>Education on innovative study designs – currently some designs e.g. basket studies are viewed less favourably by HTA bodies, so more education might help with convergence.</li> <li>HTA input at an earlier timepoint e.g. phase I/II.</li> </ul>	<ul style="list-style-type: none"> <li>How to deal with uncertainty in the system – “saturation point” might be reached as pressure on payers continues to increase.</li> <li>Measures of success for industry still need to be defined - tendency to be regulatory focused (or just FDA focused).</li> </ul>	<ul style="list-style-type: none"> <li>Early dialogue - maybe a cluster approach would work in the first instance (Reg-Reg, followed by Reg-HTA).</li> <li>Educate/inform FDA on the needs and requirements of HTA bodies.</li> </ul>	<ul style="list-style-type: none"> <li>There is a perception that the more advice is sought (particularly involving HTA), the worse the outcomes.</li> <li>Internal structure within companies not always conducive to parallel engagement.</li> </ul>
Support evidence generation post-approval	<ul style="list-style-type: none"> <li>Building in comparative effectiveness evidence needs – key from a HTA perspective, and needs addressing in the post approval phase.</li> <li>Rare diseases and ATMPs – an opportunity for early dialogue between regulators, HTA bodies, payers, manufacturers and data custodians to ensure post-licensing evidence generation needs are addressed.</li> </ul>	<ul style="list-style-type: none"> <li>How much risk should manufacturers take on?</li> <li>What is the appetite for transparency in risk sharing agreements?</li> </ul>	<ul style="list-style-type: none"> <li>To enhance collaboration, stakeholders should be less ambitious if there is greater certainty in the evidence base. As the level of uncertainty becomes more ‘comfortable’, then it is possible to move to a more disruptive/ambitious setting.</li> </ul>	<ul style="list-style-type: none"> <li>Trust/transparency needed for all stakeholders - there is an opportunity to increase transparency using platforms such as Accumulus and through data sharing.</li> <li>Life cycle approach is needed in this space.</li> </ul>

*Q2. Improving probability of regulatory and reimbursement success through more convergence – what opportunities are there for more convergence or alignment across and within stakeholders and what would be the impact if the opportunity is realised?*



*Q3. What solutions or policy changes are required and with which interactions that could lead to increased convergence?*

1. CIRS should further explore the view that more HTA interaction leads to worse outcomes.
2. Develop a template for collaboration success/failure that can be shared – CIRS might play a role in this.

## Breakout C

**Focus on 2030 and an ideal ecosystem for interactions and collaboration – what should be considered as the key building blocks to ensure each interaction provides value to stakeholders and improved outcomes for patient access?**

<b>Chair</b>	<b>Prof Hubert Leufkens, Professor of Pharmaceutical Policy &amp; Regulatory Science, Utrecht University, The Netherlands</b>
<b>Rapporteur</b>	<b>Dr Melinda Goodall, Director, HTA Policy Research, MSD, UK</b>

### Background

Although it is clearly understood that regulators, HTA and payers have different remits, there is common ground as well as rational divergences based on the different remits. Over the last five years, interactions and collaborations have evolved in thinking and mutual activities, both at a product level as well as at a policy and cross jurisdictional level. This is not just around collaborating to provide early scientific advice, but also on other activities such as post-approval evidence generation to ensure work done by one agency can be reused or understood by another. At the global level (ICH, ICMRA, INHATA) there has been increased collaboration on both technical and policy issues and within jurisdictions there is increasing cross agency collaboration and interaction at the product level e.g. NICE and MHRA.

As both collaborations and interactions evolve it is important that these are adding value. In the regulatory space, the initiative 30 years ago to harmonise technical requirements under ICH has led today to convergence, underpinning the quality of evidence generation leading to regulatory work sharing and reliance models. In terms of regulatory-HTA and HTA-HTA interactions and the increasing role HTA plays in the development and access of new medicines, is there a vision or direction that stakeholders would like interactions and collaborations to evolve to, or do they see them being as they are today? Will the types of therapies, the needs of the health care space and the different stakeholders change the dynamics of the interactions?

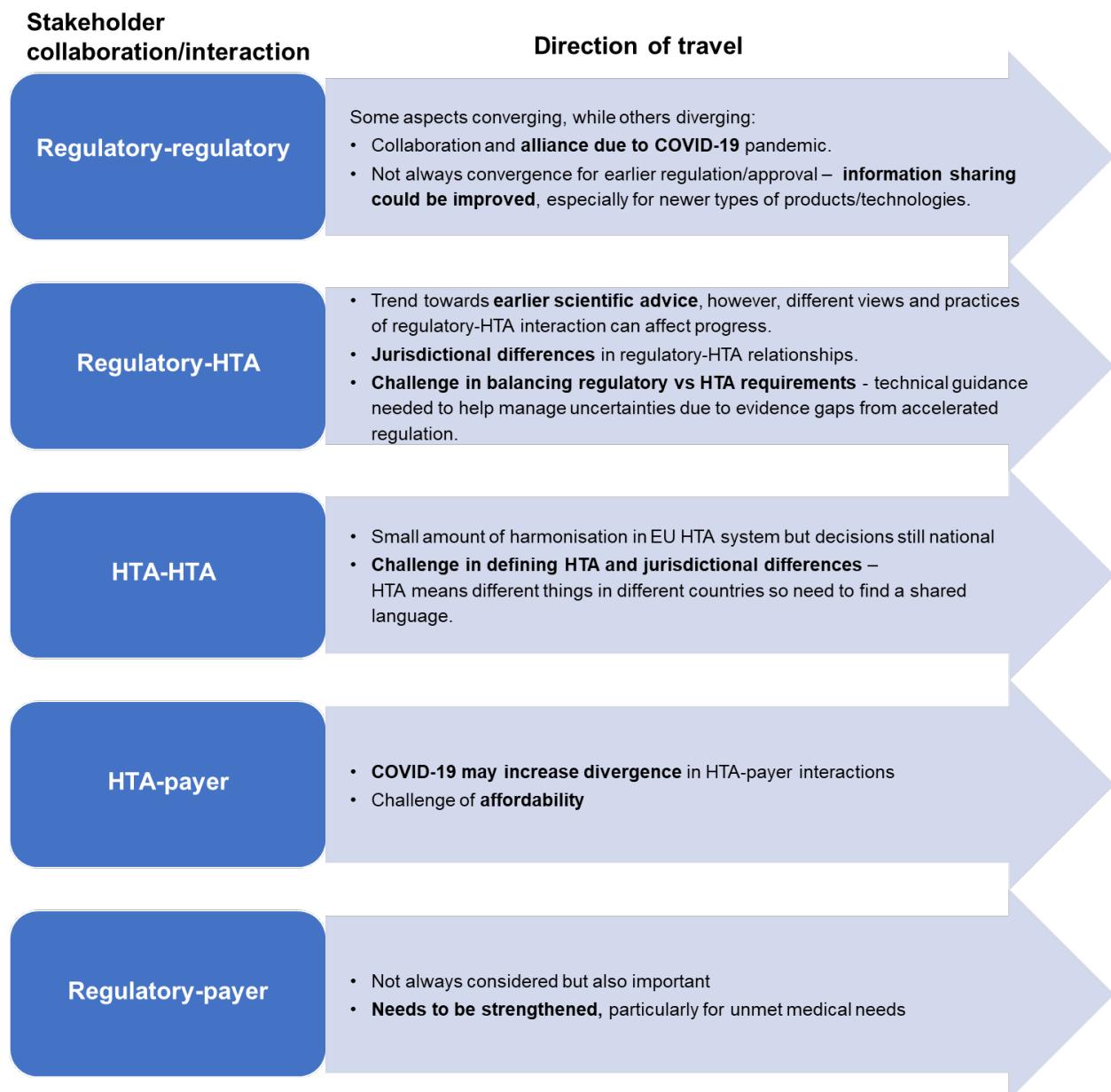
The key consideration for this breakout group was to be future looking by focusing on 2030 and what an ideal ecosystem for interactions and collaboration would be. To frame the discussion, it was suggested that the group should explore the evolution of regulatory-HTA and HTA-HTA interactions, and if of interest, the evolving role of the payer.

Key questions for the discussion are to:

- **Identify the potential directions of travel** between the different stakeholders on interactions and collaborations.
- **Outline an ideal 2030 ecosystem** for interactions and collaboration and the roles each stakeholder plays to enable improved outcomes for patient access.
- **Recommend what should be considered as the key building blocks to reach the ideal 2030 ecosystem** in terms of potential success factors to enable this system to develop as well as perceived challenges and possible solutions.

## Discussion results

*Q1. Identify what the group believe are current directions of travel or evolution between the different stakeholders on interactions and collaborations - separate, aligned, converged, harmonised, collaborative, reliant, jurisdictional, cross jurisdictional? Which should be encouraged, which should be discouraged and why?*



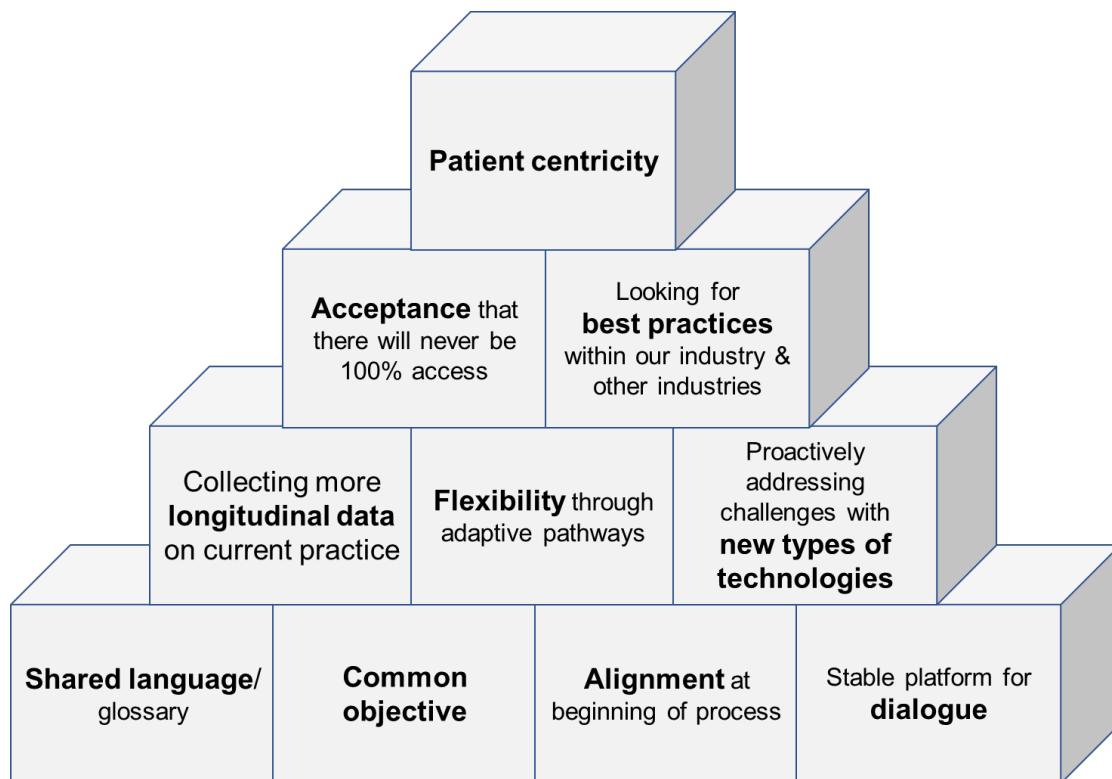
The group also discussed the impact of the COVID-19 pandemic on cross jurisdictional interactions. Although the pandemic has changed ways of working, provoking more global and less local interactions, there is a concern that “vaccine nationalism” will reverse this and potentially lead to more divergence.

*Q2. Focus on 2030 – what would you like to see as an ideal ecosystem for interactions and collaborations across stakeholders? What type of interactions would be most effective and when?*

The group were asked to consider two scenarios: evidence generation for licensing and evidence generation post-licensing. The group believed that an ideal ecosystem focused on evidence generation for licensing would utilise a **shared language/glossary** that gives alignment on the definition of clinical effectiveness, uncertainty, HTA etc. There would be **early stakeholder engagement**, even before scientific advice, and in particular with HTA agencies and payers. **Networks** would also be in place to help foster valuable collaborations.

In the context of post-licensing, an ideal ecosystem would have **technical guidance** to help manage uncertainty arising from evidence gaps. There would also be better use of **historical control data** and **clear requirements and standards** for post-approval data collection.

*Q3a. Recommend what should be considered as the key building blocks to reach the ideal 2030 ecosystem in terms of potential success factors to enable this system to develop.*



*Q3b. What challenges are perceived, and possible solutions or policy changes required?*

Potential challenges:

- Media pressure and/or government intervention following negative decisions
- Trust
- Being realistic about different objectives at the HTA level
- More divergence in budgets due to COVID-19
- Being realistic about what can be achieved within the 2030 timeframe.

Solutions or policy changes required:

- Building trust through communication and empowerment – this will help to create an inclusive ecosystem.
- Having shared objectives
- Developing shared language/glossary to communicate effectively
- Distinct pathway to bring stakeholders together and share the understanding/responsibility of decisions.
- Making clinical data available during processes so that comparisons can be made with new standards of care.
- Collecting more longitudinal data on current care practices.
- Shared priority setting
- Tailor-based working and degree of flexibility i.e. different products need different approaches
- New global host to enable stakeholder dialogue

## Breakout discussion D

**Ensuring interactions and collaborations between different stakeholders are adding value – how can success be measured and what processes should be put in place to ensure iterative improvements as the landscape evolves?**

Chair	<b>Dr Mark MacGregor, Chair, Scottish Medicines Consortium, Scotland</b>
Rapporteur	<b>Dr Álmuth Spooner, Director, Regulatory Policy and Intelligence, AbbVie, Ireland</b>

### Background

There are now a number of stakeholders that play a significant role in the process of getting a medicine to patients. The interactions between the different stakeholders (regulatory, HTA, payer, patient and company) are raised consistently by companies and agencies as key components of building improved predictability into development and enabling more positive regulatory and access outcomes.

Although it is clearly understood that regulators, HTA and payers have different remits, there is common ground as well as rational divergences based on the different remits. Over the last 5 years, interactions and collaborations have evolved in thinking and mutual activities both at a product level as well as at a policy and cross jurisdictional level. This is not just around collaborating to provide early scientific advice, but also on other activities such as registries and other forms of post-approval evidence generation to ensure work done by one agency can be reused or understood by another.

At the global level (ICH, ICMRA, INHATA) there has been increased collaboration on both technical and policy issues. Within jurisdictions there is increasing cross agency collaboration and interaction at the product level e.g. NICE and MHRA, ZIN and MEB, CADTH and Health Canada.

As both collaborations and interactions evolve it is important that these are adding value and the return on investment for each of the stakeholders involved in the interactions/collaboration is positive. The key consideration for this breakout is to discuss are:

- **Can the added value that different interactions and collaborations **between different stakeholders** be articulated and mapped?**
- **What are possible quantitative or qualitative measures of success/impact to ensure interactions/collaborations are adding value?**
- **What processes and procedures should be put in place to ensure iterative improvements as the landscape evolves?**

## Discussion results

*Q1. Mapping the key or main perceived added value of interactions and collaborations between different stakeholders – does this differ by stakeholder?*

The group agreed that while there is value in multi-stakeholder interactions, these interactions occur at different levels and **expectations of value can differ**. The intangible aspects of interactions are important, such as **relationship building**, as well as having tacit knowledge and understanding of the other organisations involved e.g. how their decisions are made, who from the organisation should be involved etc. From an industry perspective, the greatest value can be gained from multistakeholder interactions when there are **well-defined objectives and goals**; a clear agenda supports explicit value, and this can be facilitated through early engagement. **Clear documentation** of interactions is also important; for example, written reports can be impactful for development decisions.

*Q2. What are possible quantitative or qualitative measures of success/impact to demonstrate that the interactions/collaborations are adding value?*

The group agreed that measures of value of interactions cannot be unidimensional, as there are trade-offs, particularly in relation to speed. In addition, value that cannot be easily measured is not necessarily devoid of importance; some of the value of interactions is about educating and improving knowledge of the molecule/technology, which is a more qualitative outcome that is hard to measure. Collaboration at the policy level may also require different measures, for example, in relation to new processes or tools and their value to stakeholders.

Success/impact indicators	Considerations	At what level is the impact? (Definitions/examples below)		
		Product	Therapeutic	Policy
<b>Speed</b> (time to access) 	Collaboration between industry, regulator and HTA agency to ensure downstream consequences of accelerated approval considered – where are the differences, alignment, resolution of differences?	✓	✓	
<b>'Correct-ness' of decision</b> 	What do different stakeholders consider to be a "correct decision"? More work is needed to define across stakeholders.  Key to balance measure with speed.	✓	✓	✓
<b>Patient centric measures of value / patient relevance of evidence generated</b> 	How is value measured for new technologies from a patient perspective?  Are different tools required to ensure patient experience data collected in development is relevant in decision making?	✓	✓	✓
<b>Equity</b> 	Equity of access across interventions, by population subgroup and across countries – building trust to facilitate transparency between stakeholders.			✓

Examples of areas where success indicators could be built for different levels:

Level	Key areas to build success indicators
Product	Shape the development plan Support the PLEG plan Improve the timeline of regulatory process Positive HTA recommendation Faster patient access
Therapeutic	Internal expertise development Knowledge on the therapeutic area Understanding of the disease pathway Horizon scanning Value framework/evidence standard for the disease
Policy	Input into guideline development Regulatory strengthening Best regulatory review practice HTA capacity building Good HTA review practice

*Q3. What mechanism, measures or tools should be put in place to ensure iterative improvements in interactions/collaborations as the landscape evolves? What are the potential barriers to initiating these and possible solutions and next steps?*

- **Surveys on interactions** – potential barrier in developing meaningful survey questions e.g. will this interaction change practice.
- **Other analysis of value of interactions** – though there may be resource challenges.
- **Information/data sharing** – this will help to build trust and increase transparency, though there are likely to be legal barriers.

## Appendix: Workshop attendees

Affiliations are stated as they were at the time of the meeting (10-11th March 2021).

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