Building on regulatory and HTA agilities for high unmet need —

Has the development, review, and HTA assessment for priority treatments changed?

22nd – 23rd September 2022

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 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

In 2020, coronavirus disease (COVID-19) spread rapidly around the world and halted regular social, business, and research activities. The pandemic impeded normal functioning across several fields, and businesses and agencies alike were forced to adapt. Under conditions of immense pressure in the healthcare sector due to the pandemic, regulatory agencies and companies had to reformulate and modify their regulatory and health technology assessment (HTA) processes in order to reduce redundancies while still maintaining high standards of decision making. Facing these challenges head-on, agencies and companies developed agilities that helped them bring new therapeutics and vaccines for COVID-19 to the public in a safe and timely manner following adequate development and assessment.

Today, the world is inching closer to a "post-pandemic" era in which most COVID-19 restrictions have been lifted. Meanwhile, companies, regulatory bodies, and HTA agencies are actively assessing how the new frameworks built to bring COVID-19 vaccines and therapies to the market can be sustained. Some of these regulatory agilities achieved during the pandemic include:

- Increased use of facilitated regulatory pathways, such as conditional approvals
- Greater acceptance of digital health technologies in the field of medical development and the post-approval space
- Increased application of real-world evidence (RWE)
- Consideration of Cloud-based submissions.

Given that these fine-tuned processes developed during the pandemic appear to be effective, there could be benefits to maintaining them in the future and extending them to other areas of medicine. It is believed that the regulatory agilities implemented during the pandemic to maintain the smooth functioning of regulatory systems should be made permanent parts of the regulatory framework and/or built upon so as to reduce redundancies and improve efficiency. Indeed, some of these learnings are already being incorporated into new initiatives, such as the Prescription Drug User Fee Act (PDUFA) VII in the USA and the European Commission Pharmaceutical Strategy.

There are, however, some key challenges that need to be addressed. Different bodies have identified different approaches and limitations based on their own missions and targets, and an overall synthesis of what can be eliminated and what should be retained from multiple perspectives is not fully clear. Further, how the new policies and agilities can be improved upon in a post-pandemic world also needs to be delineated, especially from the purview of clinical trial design and conduct and the review and reimbursement of new medicines.

In this context, the workshop aims to discuss whether the processes and frameworks for the development, regulatory review, and HTA assessment of COVID-19 treatments that were developed or adopted during the pandemic are sustainable. Another key question the workshop seeks to answer is whether these policies can also be extended to other diseases and areas of medicine for which there are high levels of unmet need.

Workshop objectives

- Identify any agilities, process frameworks, policies, and practices developed or utilised by regulatory and HTA agencies to adapt to the pandemic and discuss the feasibility of extending these ideas or innovations to other clinical areas related to the development, assessment, and introduction of therapeutics for diseases with high unmet needs.

- Discuss the overall impact of current agency and company initiatives aimed at facilitating medicine development, evaluation, and access and further deliberate their sustainability.
- Provide recommendations on factors that can help incorporate regulatory and HTA agility into current and future frameworks for the development, evaluation, and reimbursement of new medicines.

Venue

The workshop was held at Hyatt Regency Tysons Corner Hotel, Virginia, USA, over 2 days: 22nd and 23rd September 2022.

Workshop Programme

Affiliations are stated as they were at the time of the meeting (22–23rd September 2022).

CIRS introduction and welcome	**Anna Somuyiwa,** *Head, CIRS*
Chair introduction and welcome	**Dr Theresa Mullin,** *Associate Director for Strategic Initiatives, CDER, FDA, USA*
Session 1: Regulatory agilities utilised during the pandemic: is it important that these are embedded as part of future approaches?	
Keynote: Health systems' resilience in managing the COVID-19 pandemic: What was needed to deliver treatments for COVID-19 and what lessons have been learnt?	**Dr Supriya Sharma,** *Chief Medical Advisor to the Deputy Minister, Health Canada*
What has the pandemic taught us about redundancies, challenges and opportunities for medicine development and review?	
Company reflection	**Dr Virginia Acha,** *AVP, Global Regulatory Policy, MSD, UK*
Regulatory agency reflection	**Dr Khair ElZarrad,** *Director of the Office of Medical Policy, CDER, FDA, USA*
Session 2: Building in changes to development: what regulatory and HTA agilities should be embedded or evolved?	
Rapid scientific advice and enhanced communication between sponsors and agencies during development: what are the opportunities and what is sustainable?	
Agency perspective	**Melissa Hunt,** *A/Senior Executive Director – Director of Bureau of Metabolism, Oncology and Reproductive Sciences, Health Canada*
Company perspective	**Dr Carlos Garner,** *Vice President, Global Regulatory Affairs, Eli Lilly & Company, USA*
HTA perspective	**Dr Nick Crabb,** *Programme Director, Scientific Affairs, NICE*

Facilitating innovative trial designs and conduct of clinical trials during the COVID-19 pandemic: what were the enabling activities and key areas that could be routinely considered for all medicines?	
Regulatory agency perspective	**Leonoor Wijnans,** *Senior Clinical Assessor, Medicines Evaluation Board, The Netherlands*
Company perspective	**Dr Herbert Pang,** *Expert Statistical Scientist, Genentech/Roche, USA*
Session 3: Building in changes to review and reimbursement: what regulatory and HTA agilities identified can be kept post-pandemic?	
Chair introduction	**Prof Hans-Georg Eichler,** *Consulting Physician of the Association of Austrian Social Insurance Institutions*
Accelerating the registration of new medicines: what are the learnings and what would be of value to implement for high unmet need medicines beyond COVID-19 treatments	
Regulatory agency perspective (part 1)	**Dr Junko Sato,** *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*
Regulatory agency perspective (part 2)	**Claus Bolte,** *Head of Sector Marketing Authorisation, Swissmedic*
Company perspective	**Jerry Stewart,** *VP, Global Regulatory* Policy and Intelligence, Pfizer, USA
Strengthening regulatory systems for the development and review of medicines: What future changes are being considered	
EMA perspective	**Steffen Thirstrup,** *Chief Medical Officer, EMA*
FDA perspective	**Dr Mary Thanh Hai,** *Deputy Director for Clinical, Office of New Drugs, CDER, FDA, USA*
What are the implications of an increasing agile regulatory pathway for HTA and payer decision making?	
HTA agency perspective	**Suzanne McGurn,** *CEO, CADTH*
Payer perspective	**Jessica Daw,** *Vice President, Pharmacy, Sentara Health Plans, USA*
Session 4: Syndicate sessions	
Introduction to Syndicate sessions	
Breakout discussions	
Breakout A: Enhanced communication developed in the pandemic between sponsors and agencies during development: how sustainable are the processes, and what should be retained?	**Chair: Dr Brian O'Rourke,** *Chair, CIRS HTA Steering Committee* **Rapporteur: Erin Greene,** *Senior Manager, Global Regulatory Policy & Intelligence, Pfizer, USA*

Breakout B: What changes to clinical trial design and conduct during the pandemic could be embedded in future decision making?	**Chair: Fabio Bisordi,** *Global Head International Regulatory Policy, F.Hoffmann-La Roche, Switzerland* **Rapporteur: Dr Rebecca Lumsden,** *Head of Regulatory Science & Policy EU/AMEE, Sanofi, UK*
Breakout C: Which regulatory and HTA process and operation efficiencies identified or utilised during the pandemic can be applied in the future?	**Chair: Dr John Lim,** *Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Senior Advisor, Ministry of Health, Singapore* **Rapporteur: Dr Brenda Huneycutt**, *Director, Global Regulatory Policy, Merck & Co, UK*
Session 5: Syndicate sessions: feedback and stakeholder perspective	
Chair introduction	**Adjunct Prof John Skerritt,** *Deputy Secretary for Health Products Regulation, Department of Health, Canberra, Australia*
Feedback on Syndicate discussions and participants' viewpoints	
New ways of working to enable the development review and reimbursement of innovative medicines: Has or should the development review and HTA assessment for priority treatments change(ed)?	
Regulatory perspective	**Finnuala Lonsdale,** *Director of Human Products Authorisation and Registration, Health Products Regulatory Agency, Ireland*
Company perspective	**Ginny Beakes-Read,** *Executive Director, GRR&D Policy, Amgen, USA*
HTA perspective	**Finn Borlum Kristensen,** *Professor of Health Services Research and HTA, University of Southern Denmark*
Payer perspective	**Mark Trusheim,** *Strategic Director, NEWDIGS, MIT, USA*
Chair's summary and close of meeting	**Summary: Adjunct Prof John Skerritt,** *Deputy Secretary for Health Products Regulation, Department of Health, Canberra, Australia* **Closing remarks: Dr Neil McAuslane,** *Director, CIRS*

Key points from presentations

Please note, affiliations are stated as they were at the time of the meeting (24-25th June 2021).

Session 1: Regulatory agilities utilised during the pandemic: is it important that these are embedded as part of future approaches?

Dr Supriya Sharma, *Chief Medical Advisor to the Deputy Minister, Health Canada, Canada,* provided an overview of the key challenges healthcare systems and regulators faced because of the COVID-19 pandemic, along with the lessons they learned. One important learning was that appropriate human resource management is essential for the smooth functioning of agile regulatory frameworks. COVID-19 introduced flexibilities into regulatory systems that enabled the efficient approvals of lifesaving pharmaceuticals and medical devices. Although the effectiveness of changes such as fee waivers for new submissions remains to be verified, the commitment to transparency – especially amidst increased public scrutiny – ensured open dialogue and fostered trust in regulatory systems. The pandemic also exposed major gaps in healthcare access, especially among underserved and vulnerable populations, and created shortages of drugs and medical devices worldwide. These challenges can be tackled through supply chain improvements and new measures for procuring essential drugs. As a post-pandemic era looms closer, it will be essential to maintain the flexibility established during COVID-19 to prevent any regressions into the 'status quo' of drug development and clinical trials. In this way, regulators can continue to make these processes more efficient and sustainable.

Dr Virginia Acha, *AVP, Global Regulatory Policy, MSD, UK,* addressed the impact of COVID-19 regulations on the pharmaceutical industry from MSD's perspective. In order to help the pharmaceutical industry meet the challenges imposed by the pandemic, regulators introduced several flexibilities to existing processes. Surveys conducted by MSD via the European Federation of Pharmaceutical Industries and Associations (EFPIA) demonstrate the positive impact of these flexibilities on drug development, especially in key areas such as clinical research. Findings show that the most beneficial of these changes are the use of rolling reviews and the provision for continuous communication with regulators. These flexibilities have helped to accelerate the development of COVID-19 treatments and, according to Dr Acha, could continue to benefit stakeholders in the post-pandemic era if retained. In the future, industry and regulatory frameworks must complement one another to support a more efficient drug development system in preparation for the next pandemic.

Dr M. Khair ElZarrad, *Director of the Office of Medical Policy, CDER, FDA, USA,* highlighted the ways new digital modalities can impact the future of drug development and how regulators' views toward the technologies have adapted and evolved due to COVID-19. Some of the technologies born from necessity during the pandemic – such as remote clinical outcome assessments and provisions for shipping drugs directly to patients' homes – have the potential to further improve trial recruitment and retention, ultimately improving their probability of success. In addition, artificial intelligence – which is under careful regulatory evaluation – can automate many healthcare processes and workflows. While RWE has proven useful for supporting the development of COVID-19-related therapeutics, its future impact will be informed by the FDA's guidelines, which cover data quality, data validity, standardised terminologies, and consistency of findings.

Session 2: Building in changes to development: what regulatory and HTA agilities should be embedded or evolved?

Melissa Hunt, *A/Director General – Director of Bureau of Metabolism, Oncology and Reproductive Sciences, Health Canada, Canada,* provided an overview of pandemic-era amendments to Canadian regulatory frameworks that drove positive results from an agency perspective. In response to the COVID-19 pandemic, there was an urgent need to strengthen communications between Health Canada and sponsors. As a result, Health Canada established a central point of contact and provided end-to-end services that facilitated the completion of the review process. Timelines for pre-trial application meetings were shortened to one week, and Health Canada performed significant outreach to trial stakeholders via webinars, faster resolution of queries, and regular meetings with government departments. There was a renewed focus on relationship building and process transparency. Given the effectiveness of the agile responses elicited during COVID-19, it is important to extend useful procedures such as rolling reviews and better communication with stakeholders and the industry to introduce products that fill unmet clinical needs.

Dr Carlos Garner, *Vice President, Global Regulatory Affairs, Eli Lilly & Company, USA,* discussed Eli Lilly's experience in obtaining emergency use authorisation (EUA) for their COVID-19 therapeutic and ways to extrapolate these achievements to other major threats to public health. Eli Lilly shortened development timelines significantly for its COVID-19 therapeutic, which was administered to a human patient after just two months rather than the usual 17 months. The drug was also authorised within 245 days, indicating the robustness of the drug review process. This feat was achieved through significant collaboration with the FDA, which shared Eli Lilly's resolve to act with urgency and therefore expedited protocol approvals with exemplary speed. This efficiency and scientific transparency enabled the FDA and Eli Lilly to resolve outstanding issues and ensure productivity. The learnings suggest that in the future, engaging with leadership, acting on a shared sense of urgency, ensuring scientific transparency, using regulatory science tools, and maintaining flexibility could help in the swift development of drugs and devices for other diseases and disorders.

Dr Nick Crabb, *Programme Director, Scientific Affairs, the National Institute for Health and Care Excellence (NICE), UK*, spoke about the initiatives NICE started in response to COVID-19. One key success was the RAPID-C19 initiative, which facilitated access to innovative therapeutics. NICE started an expedited scientific advice programme, including a three-hour-long virtual meeting, a detailed standalone report, and expert feedback on the company's development plan. NICE also developed managed access agreements (MAAs) to facilitate timely patient access to promising new drugs, along with an HTA Innovation Laboratory to develop a financially sustainable framework for rapid entry into the managed access programs. The agency is also evolving its scientific advice model to meet other unmet clinical needs.

Leonoor Wijnans, *Senior Clinical Assessor, Medicines Evaluation Board, The Netherlands*, gave an overview of the factors that contributed to clinical trials' successes and failures during the COVID-19 pandemic, citing tocilizumab and remdesivir as examples. In the case of remdesivir, most evaluations were complicated by observations that the data were not comprehensive and did not provide conclusive evidence regarding the effect of disease duration and virological effects. Researchers also failed to replicate their findings on remdesivir. Meanwhile, the RECOVERY trial for tocilizumab recruited a large sample size and identified clinically relevant endpoints, ultimately providing compelling results. Therefore, healthcare stakeholders learned that platform clinical trials can provide fit-for-purpose evidence to support the authorisation and licensing of drugs. To provide a better environment for drug development, the Accelerating Clinical Trials in the EU (ACT EU) programme has been developed and aims to improve cooperation and transparency for clinical trials and product approvals in Europe.

Dr Herbert Pang, *Expert Statistical Scientist, Genentech/Roche, USA,* provided learnings from clinical trials conducted during the COVID-19 pandemic. His experience suggests that clean and high-

quality clinical data, good-quality data assessments, and the monitoring of trial sites are key for trial monitoring and filing. Other useful measures that could help in improving the design and value of clinical trials include the use of continuous endpoints and RWE. For example, a hybrid control design in which the control arm is supplemented with external controls increases the likelihood that patients are randomised to treatment arms. Another potential approach is the use of decentralised trials, which can be conducted on virtual platforms or even at virtual sites. These changes could prove to be valuable for developing urgently needed drugs in the future and warrant early collaboration with all stakeholders as well as transparent multistakeholder communication.

Session 3: Building in changes to review and reimbursement: what regulatory and HTA agilities identified can be kept post-pandemic?

Dr Junko Sato, *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan,* spoke about PMDA's experience in accelerating the registration of drugs and treatments for COVID-19. Key parts of the PMDA's strategy include special approvals for emergency use, rapid marketing approvals, the acceleration of COVID-19-related products, the maintenance of ongoing clinical trials and product reviews, and the utilisation of real-world data. These steps were taken in the context of government-issued regulations such as the PMD Act, which served to provide a mechanism for early approval and electronic prescribing. In the future, the Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) will aim to invite regulatory representatives from across Asia to share knowledge and experiences in regulatory adaptations to the COVID-19 pandemic.

Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic, Switzerland,* provided insights into the regulatory agilities that helped speed medicine registration during the COVID-19 pandemic. Regulatory agility depends on a combination of efficiency and collaboration of legal provisions and regulations. During the COVID-19 pandemic, an industry-wide openness to international collaborations and the use of RWE helped ensure the scientific integrity of drug approvals. While the same regulatory agilities may become difficult to retain in the future, retaining certain aspects – such as digitisation, cloud-based solutions, mobile tools, and video technologies as well as the increased use of decentralised clinical trials, hybrid study approaches, telemedicine, digital tools to measure endpoints during development, and direct shipment of study medicines to patient homes – could help accelerate drug registration and approval in the future.

Jerry Stewart, *VP, Global Regulatory Policy and Intelligence, Pfizer, USA,* described the transformation of regulatory and industry frameworks during the COVID-19 pandemic. Pfizer succeeded in obtaining EUA for two of its drugs — PAXLOVID and COMIRNATY. Adaptations such as faster, real-time interactions between sponsors and regulators; risk-based pre-clinical safety requirements; chemistry, manufacturing, and controls flexibilities; and innovative clinical evidence generation were key in this regard. Additional changes that supported the dissemination of the drugs to areas of need included conditional approvals and waivers of local testing and labelling guidelines. In the future, it will be important to identify diseases that could benefit from the sense of urgency seen for COVID-19 and create a unified effort grounded in risk-based principles and collaboration to fulfil high unmet needs.

Steffen Thirstrup, *Chief Medical Officer, EMA, Netherlands,* discussed the regulatory innovations adopted by the EMA during the COVID-19 pandemic and how the organisation envisions its way forward. During the pandemic, the EMA approved six vaccines and eight therapeutics, rolled out in record time across its 27 member states. In order to maintain regulatory agility, it established the Health Emergency Preparedness and Response Authority (HERA). RWE became crucial for close safety and effectiveness monitoring. To this end, the EMA created the Data Analysis and Real-World Interrogation Network (DARWIN EU) — a federated network of data, expertise, and services that supports better decision-making throughout the product life cycle by generating reliable evidence from

real-world healthcare data. Steffen also addressed the need to maximise the global supply of products, increase transparency and proactive communication, and foster new approaches to counter misinformation. To ensure harmonised regulatory action globally, the EMA worked closely with the International Coalition of Medicines Regulatory Authorities (ICMRA). The EMA also launched the Accelerating Clinical Trials in the EU (ACT EU) initiative to transform the EU clinical trial environment and support medical innovation. The effort has thus far improved patient outcomes, and the EMA wishes to continue to improve the clinical trial landscape in Europe with ACT EU in the future.

Dr Mary Thanh Hai, *Deputy Director for Clinical, Office of New Drugs, CDER, FDA, USA,* highlighted the steps the FDA has taken to build upon regulatory and HTA agilities in order to address high unmet clinical needs. Dr Thanh Hai flagged the role of the Prescription Drug User Fee Act (PDUFA) legislation from Congress, which authorises the FDA to collect user fees from companies that produce certain human drugs and biological products. As PDUFA VII looms closer, discussions between the FDA and industry have spanned many themes and incorporated different teams to gain their perspectives on the legislation. For example, the Center for Biologics Evaluation and Research (CBER) plans to create an enhanced capacity to guide development and review innovative products for cell and gene therapy, and the pre-market group seeks to create new strategies for improving efficiency and expanding communication in the Human Drugs Review program. In addition, PDUFA VII will run the following programs: (i) Split Real-Time Application Review (STAR) Pilot Program, which will provide efficacy supplements in any therapeutic area that seeks to expedite patient access to novel uses for existing therapies; (ii) the Rare Disease Endpoint Advancement (RDEA) Pilot Program, which aims to advance the development of drugs for rare diseases by enabling sponsor discussions with the FDA throughout the efficacy endpoint development process; and (iii) the Advancing RWE Program, which aims to improve the quality and acceptability of RWE-based approaches for new labelling claims.

Suzanne McGurn, *CEO, CADTH, Canada,* provided an HTA perspective of the impacts that agile regulatory pathways have had on the Canadian regulatory environment. She explained that one of CADTH's greatest learnings was the importance of initiating dialogue with the industry and using data to accelerate the time required for bringing products to market. In the future, it will be important to continue to foster strong communication and relationships between regulators and industry to enable agile regulatory pathways. Other notable approaches were rolling reviews and "living reviews". Collaboration with researchers helped in gaining early scientific advice and enabled the use of RWE for managing market entry agreements. In the future, it will be key for HTA bodies to prioritise areas of high unmet needs that consider the public perspective, while also ensuring clinical efficacy and cost-effectiveness.

Jessica Daw, *Vice President, Pharmacy, Sentara Health Plans, USA*, discussed how payer bodies responded to changes in regulatory frameworks introduced during the COVID-19 pandemic. In the USA, decisions for drug coverage are often made by payers' Pharmacy and Therapeutics (P&T) Committees after reviewing the available evidence. But during COVID-19, payers had little evidence to inform their decisions because of the EUAs regulators used to rapidly authorise new treatments. As a result, the amount of evidence payers needed to support coverage was unclear. The pandemic also marked the first time in the USA when the cost of vaccines was borne by the government instead of patients. While payers made population-level decisions, they also reviewed individual patient requests and granted coverage as long as there was sufficient support in the literature or compendia. In the future, we should examine what worked in the EUA process during COVID-19 and apply the learnings for accelerated approval and access.

Session 4: Syndicate sessions

A) Enhanced communication developed in the pandemic between sponsors and agencies during development: how sustainable are the processes, and what should be retained?

The values and lessons learned by regulatory agencies, health technology assessment (HTA) bodies, and the industry with respect to enhanced communication could be extended to other products. Focusing on the experience of the last two years can help identify the drivers for the sustainability of this concept. This breakout session was aimed at understanding and identifying these values and identifying the areas that need to be embedded for future health emergencies and some that could even be retained for non-emergencies.

Several procedures were found to have worked well and contributed to facilitating the development process. The Syndicate recommended extending the use of assessment reports to the review of other types of critical products; using structured pathways for iterative communication amongst stakeholders, especially when contentious or difficult topics arise; ensuring the use of existing facilitated pathways and seeking to develop new pathways in response to specific needs; and ensuring transparency in decision making processes and documenting the outcomes.

Recommendations for CIRS and other groups:

1. Assess the clinical/surrogate outcomes
    - What is considered meaningful?
    - What is the acceptability among stakeholders?
    - What are the risks and benefits?
2. Identify frameworks for prioritisation
3. Manage uncertainty by using tools for grading and communicating uncertainty

B) What changes to clinical trial design and conduct during the pandemic could be embedded in future decision making?

Future drug development could benefit from the application of measures that expedited the development of COVID-19 treatment, across both clinical and regulatory settings. Modification, innovation, and improvement were achieved in trial population dynamics and patient-centric drug development via the simplification of trial design, integration of decentralised approaches, and rigorous use of real-world data. This syndicate session was aimed at understanding if these learnings can improve the quality of clinical trials and reduce redundancies. Moreover, which areas can help improve the routine conduct of clinical trials and be applied to non-COVID-19 treatments?

This Syndicate reflected that many of the tools used during the pandemic had already been in place in some form, but their use was catalysed by the pandemic. For example activities that worked well were the use of basket studies that spanned healthcare systems; the expanded use of telemedicine, virtual recruitment and remote sampling; and the use of post-EUA observational studies. Cross-organisational data exchange and communication were seen as paramount in aligning study needs (e.g. endpoints, enrolment diversity), and the use of RWE to support these outcomes was an invaluable asset.

Recommendations for CIRS and other groups:

1. Include sponsor, regulator, and HTA perspectives in future CIRS surveys on products registered based on the data collected during the pandemic.
2. Conduct workshops on decentralised clinical trials (DCTs) to identify:
    - Obstacles, challenges, and recommendations in DCT delivery based on learnings

- New skillsets required for DCT delivery and how to integrate digital health (DCT convergence)
- Patient insights on DCT versus randomised controlled trials

3. Address the concerns on representativeness, diversity, misinformation, and rebuilding trust in drug development and involvement of patients across the full drug discovery pathway.

C) Which regulatory and HTA process and operation efficiencies identified or utilised during the pandemic can be applied in the future?

The COVID-19 pandemic also warranted a relook at process redundancies, operational inefficiencies, and rigidities to facilitate the provisioning of medications to patients. A number of these changes helped deliver flexibility and improve process outcomes. These improvements can further inspire permanent improvements in drug development, reviews, reimbursement practices, and processes in the face of unforeseen public health emergencies (PHE) in the future. The majority opinion is to retain these changes, and this necessitates identifying the most value-adding and sustainable changes. This breakout session was aimed at the range of operational efficiencies or flexibilities that were incorporated by agencies and companies.

This Syndicate recognized the value of engaging the public, especially as regulators became the public advocates to raise important issues about healthcare during the pandemic. Using reliance authorization pathways and other facilitated pathways improved process efficiency and also opened organizations to the benefits of using these approaches. Because so many of the issues during the pandemic had international impact, the use of virtual meeting technologies found a ready audience amongst drug developers and regulators. Digital technologies allowed the real-time collection of data and rapid measurement of the observations. Further, Procurement Agreements conditional on regulator and HTA agreements proliferated and accelerated access to important therapeutics. All of these activities built flexibility into the process while maintaining public engagement and confidence.

Recommendations for CIRS and other groups:

1. Conduct another CIRS workshop with regulators, HTAs, patient organisations, and industries to identify areas requiring continued agility and prioritise and sequence the future course of action.
2. Create action-oriented plans and outline the elementary steps to move forward.
3. Conduct a SWOT analysis to identify what worked and what did not; identify the reasons for failure or success.
4. Explore issues with the workforce: identify the global and country-level investments in terms of people and capabilities.

Session 5: Syndicate sessions: feedback and stakeholder perspective

Finnuala Lonsdale, *Director of Human Products Authorisation and Registration, Health Products Regulatory Agency, Ireland,* highlighted the challenging road ahead for regulatory bodies as they attempt to cement the innovations that emerged during the pandemic. The predictability of the regulatory landscape shifted considerably with the pandemic; at this stage, regulatory affairs organisations (within industry and agencies) have become more collaborative. Regulators have had to engage regularly with health care systems and have played a role in imparting scientific advice during the public health crisis. As a result, regulatory officials needed to build on communication skills. In addition, Finnuala discussed the need for a perspective shift in drug review, drug labelling, and human resource management in regulatory processes – despite barriers to change such as geopolitical considerations, conflicts of interest between the nation-state and regional states, organisational silos, and culture and capability. To reach a common regulatory vision and build new capabilities for the post-pandemic era, it will be critical for regulators to develop capabilities to

interpret RWE and pharmacometrics, sharpen focus on clinical impact, manage alliances, and improve digital literacy.

Ginny Beakes-Read, *Executive Director, GRR&D Policy, Amgen, USA,* spoke about the learnings and improvements in drug development processes during the pandemic and the adjustments this required from companies and regulators. One of the primary changes was the adoption of new data collection approaches. This change occurred alongside increased public awareness of clinical trials, offering a new opportunity for regulators to engage with people at a deeper level than before. For example, industry developed innovative methods of reaching a greater number of potential trial participants, with a focus on decentralised trials. These changes give a fresh impetus to clinical trial diversity, and new tools can help improve representation from underserved communities in clinical trials in the future. Nevertheless, it's important to acknowledge that the use of novel trial designs, regulatory science tools, and aspects of decentralised trials have created a new type of uncertainty that regulators must contend with. Companies need to help bridge this gap and work together towards accelerated drug introduction. To bring stakeholders together and reduce uncertainty in the system, industry and regulators can use grants and workshops to encourage peer-peer communication and ultimately help embed new technologies and approaches into drug regulation.

Finn Borlum Kristensen, *Professor of Health Services Research and HTA, University of Southern Denmark,* used Europe's efforts toward joint clinical assessment to demonstrate a potential method for improving clinical trials in the future post-pandemic era. The European Network for Health Technology Assessment (EUnetHTA) published collaborative studies in late 2020, yielding several important observations. Going forward, EUnetHTA-21 seeks to develop methodological guidances regarding choice of comparators, scoping questions, PICO (Population, Intervention, Comparator(s), Outcomes), and the structure of the cooperative HTA process, including interactions with regulators. Their experiences revealed both the advantages and drawbacks of such collaborative efforts, highlighting the need for guidelines surrounding cross-border collaboration to ensure the feasibility of recommendations for the group of interest. Beyond COVID-19, joint clinical assessments could help test drugs on the cutting edge of innovation, including new cancer drugs and advanced therapies. This continuous learning will nevertheless require a significant shift, both in terms of individuals' skills and policy changes.

Mark Trusheim, *Strategic Director, NEWDIGS, MIT, USA,* provided insights into the impact of COVID-19 on the cost of healthcare and complications for both payers and patients. When the COVID-19 pandemic struck, there was a decrease in the use of non-emergency care, as well as a push for disinvestment from some quarters. Drug shortages became more severe, leading to a major paradigm shift in healthcare's financial landscape. Today, several uncertainties remain, both for COVID-19 and other conditions, and treatment development for Long COVID is under assessment. In such a scenario, there is a greater push for payers to be involved through horizon scanning with the pre-authorisation process in order to safeguard value for money, predictability, and total spending. Payers are working to engage more with patients and use digital tools to aggressively manage populations. The shared aim for all parties is to safeguard patient interest, so stakeholders need to chart a sustainable path toward this goal.

Section 2: Presentations

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Keynote: Health systems' resilience in managing the COVID-19 pandemic: What was needed to deliver treatments for COVID-19 and what lessons have been learnt?

Dr Supriya Sharma, *Chief Medical Advisor to the Deputy Minister, Health Canada*

Shortly before the pandemic hit, Health Canada put together its 'Agile' regulatory framework. The new framework, which had been in the works for several years, had three main goals—trial modernisation, improving the response to new advanced therapeutics, and creating a more AGILE pathway for pharmaceuticals and medical devices.

Although the COVID-19 pandemic significantly changed the healthcare landscape, Health Canada was prepared to deal with the challenges it introduced. The organisation knew what aspects of its regulatory framework needed to remain unchanged and what aspects needed to evolve with the pandemic. However, finding dedicated human resources to implement these changes proved to be a major challenge.

At the beginning of 2020, Health Canada reassigned some of its reviewers to newly formed COVID-19 teams working on COVID-19 therapeutics and vaccines. The positions that went vacant as a result were backfilled in advance to sustain the day-to-day functioning of the organisation. However, as time went on and more resources were devoted to COVID-19, stakeholders from different quarters felt that their causes were being side-lined. but that did not occur because Health Canada ensured that dedicated staff that were continuing to assess, for example, other priority submissions that were not COVID-19 related.

In order to enable COVID treatments, the regulatory pathways as well as process had to evolve and needed to become more efficient, nimble and flexible, without compromising on standards for safety, efficacy and quality. Furthermore, it was essential to ensure that the right people were stationed at important levels of the regulatory machinery.

COVID-19 flexibilities

During the pandemic, Health Canada introduced several regulatory flexibilities through interim orders. These were aimed at facilitating vaccine and drug development and regulatory review, easing inspections, as well as checking drug shortages. Some flexibilities, like rolling submissions, proved to be extremely useful, while others proved to be ineffective and had to be readjusted.

Early on in the pandemic, Health Canada decided that reviewers would assess submissions cover-to-cover, given the need to have a complete understanding of data sets prior to approval and to support post authorization monitoring . There were several unknowns surrounding COVID-19, and hence, it was important for decision-makers to be adequately familiar with the vaccines, treatments, diagnostic tests, and even sanitisers being reviewed. Although there was increased international collaboration, reviewers and scientists in Health Canada were prepared to take the reins to address all eventualities.

Health Canada issued fee waivers for new submissions during the pandemic. This piece of regulatory flexibility seems to have had a positive impact on the whole. However, careful analysis is warranted before concluding that fee waivers are effective, especially since some products approved at that time are currently selling in high volumes.

Priorities, new and old

Every regulatory decision that Health Canada made was up for public scrutiny. Several steps taken during the pandemic reaffirmed the organisation's commitment to openness and transparency. Health Canada:

- conducted press conferences for every major authorisation and in intervening periods with Public Health Agency of Canada colleagues
- had an entire website dedicated to COVID-19 products – both under review and authorized
- released clinical trial information to the public including full data sets

COVID-19 brought several new and old vulnerabilities of our healthcare system to the fore. The pandemic revealed the inadequacy in data for underserved and vulnerable populations that may have been more severely impacted by COVID-19 as well as populations such as children and pregnant/breastfeeding women that aren't traditionally first to be studied in clinical trials. Since global supply chains were seriously affected, there was a spike in the shortage of drugs and medical equipment.

Health Canada was able to formulate an 'essentials' list and take measures to procure necessary drugs on a priority basis. Additionally, the organisation introduced several regulatory flexibilities to make the supply chain more efficient.

Post-pandemic challenges

As the urgency of the pandemic continues to fade and we transition to the endemic state, Health Canada is working to safeguard the progress made thus far. The pandemic brought organisations and people together in an unprecedented way. Now, as the franticness has abated, some organisations are starting to slip back to their pre-pandemic status quo.

This is not surprising, considering that the people making difficult decisions during the pandemic were stretched thin. However, business as usual will not be tenable in the post-pandemic era. Regulators must continue to improve the efficiency of the drug development process and clinical trials. Going forward, we also need to maintain our collaborative efforts and become more comfortable working while surrounded by uncertainty. In addition, we are likely entering a period of ongoing "layered crises" including environmental, economic and other emerging diseases that will continue to challenge health systems.

Altogether, Health Canada's experience as a mid-sized regulator during the pandemic suggests that preparation, flexibility, openness and transparency can go a long way in achieving much-needed, sustainable goals in healthcare and support trust in the integrity of the regulatory role.

Regulation to drive change

What has the pandemic taught us about redundancies, challenges and opportunities for medicine development and review?

Company reflection

Dr Virginia Acha, *AVP, Global Regulatory Policy, MSD, UK*

The pandemic introduced several novel challenges for the pharmaceutical industry. Drug companies worldwide faced severe time and data constraints in coming up with treatments for COVID-19. On top of improving coordination between stakeholders, global pharma had to ensure that routine activities did not suffer due to increased focus on COVID-19.

To help the pharmaceutical industry meet these challenges during the pandemic and to facilitate drug development, the European Medicines Agency (EMA) and other national regulatory agencies (NRAs) like the FDA introduced regulatory flexibilities. COVID-19 regulations have significantly changed the pharmaceutical innovation system.

How did regulatory flexibilities impact pharma?

MSD (Merck and Co.) was part of the European Federation of Pharmaceutical Industries and Associations (EFPIA) project team that conducted two surveys to collect feedback from pharmaceutical companies regarding COVID-19 regulatory flexibilities. The findings of the surveys suggest that flexibilities introduced since the early phase of the pandemic have positively impacted drug development. Some companies did not derive benefits from regulatory flexibilities as changes were implemented too late or too soon in some cases.

The surveys found that regulatory flexibilities impacted some operations more than others. Processes like clinical research, which were dependent on the healthcare setting and external actors and were more exposed to risk, benefitted the most.

Two novel regulatory solutions—rolling reviews and the provision for continuous communication with the regulator—were especially useful for companies. New virtual ways of working and digital solutions for collaboration among stakeholders also proved effective.

Meanwhile, pharmaceutical operations that were under direct control of companies, such as drug supplies, were among the least affected by flexibilities. This was because many companies had already devised workarounds in these areas.

Effect of regulatory flexibilities on pharma operations

Drug developers who participated in the EFPIA surveys said that the regulatory flexibilities helped sustain and improve the efficiency of their operations. Survey findings suggest that risk-based approaches, innovations like rolling reviews, and virtual ways of working can continue to benefit pharmaceutical development in the post-pandemic era.

COVID-19 has changed the ‘status quo’ within regulatory agencies. Hence, the pandemic offered a rare opportunity to improve the regulatory environment in Europe. For instance, regulatory authorities can revise excessive regulatory requirements, such as import testing, which entails a lot of administrative work.

Effect of regulatory flexibilities on COVID-19 drug development

Findings from the EFPIA surveys suggest that regulatory flexibilities helped accelerate the development of COVID-19 treatments. Drug companies found rolling reviews, rapid scientific advice, and supply arrangements especially helpful in drug development. The shift to virtual ways of working, improved collaboration between various stakeholders, and greater support for global supply also proved to be useful.

Regulatory agencies can facilitate drug development even beyond the pandemic by retaining regulatory flexibilities that pharmaceutical industry finds helpful. For instance, the EMA can help the industry

navigate future pandemics better by removing excessive regulatory requirements and optimizing the use of an Emergency Use Authorisation pathway.

Retaining the lessons learned from COVID-19

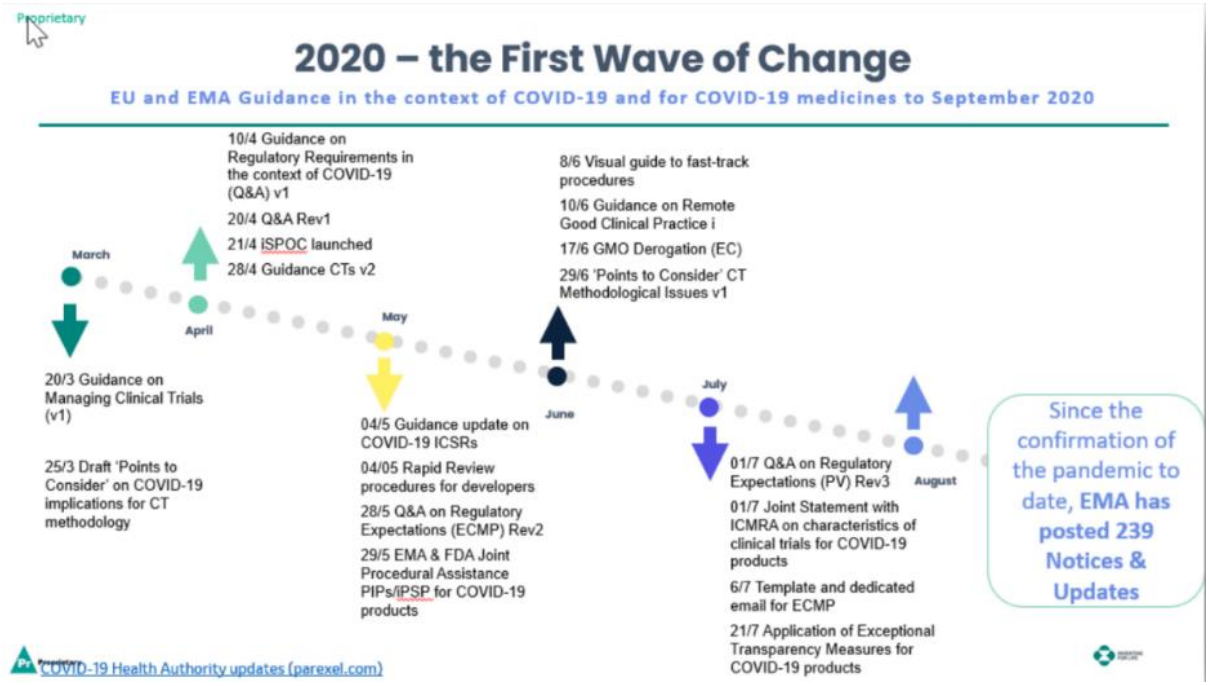
The EFPIA surveys point to clear benefits of regulatory flexibility for pharma. In addition, an Avalere study commissioned by MSD identified ten regulatory flexibilities valued by various stakeholders. Although many of these flexibilities have value in the post-pandemic era, they may not persist beyond the pandemic.

What factors decide whether the changes made during the pandemic will stay? MSD has explored this question and identified some possible candidates—the trade-offs for stakeholders that come with flexibilities, perceptions about the change, complexity and coordination within/across organisations, and alignment with legal, normative frameworks and resourcing. [2]

Role of regulators in drug innovation

The pandemic has laid bare the central role regulators play in driving healthcare innovation. The general public now has a better idea of the regulatory process, and owing to rapid access to information, decisions made by regulators receive significant public attention.

Regulators must ensure that lessons learned during the pandemic are not forgotten. Perhaps the most crucial among these lessons is that the industry and regulators must work hand in hand for more efficient drug development. A robust drug development system will ensure that we are prepared for the next pandemic.



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Advancing therapeutic development and regulations

What has the pandemic taught us about redundancies, challenges and opportunities for medicine development and review?

Regulatory agency reflection

Dr M. Khair ElZarrad, *Director of the Office of Medical Policy, CDER, FDA, USA*

The landscape of drug development and regulation has been evolving rapidly over the last few decades. Greater digitisation, and the greater diversity in ways of collecting and storing data, have heralded new and exciting changes in healthcare. The Real-world Evidence Program is a prime example of facilitating such changes. New digital solutions to data collection and innovative clinical trial designs—like decentralised clinical trials—show great promise in advancing drug development. While the pandemic accelerated innovation in healthcare, for the most part, it also exposed serious vulnerabilities in the system. Even pre-pandemic, a surprising proportion of clinical trials ended in failure, creating a huge drain on healthcare funding. A prominent reason for the failure of trials before the pandemic was poor recruitment. In the pandemic era, clinical trials faced several novel challenges.

Clinical trials during the pandemic

Many clinical trials conducted during the COVID-19 pandemic failed to produce generalisable results. Some of these trials were single-arm, while others were too small to provide statistical benefit. Although pioneering observational studies received much attention during the pandemic, concerns over sources of bias loomed large.

Studies that succeeded in producing reliable results did so using robust study design and analysis plans and optimally utilising existing healthcare infrastructure. These studies also leveraged technology to improve implementation.

FDA guidance and COVID-19 flexibilities

In guidance documents released since the beginning of the pandemic, the FDA outlined several new measures aimed at facilitating clinical trials. These new regulatory flexibilities were geared towards assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimising risks to trial integrity.

Electronic informed consent (e-consent), remote clinical outcome assessments, remote site monitoring visits, provisions for shipping drugs to homes, and the use of video conferencing for trial visits all proved to be useful during the pandemic. These are some of the elements the FDA is hoping to incorporate and discuss in future guidances, such as the decentralised clinical trials (DCTs) guidance. Decentralized elements hold the potential to expand the footprint of clinical trials and to ultimately improve recruitment and retention in trials.

As an important guiding document, the ICH guidelines on GCP codify the best practices in clinical trials. An Expert Working Group (EWG) is currently working on revising the GCP guidelines to encourage innovation in clinical trials. Upcoming changes to the guidelines will:

- encourage thoughtful design and conduct of clinical trials by focusing on areas that matters most to ensure participants safety and reliability of trial results.
- facilitate ad encourage the responsible use of innovative design elements and fit-for-purpose technology to make trials more efficient.

Digital health technologies and artificial intelligence

Late last year, the FDA published draft guidance on digital health technologies (DHTs). The draft guidance provides directions for the use of sensors, wearable devices, video recorders, interactive apps, and electronic patient reporting platforms in an effort to modernise data collection.

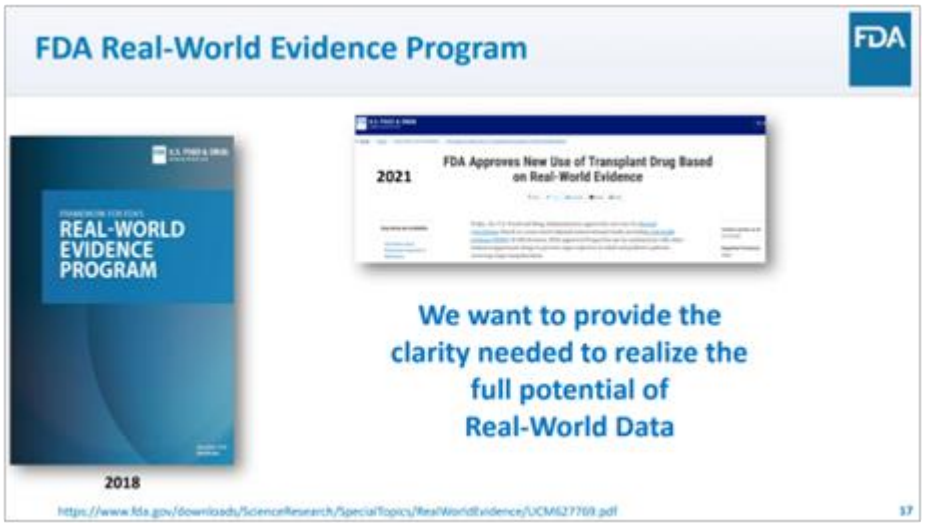
DHTs offer several benefits during data collection. Patients can be monitored remotely and continuously, in any place, and at any time. Moreover, studies incorporating DHTs have a clear advantage when investigating rare events like seizures and arrhythmias.
Advancements in artificial intelligence (AI) can help automate many aspects of healthcare innovation. The FDA is actively exploring ways in which AI can be integrated with processes in drug development, including clinical trials. To this effect, the FDA has come up with guiding principles for the development of good machine learning practice (GMLP) jointly with the UK's Medicines and Healthcare products Regulatory Agency (MHRA). Additionally, the FDA's Center for Drug Evaluation and Research (CDER) has established an AI steering committee (AISC) that will work to further coordination, education, and communication around AI.

Real-world evidence program

Real-world evidence (RWE) has contributed immensely to our current knowledge of COVID-19. However, the pandemic has taught us that more data is not always better. Real-world evidence can contribute to a better understanding of diseases but can also create more confusion depending on whether it stands up to scientific scrutiny.
As real-world data continues to accumulate and inform clinical/regulatory decisions, guidelines must evolve to address the question of data validity. The FDA's draft RWE guidances take crucial steps in this direction. Some of the important standards for RWE are:

- Is the RWE valid and fit for use?
- Does the study design provide adequate evidence to answer regulatory questions?
- Does the study meet relevant FDA guidelines?

The RWE guidance published in September 2022 highlights the importance of shared understanding across stakeholders, consistency and quality of data, and consensus around terminologies. As we increase the use of real-world data in drug development, clarity becomes paramount.



Communications and early advice during COVID-19

Rapid scientific advice and enhanced communication between sponsors and agencies during development: what are the opportunities and what is sustainable?

Agency perspective

Melissa Hunt, *A/* Senior Executive Director*– Director of Bureau of Metabolism, Oncology and Reproductive Sciences, Health Canada*

Responding to COVID-19

Health Canada responded to the public health crisis posed by COVID-19 with agility, relying on communication as a keystone for success. This included implementing a slew of measures across all levels to satisfy the urgent need for treatments, testing devices, vaccines, and disinfectants. To this end, Health Canada implemented some temporary regulatory and policy measures like 'rolling' scientific reviews to facilitate and speed-up reviews. Flexible measures were introduced to help address supply issues and provide easily accessible guidance and timely product information. Partnerships and international connections with companies and governments were leveraged to expedite product submissions and information sharing. A COVID-19 Regulatory Response Team (COVRRT) was created to coordinate communications, outreach, and liaising between internal and external stakeholders. It also helped channelise certain activities away from the review directorates and allowed them to focus dedicatedly on reviews.

Improved communications and early advice

Program-specific adaptations were aimed at implementing COVID-19 responses efficiently for the review of pharmaceuticals with a COVID-19 indication. In addition to increased management involvement, this included the creation of a single point of contact for regulatory advice and white-glove end-to-end services. The single point of contact was a key resource person who helped sponsors navigate the regulatory landscape with their expertise. End-to-end services were catered toward providing advice on regulatory incentives and filing strategies and giving unfettered advice throughout the review process. International partners across different time zones were also managed, with coordinated product-related discussions on topics such as post-marketing, procurement, and supply. With increased managerial involvement in the review process, the review team could focus on scientific reviews and deliver within unprecedented timelines.

Clinical trial-specific adaptations to communications

Responses were centred around expediting timelines (to within 1 week of request instead of the usual 2–4 months) for pre-trial application meetings, significant outreach to trial stakeholders via webinars, faster resolution of queries, and regular meetings with government departments with complementary mandates. Strengthening relationships across the spectrum (with Research Ethics Boards and funding agencies) and follow-up outreach to trial sponsors were some of the other ways of responding to the crisis.

What worked well?

Responding to the demands of the crisis with agile and nimble processes worked well, but also came at a human cost and required perseverance. Nonetheless, it helped improve the ability to respond quickly. Prioritising everything related to COVID-19 meant increased engagement and collaboration with stakeholders and partners. Ensuring transparency in processes, expediting timelines, and creating a seamless experience for sponsors also helped the organisation respond positively and facilitated early access to products for the public.

Way ahead

Moving forward, the positive and agile response elicited during COVID-19 can be extended to products for unmet clinical needs. This includes planned agile measures (e.g., terms and conditions, and rolling reviews), a National Strategy for Drugs for Rare Diseases, and better communication with stakeholders, especially targeted at improving patient involvement. Moreover, the leveraging of communications experience with the industry and retention of some aspects of the COVID-19 response within the standard timeline framework can be incorporated into future plans.

Lessons Learned from COVID-19 Response

What worked well

- More agile and nimble processes and regulations
- Significantly improved ability to respond quickly
- Increased engagement and collaboration from all stakeholders and partners
- Transparency
- Seamless experience for sponsors
- Meeting extremely expedited timelines

➢ **Ultimately resulted in earlier access to safe, effective and high quality products and positive response from industry partners**

Considerations for application to other areas including products for unmet medical needs

- Significant effort required and toll on staff
- Some changes pandemic-specific
  - E.g., point person
- Maintenance of arms-length relationship with industry
- Aspects could be retained using standard timelines

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Enhanced regulator communication models used during the COVID-19 pandemic

Rapid scientific advice and enhanced communication between sponsors and agencies during development: what are the opportunities and what is sustainable?

Company perspective

Dr Carlos Garner, Senior *Vice President, Global Regulatory Affairs, Eli Lilly & Company, USA*
The COVID-19 pandemic came as an unprecedented challenge, not only for patients but also for pharmaceutical companies. The development of therapeutics for the treatment of the novel SARS-CoV-2 virus infection involved creating monoclonal antibodies without any prior understanding of the specific disease's pathogenesis. During a public health emergency, every minute matters. As early as March 2020, Eli Lily committed itself to an aggressive therapeutic development plan for bamlanivimab and achieved the arduous feat of obtaining emergency use authorization by November 2020. This experience holds many invaluable lessons for the future.

Regulatory engagement

Iterative FDA engagement is an enabler of innovation. This engagement during the development of bamlanivimab resulted in a first patient dose being achieved within 80 days and the emergency use authorization within 245 days. Central to these accomplishments was the shared sense of urgency held by both the regulator and the sponsor. This sense of urgency brought senior leaders from both organizations to the table early and often resulting in efficient decision making and the aggressive application of a risk-based regulatory framework. The use of regulatory science tools and appropriate regulatory flexibilities were debated openly and transparently resulting in speedy alignment on plans and risks. As an example, FDA and Lilly relied upon previously acquired knowledge and experience with platform technologies resulting in use of stable bulk culture for First Human Dose drug substance manufacturing that led to a decrease in time from cell line transfection to first patient dose from 17 months to two months. Further, protocols which included adaptive trial designs and their amendments, as well as data outputs, were discussed and aligned within a matter of days. These are just two examples of what is possible when we work together with a shared sense of urgency during drug development and regulatory review to address a public health emergency.

Extending these learnings beyond COVID-19

Life expectancy in the USA is negatively impacted by highly prevalent, chronic diseases. These diseases, including mental health disorders, obesity and cardiovascular disease, and substance abuse-related conditions, have a larger negative impact on public health and life expectancy than COVID-19. Unfortunately, these are also the diseases receiving the least amount of venture capital, biotech, and pharma funding and the least number of applications for clinical trials. Going forward, ways of extending the learnings from COVID-19 and scaling them selectively toward these conditions with the largest public health impact to urgently deliver innovative medicines that can address these umet medical needs should be explored. Engagement with senior leadership, acting with a shared sense of urgency, ensuring scientific transparency, using advanced regulatory science tools, and applying regulatory flexibility are some ways in which public health improvement can be accelerated.

Key Learnings During the Development of COVID Therapeutics

- A shared sense of urgency supported scientific transparency and the aggressive application of a risk-based regulatory framework
- Prospective engagement with senior and experienced leaders at both the sponsor and regulatory agencies enabled innovation & speed
- Prioritized and rapid learning cycles along with the use of regulatory science tools and flexibilities (e.g. adaptive trial designs and platform knowledge).
- Healthy debate speeds alignment on plans and risks

Building on regulatory and HTA agilities for high unmet need

Rapid scientific advice and enhanced communication between sponsors and agencies during development: what are the opportunities and what is sustainable?

HTA perspective

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

The unprecedented levels of unmet public health needs during the COVID-19 pandemic rightly stimulated an unprecedented response from pharmaceutical companies, regulators, and other agencies. In the UK, the National Institute for Health and Care Excellence (NICE) initiated and coordinated several measures to respond to the health emergency.

RAPID-C19 initiative

NICE initiated the RAPID-C19 programme to facilitate coordination with all the UK system partners across the 'research to access pathway' for innovative drugs. The initiative managed to:

- Actively pull drugs from trials to the clinical as and when evidence of benefit emerged
- Interface closely with emergency procurement arrangements
- Provide value signals based on emerging clinical evidence

Express scientific advice from NICE

The role of rapid scientific advice in eliciting agile and timely responses cannot be underestimated. Notably, advice from regulators and HTA agencies helped support efficient clinical trial designs and reduced development time and costs.

Joint/parallel scientific advice may be appropriate when two or more agencies are involved in the regulatory process. However, the capacity for HTA scientific advice is limited in some jurisdictions and is resource intensive in cases requiring advice for individual products. Keeping in mind the need of pharmaceutical companies for scientific advice against the challenging timelines, NICE initiated a 12-week-long expedited expert scientific advice service. While retaining the critical components of normal scientific advice, this expedited service was designed to support efficient study designs and save stakeholder resources (money and time). The service included a 3-hour-long virtual meeting, a detailed standalone report, and feedback on the company's development plan from a panel of experts—including patients, HTA, and clinical and health economics specialists.

During the COVID-19 pandemic, this service was expedited to deliver advice within 6 to 8 weeks. As opposed to the normal practice of relying on external experts, NICE employed internal expertise to facilitate the delivery of express 'plus' scientific advice.

Potential developments in HTA scientific advice

As mentioned earlier, scientific advice is absolutely essential. Yet as noted, the capacity and efficiency of advisory services are limited in some jurisdictions. Capacity constraints can be managed by building a 'pay for service' model, which can also help the agency grow much-needed resources without depending on government finances. Moreover, shifting the focus from advice on specific products to advice on key disease areas (like agreement on core outcome sets, qualification of surrogate endpoints, and validation of core health economics models) can help surpass the challenge of limited resources and improve efficiency. Additionally, international coordination on these activities via, for example, HTAi and the International Society for Health Economics and Outcomes Research (ISPOR) can ensure added value to the global business of developing innovative medicines.

Managed access

Sponsors and agencies also face the challenge of providing patients access to promising new medicines while the evidence is still emerging. Ensuring the cost-effectiveness of these programs is

an added consideration. In this regard, managed access agreements (MAAs) have been developed to improve patient access and achieve equitable sharing of risk across stakeholders. These agreements are time-limited and are aimed at facilitating timely patient access to promising new drugs.
Some other initiatives to improve patient access include:

- Innovative pricing and reimbursement models that help in getting innovative products to patients in a timely way
- Increased emphasis on 'recommended with research' type recommendations in HTA/Payer decision frameworks
- Allowing 'real world' data collection after authorisation to reduce uncertainties with time

In England, NICE and NHS England collaborate in running the reformed Cancer Drugs Fund (since 2016) and Innovative Medicines Fund (since 2022).

The two funds operate in a similar way. The introduction of the Innovative Medicines Fund was aimed at creating an equal opportunity for access to both patients with cancer and other conditions. The two funds target promising medicines that are plausibly cost effective, where uncertainty is too high for a recommendation for routine commissioning and where the uncertainty can be resolved through a period of further evidence development while in managed access.

Developments at NICE
The pandemic has reinforced the need for early and financially sustainable patient access to promising new medicines. NICE is committed to working on new models for improving patient access and optimising the UK Innovative and Licensing and Access Pathway (ILAP). NICE has also established a NICE HTA innovation Laboratory (HTA Lab) to address complex HTA issues. The first project is to develop a framework for rapid entry to the managed access programs. Based on the experience of express scientific advice services during COVID-19, NICE is also developing a new service for cost-effectiveness modelling.

Innovative trial designs & conduct of clinical trials during the COVID-19 pandemic

Facilitating innovative trial designs and conduct of clinical trials during the COVID-19 pandemic: what were the enabling activities and key areas that could be routinely considered for all medicines?

Regulatory agency perspective
Leonoor Wijnans, *Senior Clinical Assessor, Medicines Evaluation Board, The Netherlands*

Through its nature, a pandemic is dynamic with many factors which may affect clinical trials and the drugs being tested in these trials are continuously changing. In a conventional trial this may introduce bias and lead to complexity in the interpretation of results. Additionally, there is a higher risk of trials failing, which was especially seen in the earlier phases of the pandemic where many clinical trials were initiated with limited knowledge on relevant endpoints, anticipated effects on these endpoints and a very dynamic incidence of endpoints in the population. Not all of the trials survived. Many of them were underpowered or halted recruitment.

So called 'complex clinical trials' – platform trials with adaptive features – have played an important role in providing evidence on what works and what does not work in the treatment for COVID-19. Complex trials may have the flexibility to overcome the limitations of smaller more conventional trial designs in a pandemic setting. However, complex trials also come with other challenges, for example through the use of a shared control group, contemporaneous randomisation to multiple treatments, changes in standard of care introduced at varying timepoints due to amongst others shortage of supply, adaptations to the randomisation ratio to name a few. Further, the open label nature of some platform trials forms a real concern – but even when there is (partial) blinding this may vary and decrease over time as information accumulates over potential treatment effects.

Nonetheless, such trials were important for the regulatory approval of two COVID-19 therapeutics in Europe.

Veklury (remdesivir)

- Several trials were initiated for Veklury; however, the data obtained from these trials remained non-comprehensive as they were underpowered, lacked a relevant control arm or were open label, which was not compatible with subjective primary endpoints.
- The pivotal evidence supporting licensing of Veklury in Europe was obtained from the Adaptive COVID-19 Treatment Trial. Whilst only top-line data were available for assessment, it was concluded that the study provided compelling evidence of a clinically relevant impact on time to recovery in patients with "severe disease".
- The trials could not provide conclusive evidence regarding the effect on disease duration and virological effects and also failed to replicate the~~ir~~ findings.

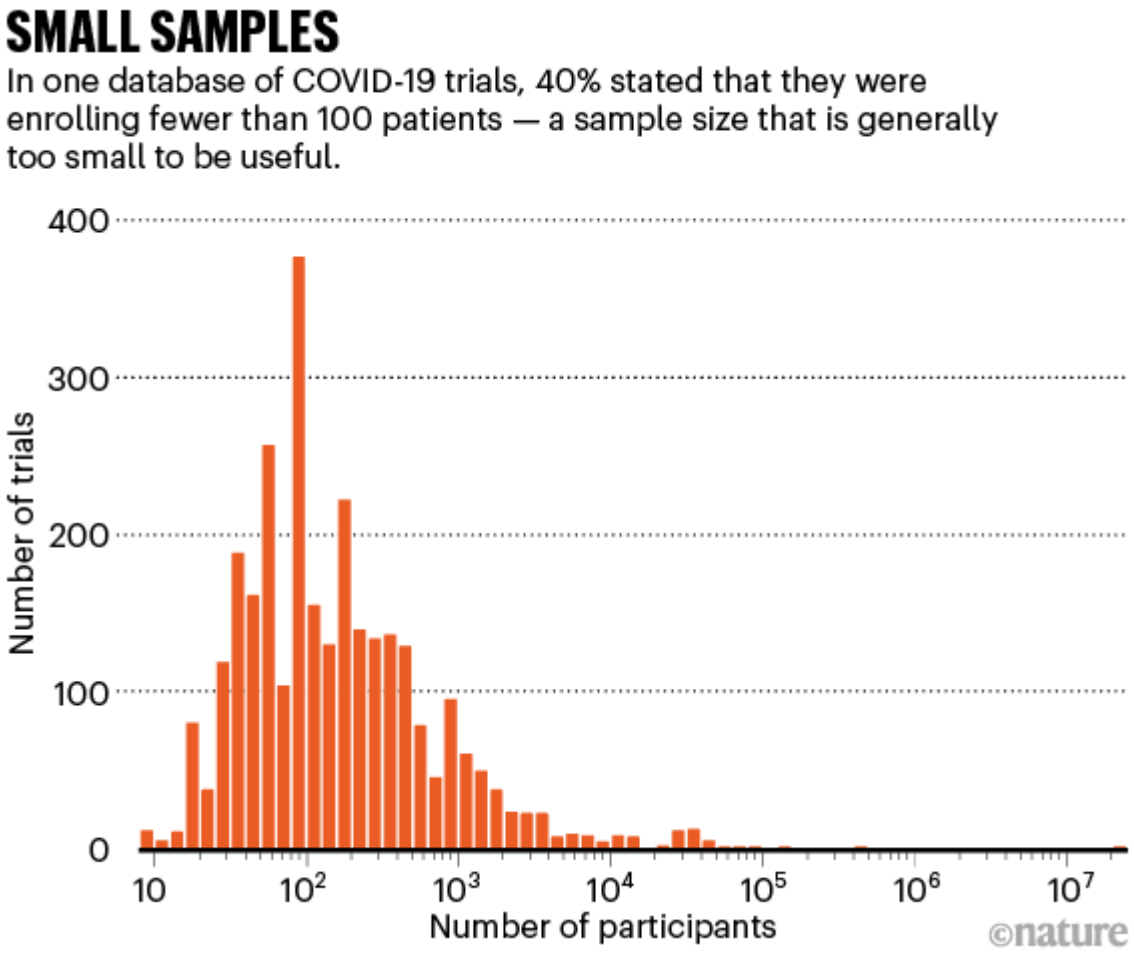
RoActemra (tocilizumab)

- Several trials were initiated which evaluated tocilizumab in severe COVID-19 (Covacta, Empacta, Remdacta); these failed to deliver conclusive and compelling evidence..
- Toculizumab was also evaluated in the RECOVERY platform trial where a significant impact on mortality was seen. This evidence was instrumental for the EU regulatory evaluation of toculizumab

- The RECOVERY trial (Randomised Evaluation of COVID-19 Therapy) was an international, randomised, controlled platform trial evaluating a range of possible treatments for COVID-19 in hospitalised patients.
- The RECOVERY trial recruited a large sample size and identified clinically relevant endpoints, which helped in generating compelling results.
- Concurrent controls were also used in these trials.

Conclusion

Complex clinical trials, like RECOVERY played a decisive role in providing evidence to support the authorisation and licensing of COVID-19 medicines. They continue to generate evidence more efficiently for COVID-19 treatments. Learning from the lessons during the pandemic, the EMA Emergency Task force has steered towards large clinical trials. Early engagement with regulators is highly recommended for any complex clinical trials and available for any sponsor, including academia and those acting as co-sponsors. Moreover, the Accelerating Clinical Trials in the EU (ACT EU) programme has been developed to address the need for increased cooperation and transparency around clinical trials and their approval in Europe.



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Impact of COVID-19 trial protocols on the future of drug development

Facilitating innovative trial designs and conduct of clinical trials during the COVID-19 pandemic: what were the enabling activities and key areas that could be routinely considered for all medicines?

HTA perspective

Dr Herbert Pang, *Expert Statistical Scientist, Genentech/Roche, USA*

Learnings from Roche trials during the COVID-19 pandemic

Needless to say, COVID-19 impacted the conduct of clinical trials. Based on the experience of trials conducted by Roche, the following aspects pertaining to trial data were identified to be crucial for trial monitoring and filing:

- Clean and high-quality critical data
- Good quality data assessments
- Monitoring of trial sites
- Assessing the impact of COVID-19

Trials with continuous endpoints

COVID-19 also emphasised the need to design trials with continuous endpoints and factor 'pandemic-related intercurrent events' in these trials. Roche introduced these changes with a 'hypothetical treatment strategy' in its Phase III trials. While the original analysis plan with the primary endpoint was retained, a hypothetical strategy was introduced for pandemic-related events.

Increasing use of real-world evidence in trials

The Pharmaceutical Research and Manufacturers of America (PhRMA) 2021 letter emphasised the need to incorporate real-world evidence based on the learnings from COVID-19. Sources such as natural history studies, registries, real-world evidence models, and real-world data are opportunities for generating this evidence. Incorporating real-world evidence in clinical trials also requires good trial designs.

An ongoing Roche project funded by the FDA under the NIH UO1 mechanism can exemplify the use of real-world evidence in trial designs. The project incorporated a 'hybrid control design', wherein the control arm was supplemented with external controls. This saved the recruited patients from being randomised to the internal control arm of a typical RCT, increasing their chances of being assigned to the treatment arm.

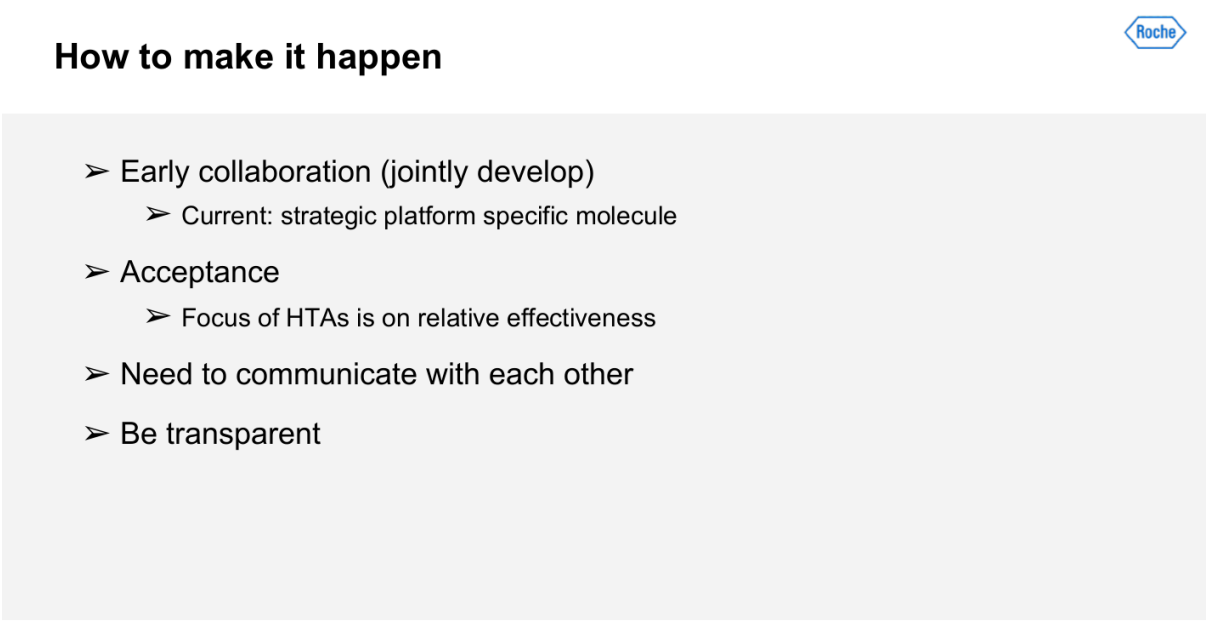
In practice, dynamic borrowing, pooling, and test-and-pool strategies are some of the approaches that allow this adaptive down-weighting of external control information.

Promoting decentralised clinical trial approaches

The PhRMA 2021 letter also emphasised the importance of decentralised trials (DCTs), which represent a unique opportunity within the trial design spectrum. Unlike traditional trials, these can be conducted on virtual platforms or even at virtual sites. This evolution in trial design presents an opportunity for selecting a treatment-appropriate design, which can also retain the integrity and comparability of data.

To ensure pragmatism in such trial designs, it is important to consider including innovative data sources and data management tools such as electronic patient reported outcomes. Moreover, fulfilment of the regulatory requirements must be ascertained to ensure the sustainability of remote data collection tools.

Incorporating these changes requires early collaboration with all the stakeholders and engaging in transparent and multistakeholder communications to resolve potential issues.



Improvements in the process of drug registration

Accelerating the registration of new medicines: what are the learnings and would be of value to implement for high unmet need medicines beyond COVID-19 treatments

Regulatory agency perspective (part 1)

Dr Junko Sato, *Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*

Experiences during the COVID-19 pandemic provided some crucial lessons to the Pharmaceuticals and Medical Devices Agency (PMDA). Some prominent outcomes were special approvals for emergency (SAEs), the use of emergency marketing approvals, the acceleration of COVID-19-related product development and authorizations, the maintenance of ongoing clinical trials and product reviews, and the utilisation of real-world data (RWD).

SAEs

Under Article 14-3 of the Pharmaceutical and Medical Device Act (PMD Act), a certain medical product may be approved when:

1. An emergency situation requires an unapproved medical product to be used to prevent any damage to public health caused by disease spread.
2. Such an emergency cannot be managed appropriately by any means other than the use of the unapproved product.
3. The product is legally available in a country with a regulatory system for medical products that is equivalent to Japan's.

In the case of COVID-19, the scope of SAEs was expanded to (i) include drugs for COVID-19 and (ii) add the USA to the list of countries with a regulatory system for medical products that is equivalent to Japan's. The cabinet order was amended on 2nd May 2020 in prompt response to the emergency use authorisation (EUA) of remdesivir by the U.S. FDA on 1st May 2020.

On 4th May, Gilead Sciences put forth a regulatory submission, and PMDA prepared the report of available information and approval conditions. After three days of discussions by the Pharmaceutical Affairs and Food Sanitation Council of the Ministry of Health, Labour and Welfare (MHLW), the SAE of remdesivir was granted on 7th May 2020 with several conditions such as:

- Requirement of written informed consent prior to administration
- Implementation of a risk management plan
- Submission of the results of additional clinical trials as soon as possible, latest by 9 months
- Surveillance/registry of all patients treated during the designated period

Marketing approval in emergencies

The PMD Act was passed on 13th May 2022 and became effective on 20th May 2022. The aim of amending the act was to enable a mechanism of early approval. Conditional, time-limited marketing approval could be granted in emergencies if the efficacy of the pharmaceutical, medical device, or regenerative medicine has been estimated and its safety confirmed. A secondary aim was to enact a mechanism of electronic prescriptions.

Eligibility of pharmaceuticals for early approval

A pharmaceutical that needs to be used urgently in order to prevent the spread of a disease or other health hazards that could seriously affect the lives and health of people is eligible for early approval if there is no alternative existing treatment.

Application standards

Assuming that safety has been confirmed, approval may be granted if the efficacy of the pharmaceutical has been estimated.

Conditions and terms of approval

As approval is granted at the early stage where efficacy has been estimated, conditions are provided to ensure the proper use of the pharmaceutical, with restrictions that limit the duration of the approval to a short term.

Special measures to expedite the review process

Special measures are introduced for good manufacturing practice (GMP) inspections, national verifications, as well as regulations on containers and packaging in order to expedite the review process for approval.

Evaluating vaccines against SARS-CoV-2

To ensure the efficacy and safety of vaccines used in Japan and accelerate vaccine development, the first guidance was issued on 2nd September 2020, summarizing principles for the evaluation of non-clinical and clinical study data required for the initiation of a clinical study and application for approval.

Appendix 1 issued on 5th April 2021 presented an evaluation of the efficacy and safety of vaccines against variants detected in Japan, based on current knowledge and overseas guidance on variant vaccine development. Appendix 2 issued on 11th June 2021 covered the ethical considerations for subjects in placebo-controlled clinical trials once the Official Vaccination Program in Japan was initiated.

Appendix 3, issued on 22nd October 2021, stated the principles for the immunogenicity-based evaluation of vaccines against the novel coronavirus. It presented principles for the design of confirmatory clinical trials to evaluate the efficacy of new vaccines against SARS-CoV-2 in unvaccinated subjects on the basis of immunogenicity in accordance with the International Coalition of Medicines Regulatory Authorities (ICMRA) consensus from an ethical viewpoint since official vaccination programs had progressed worldwide, making it increasingly difficult to evaluate preventive effects of vaccines on the basis of clinical events (onset, etc.) in placebo-controlled trials.

Utilisation of registry data

Guidelines were developed on the utilisation of real-world registry data for the following cases:

1. Utilisation of registry data as an external control for clinical studies of efficacy and/or safety evaluation
2. Utilisation of registry data as a complement or substitute to clinical studies of efficacy and/or safety evaluation
3. Utilisation of registry data in the evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional time-limited approval
4. Utilisation of registry data for post-marketing efficacy and/or safety evaluation

Collaboration with ICMRA

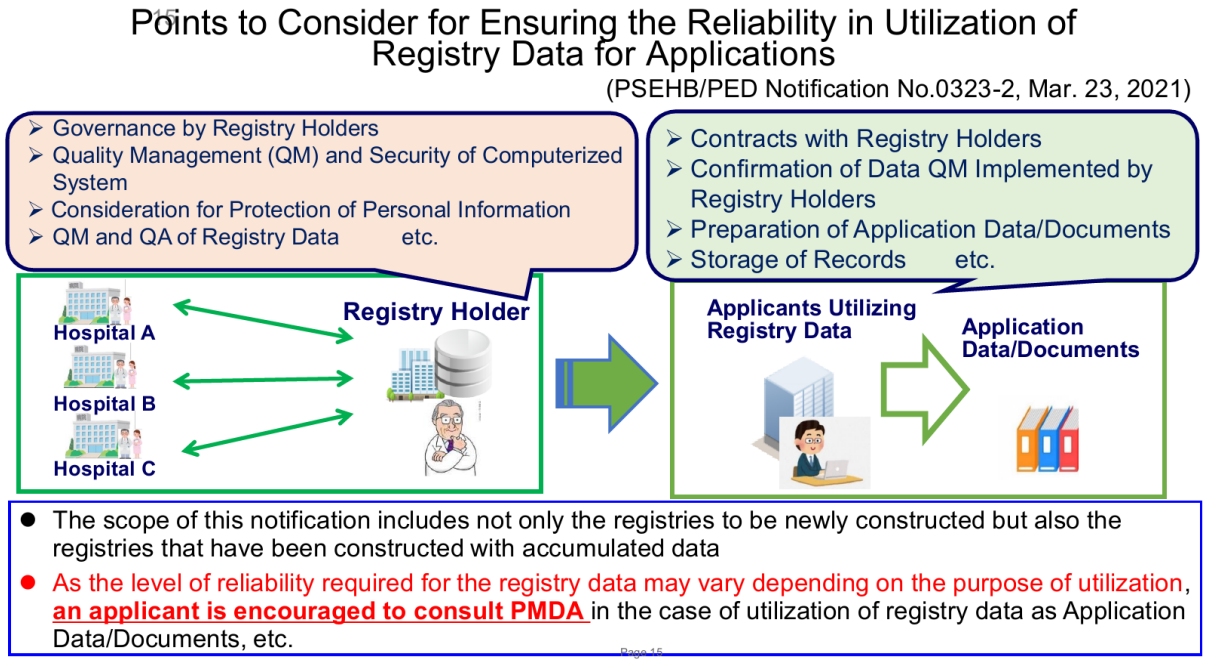
ICMRA is a voluntary, executive-level, strategic coordinating, advocacy, and leadership entity consisting of 39 international regulatory authorities. ICMRA helped many countries and regions begin remote inspections. As a result, a pilot project for hybrid (on-site/remote) inspections of post-approval changes is now under consideration.

ICMRA workshops

1. Global regulatory workshop on COVID-19 vaccine development
2. Global regulatory workshop on COVID-19 therapeutic development
3. Global regulatory workshop on COVID-19 Real-World Evidence and Observational Studies
4. Vaccine Safety Collaboration Workshop
5. Pregnancy and Lactation Workshop
6. ICMRA-Industry Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic
7. COVID-19 Virus Variants Workshop

Collaboration with Asian countries

The Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) in Japan invites Asian regulatory representatives from across the continent and offers training seminars to share Japan's knowledge and experiences with other countries. The action policy of the PMDA-ATC is to contribute to universal health coverage in Asia by developing a foundation for regulatory harmonisation in the Asian region. Such collaboration promotes capacity building and human resource development.



Regulatory agility during the COVID-19 pandemic

Accelerating the registration of new medicines: what are the learnings and would be of value to implement for high unmet need medicines beyond COVID-19 treatments

Regulatory agency perspective (part 2)

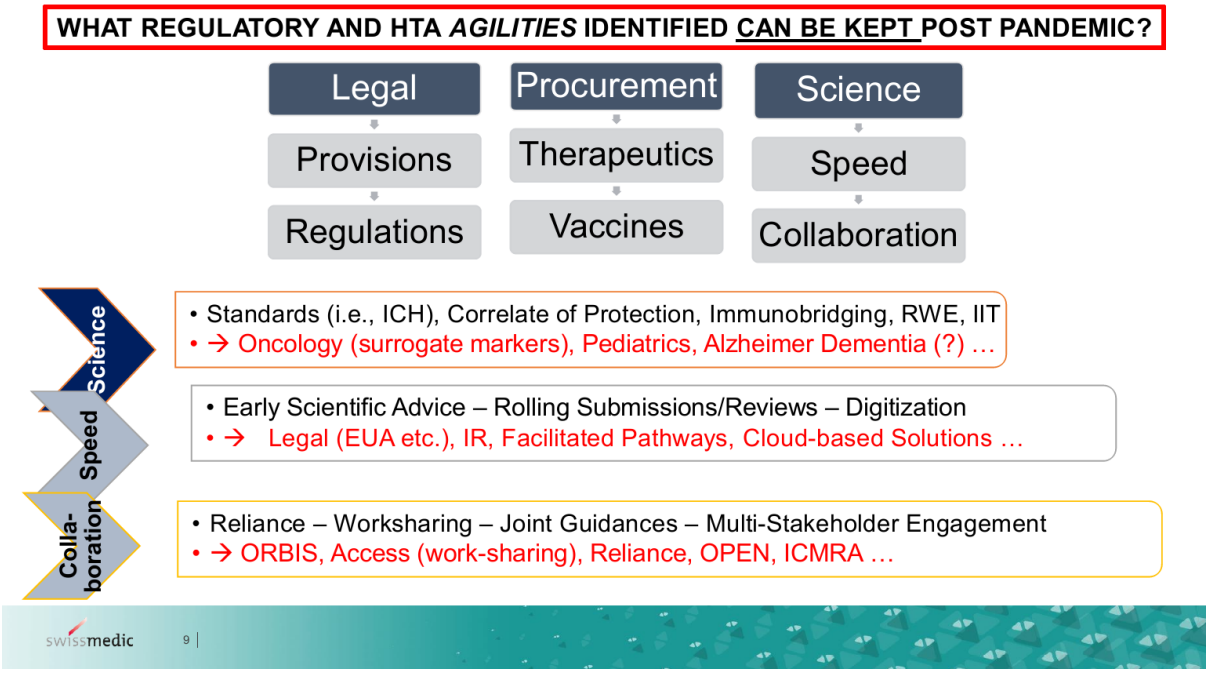
Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic*

Regulatory agility is an essential aspect of every healthcare system's emergency response. During COVID-19, regulators were challenged to evaluate diagnostics and medical interventions with limited evidence of benefits weighed against contextual risks, while simultaneously keeping track of their quality, safety, efficacy, and performance as further data became available.

Regulatory agility depends upon speed and collaboration, the procurement of therapeutics and vaccines, and legal aspects like provisions and regulations. Science is the foundation upon which regulators jointly develop guidelines and technical requirements. Given the high uncertainty of the pandemic, regulators took a risk-based approach to ensure that diagnostics and medical interventions were effective despite constraints on time, data, and evidence. A high emphasis on speed provoked public anxieties about the safety and effectiveness of vaccines [1]. Decisions to grant line extensions or Type--two variations were made based on observational data, and a single publication that explored the extent that different platform vaccines could be mixed and matched was the basis that regulators used to approve the Novavax protein-based vaccine as a booster.

International collaborations amongst research groups, federal agencies, and the industry helped overcome supply chain issues, manufacturing issues, and aspects such as good manufacturing practice (GMP) and good storage practice (GSP). Collaborations during this time shifted the operating mode for regulatory bodies through early scientific advice, pre-submission meetings, rolling reviews, and rolling submissions. These collaborations were facilitated by third-party advisory groups so that the regulatory bodies involved could remain independent and objective. Multi-national collaborations such as the European Medicines Agency (EMA) OPEN Project for COVID-19 vaccines and therapeutics development, Project Orbis in the space of oncology, and Access Consortium promoted work sharing and simultaneous reviews.
There were also legal aspects that facilitated regulatory agility. To facilitate drug development and expedite market authorisation, emergency use pathways (EUPs) were issued by seven major regulatory bodies and the WHO. A briefing document highlighted the pathways that expedite drug development, review, or assessment processes for ease of access [2].

What regulatory activities should be kept post COVID-19?
Digitisation, cloud-based solutions, mobile tools, and video technologies helped speed up product development as well as the (rolling) regulatory review during the health crisis. Decentralised clinical trials, hybrid study approaches, increased use of telemedicine, use of digital tools in development to measure endpoints, and direct shipment of study medicines to patient homes were some operational efficiencies that worked well for contract research organisations (CROs) and research-based companies and will be carried forward into the "new normal" [3].



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Securing the future of agile drug regulation

Accelerating the registration of new medicines: what are the learnings and would be of value to implement for high unmet need medicines beyond COVID-19 treatments

Industry perspective

Jerry Stewart, *VP, Global Regulatory Policy and Intelligence, Pfizer, USA*

We have seen remarkable regulatory and industry flexibility and expediency with the COVID-19 crisis, resulting in a transformation in the global regulation of medicine and vaccines. These adjustments can drive breakthroughs globally for years to come. How may we now future-proof the regulatory system for the benefit of patients?

Pfizer has categorised this opportunity into three buckets: (i) building digitally resilient clinical trial systems; (ii) enhancing platforms for secure data sharing to enable collaboration, work sharing, and reliance; and (iii) appropriately streamlining the development and review of other severely debilitating and life-threatening conditions.

In emerging market regions such as most of Asia, Latin America, and Africa, there were no digital technologies to replicate the advances being made in the USA, Europe, and certain parts of Asia. Even still, the regulators in these regions were able to employ adaptability despite limited resources [1].

Some positive signals were global collaboration, an increasing use of digital tools and capabilities, and regulator responsiveness. Reliance practices and work sharing among agencies were emphasised as a core requirement. The pandemic showed the value of having new trial approaches and the value of having global data, not just country-specific or regional data. International forums of regulators like the International Coalition of Medicines Regulatory Authorities (ICMRA) played a central role in harmonizing the flexibilities and policies that could expedite decisions. Regulators' responsiveness and speed in issuing practical guidance were remarkable.

Best practices for the efficient implementation of reliance

Requirements: Articulate requirements and formulate a shared understanding of best practices for regulators and the industry that add value and do not negate the aim of reliance

Timelines: Set realistic target timelines

Transparency and trust: Collaboration and dialogue; outline any differences in the dossier when submitted to multiple agencies

Assessment reports: Utilisation of assessment reports; efficiently share reports

Product life cycle: Apply to all stages of the life cycle; not just the beginning or post-approval period

Learnings and innovations from PAXLOVID and COMIRNATY emergency use authorisations (EUAs)

Faster, real-time interactions between sponsors and regulators

Rapid decision making was enabled by protocols and allowed for reviews within days. Investigational New Drug (IND) review times were shortened, and there were sufficient provisions for Clinical Trial Applications (CTA). Further, the delivery of scientific advice in real-time and rolling submissions allowed regulators to view real-time data.

Risk-based pre-clinical safety requirements

PAXLOVID: Regulators accepted the unaudited top-line report (two species) to support first-in-human (FIH) studies, with the final report added to rolling submission.

COMIRNATY: Pfizer leveraged mRNA technology and toxicological data across platforms and disease areas in addition to interim data from ongoing toxicology studies with vaccine candidates to support first-in-human (FIH) studies. The initial EUA submission was supported by preliminary, high-level developmental and reproductive toxicology (DART) results. Instead of the 6 or more months that it takes on average from the initial toxicology studies to FIH, flexibilities allowed for FIH within 39 days from the start of the toxicology studies without compromising on safety.

Chemistry, manufacturing, and controls (CMC) Flexibilities

Pfizer conducted real-time data submission and review for the Center for Biologics Evaluation and Research (CBER), FDA. Batch release with CBER was waived by relying on the management systems that Pfizer and other companies had in place.

Innovative clinical evidence generation

Decentralised trials for PAXLOVID and COMIRNATY were made possible. In PAXLOVID trials across the USA and Europe, Tasso—a novel sampling device—was used, allowing for at-home pharmacokinetic sampling by subjects. This reduced the need for in-person draws. In COMIRNATY trials, there was the option to perform illness visits via telehealth systems in case of potential COVID-19 symptoms, with the participants self-swabbing and shipping the swabs to the site. Both programs utilised a seamless Phase 1, 2, and 3 approach. Digital labelling allowed for timely updates and rapid distribution. In the case of COMIRNATY, real-world evidence was used with FDA knowledge to authorise the third primary series and then also the booster for individuals between 12 and 15 years of age.

Regulatory flexibility and waivers

Pfizer observed instances of the acceptance of local clinical data and bridging data, particularly overseas. In Korea, conditional approval was granted with a commitment to conduct an immune-bridging study within approximately 2 years of approval. In India, post-approval bridging clinical trial (COMIRNATY) & local release testing were waived for COVID-19 vaccines that were already approved by the US FDA, European Medicines Agency (EMA), UK Medicines and Healthcare products Regulatory Agency (MHRA), Pharmaceuticals and Medical Devices Agency (PMDA) Japan or were listed in the WHO Emergency Use Listing Procedure.

Other waivers include a single product license for multiple sites, lot summary protocols and National Regulatory Authority (NRA) batch release, country-specific annexe for risk management plans (RPMs), certificate of Pharmaceutical Product, and raw material Certificate of Analysis (CoA).

Documentation and labelling requirements

Additionally, regarding documentation and administrative steps and labelling requirements, there were a number of flexibilities in the emerging markets around some administrative-type documents.

Pfizer successfully negotiated to submit a softcopy of good manufacturing practice (GMP) certificates for COMIRNATY in Vietnam, with the justification that they are available on the Eudra GMP/FDA website. Although the country-specific requirements in Vietnam include a signed and stamped copy of specifications and stability data, they were waived for COMIRNATY.

Compromises were made with Board of Health in terms of artwork and labelling to accept USA and Europe packs as is, since country-specific packs were not possible due to the pandemic supply state. E-labelling was encouraged to avoid physical leaflets accompanying shipments. No redressing was required for the initial launch.

A call to action: next steps

We must start by identifying diseases that would benefit from this sense of urgency and a unified effort grounded in risk-based principles. It would be beneficial to have global and transparent guidance not only on identifying these diseases but on how to develop treatments for them. The first steps would be pre-clinical and clinical assessments and manufacturing approaches informed by therapeutic context. A challenge that can come up is capacity. If regulators don't have the resources or capabilities, the challenge is how to harmonise and standardise reliance practices for those health authorities. Finally, outline international best practices to harmonise the risk-based expedited pathways in those areas for health authorities that have the capabilities to run such types of risk-based reviews [2].

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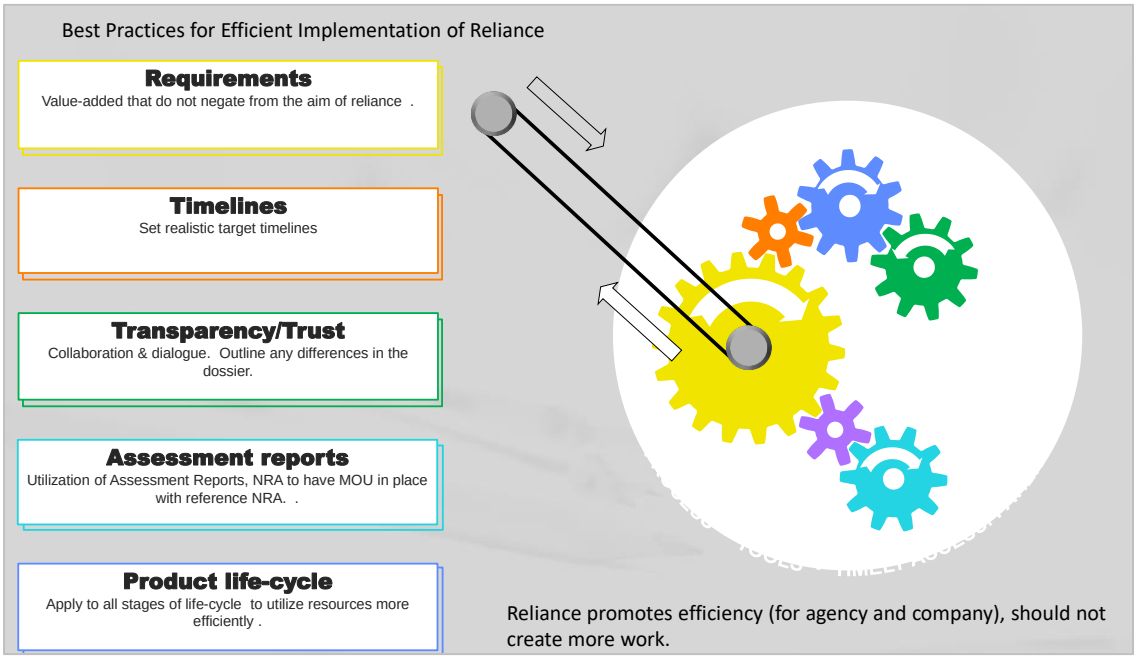


Fortifying the regulatory system for medicine development

Strengthening regulatory systems for the development and review of medicines: What future changes are being considered

EMA Perspective

Steffen Thirstrup, *Chief Medical Officer, EMA*

COVID-19 has been a game changer for the regulatory world globally. In terms of regulatory innovation in practice, the European Medicines Agency (EMA) has approved six vaccines and eight therapeutics, rolled out in record time across its 27 member states. Recently, EMA approved the first batch of adapted bivalent vaccines and is continuously working on keeping the shelf times up to date for those vaccines. In response to the crisis, a new EU authority—the Health Emergency Preparedness and Response Authority (HERA)—was established at the level of the European Commission, and EMA was given an extended mandate for crisis preparedness and shortage monitoring.

The pandemic has also been a "super catalyst" for change in the regulatory landscape. There is a need to support rapid research and development activities in response to emerging health threats. Then, there is the question of whether rapid review and authorisation can be applied to selected products in the future. The need for close safety and effectiveness monitoring gave rise to lessons in the area of pharmacovigilance and the use of real-world data to optimise signal detection, assess potential signals, and also intervene if needed. There is a need to maximise the global supply of products, and to increase transparency and proactive communication and foster new approaches to counter misinformation. Finally, the need to engage in harmonised regulatory action globally is being met by working closely with the chair of the International Coalition of Medicines Regulatory Authorities (ICMRA).

Strengthening clinical trials in the EU

The Accelerating Clinical Trials in the EU (ACT EU) initiative was recently launched with the objective of transforming the EU clinical trial environment in support of medical innovation and better patient outcomes.

Some key outputs in 2022 have included publications and workshops on complex clinical trials and decentralised clinical trials, as well as EMA's 2022–2026 workplan publication, which aims not only to implement the clinical trial regulations but also to create a multi-stakeholder platform and have cross-European discussions. A training curriculum for member states and stakeholders is also on the agenda.

Real-world data (RWD), real-world evidence (RWE), and big data

The vision for big data is ultimately its use to strengthen the regulatory system. The goal is to integrate RWD analysis effectively into assessment processes and improve decision making based on novel technologies and evidence from big data. This will bring several benefits to public health, including accelerated medicine development, improved treatment outcomes, and quicker patient access to new treatments.

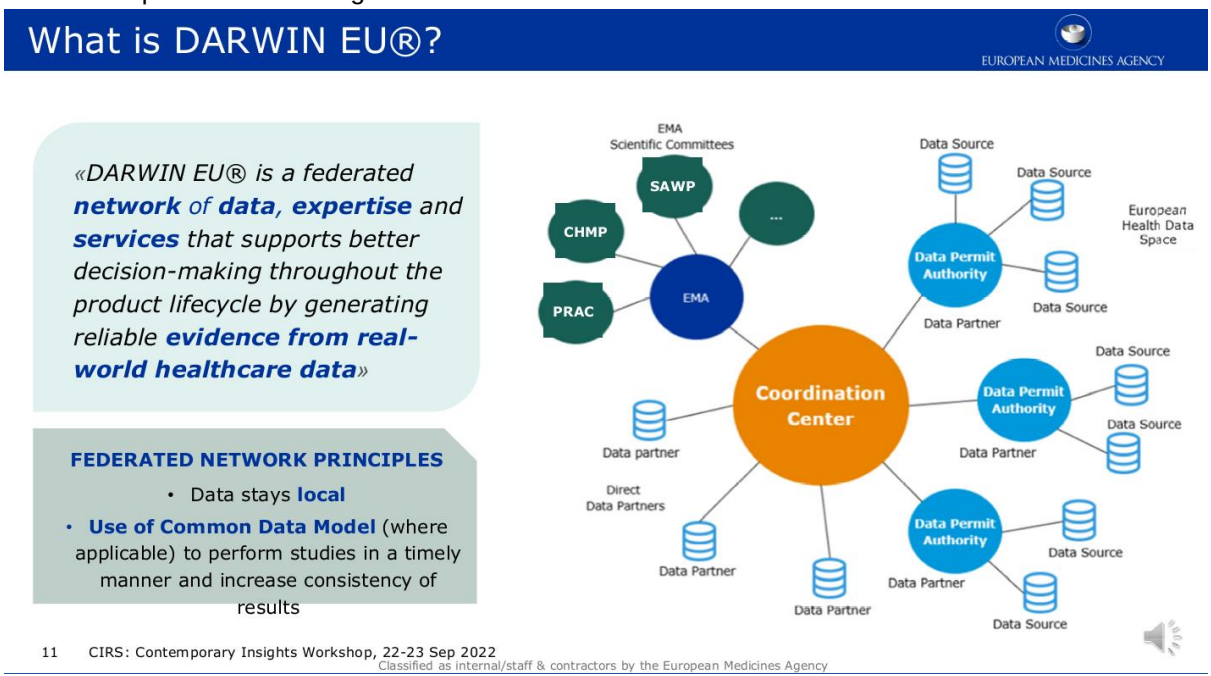
One important recommendation of the joint HMA-EMA Big Data (BDSG) workplan 2022–2025 is the establishment of the Data Analysis and Real-World Interrogation Network (DARWIN EU)—a federated network of data, expertise, and services that supports better decision making throughout the product life cycle by generating reliable evidence from real-world healthcare data. DARWIN EU will bring benefits not only to EU medicine regulators in terms of drug development, authorisation, and post-authorisation, but also to patients, healthcare professionals, the European Commission, national competent authorities, health technology assessment (HTA) bodies and payers, EU and international health agencies, academia and research organisations, and the industry. DARWIN EU is set to

increase the capacity to undertake high-quality observational studies based on RWD and reduce the time per study.
The need for new or reinforced collaborations; the effective sharing of data, knowledge, and experience in relation to observational studies; and the need to leverage experience to medicine regulation beyond COVID-19 are some of the opportunities created at this time.
The ICMRA played a central role in catalysing the increased cooperation on the use of RWE for regulatory decision making through a workshop held at the EMA on 29th and 30th June 2022. The outcome of the workshop highlighted four focus areas for regulatory cooperation: (i) harmonisation of terminologies for RWD and RWE; (ii) regulatory convergence on RWD and RWE guidelines and best practices; (iii) readiness to address public health challenges and emerging health threats; and (iv) transparency.
EMA is also in close collaboration with the HTA bodies in a partnership called EUnetHTA-21. EMA's inputs include peer review impact reports from the International Horizon Scanning Initiative (IHSI), and proactive and on-demand review of the EMA pipeline for issues concerning EUnetHTA-21.

Future directions for the EMA

The EMA has extended a mandate establishing the Emergency Task Force. The medicine shortage steering group is dealing with medicine shortages—not only shortages related to COVID-19 and monkeypox, but shortages in every therapeutic area during public health crises.

It is also important to consider how to implement a rolling review of the phased assessment of selected products in the future. The challenge is not to overburden the assessors and the network since rolling reviews can be more labour-intensive. The extended use of RWD and RWE is being considered beyond pharmacovigilance. International collaboration is also being extended, particularly via the ICMRA.
Overall, the EMA wishes to improve the clinical trial climate in Europe with the ACT EU having a broader focus than clinical trial regulation and implementation. Enhanced collaboration with EUnetHTA-21 will improve health technology assessment. And finally, the EMA foresees the revision of the EU's pharmaceutical legislation.



Building on regulatory and HTA agilities for high unmet need

Strengthening regulatory systems for the development and review of medicines: What future changes are being considered

FDA perspective

Dr Mary Thanh Hai, *Deputy Director for Clinical, Office of New Drugs, CDER, FDA, USA*

The Prescription Drug User Fee Act (PDUFA) is a legislation from Congress that authorises the FDA to collect user fees from companies that produce certain human drugs and biological products. Requiring reauthorisation every 5 years, the current legislative authority PDUFA VI (FDARA) expires on 30th September 2022.

Prior to reauthorisation by Congress, FDA and industry members negotiated user fee agreements (UFAs). While most commitments are continuing with little to no change, new commitments are being negotiated to improve the efficiency of the drug review process and bring in additional resources to enable successful implementation.

Performance commitments and fee funding

The PDUFA has significantly modernised its user fee structure since it was established in 1993. It is now focused on improving financial management and has created a significant capacity planning capability. Risk–benefit assessments have enabled the enhanced use of regulatory tools towards patient-focused drug development, complex innovative trial designs and model-informed drug development. The potential for real-world evidence (RWE) in regulatory decision making was explored, with a focus on communication with the industry, and increased staffing dedicated towards breakthrough therapy reviews was seen.

Themes and industry discussions

The FDA–Industry discussions leading up to PDUFA VII on 1st October 2022 spanned different themes across various teams. The Center for Biologics Evaluation and Research (CBER) will have an enhanced capacity to guide development and review innovative products for cell and gene therapy. The pre-market group will introduce new approaches to improve efficiency and expand communication in the Human Drugs Review program.

The FDA is continuing the application of innovative methods and tools to enhance regulatory decision making that will encourage patient-focused drug development. There was a heavy focus on facilitating manufacturing readiness during COVID-19 and the FDA explored the use of innovative manufacturing technologies. Post-marketing was central in the continued enhancement of the drug safety system to ensure the safe use of medicines.

Digital health and informatics are utilizing modern technology and supporting bioinformatics to enhance and streamline drug development and review. Enhancing financial management and transparency is a priority, as is the strategic hiring and retention of world-class technical and scientific staff.

PDUFA VII Pre-market commitments and pilot programs

PDUFA VII will run the Split Real-Time Application Review (STAR) Pilot Program, the Rare Disease Endpoint Advancement (RDEA) Pilot Program, and the Advancing Real-World Evidence (RWE) Program.

During the COVID-19 pandemic, two new meeting types were introduced to expand communication and feedback during the drug development process. A further addition to formal meetings was the follow-up opportunity for sponsors to submit clarifying questions after meetings or written responses to ensure the sponsor's understanding of FDA feedback. Such new processes, timelines, and performance goals for the pre-approval review of post-marketing requirements (PMRs) were aimed at ensuring the timely availability of information on the safety and efficacy of therapies. The pre-market group included the human factors and use-related risk analyses (URRAs) review.

Split Real-Time Application Review (STAR)

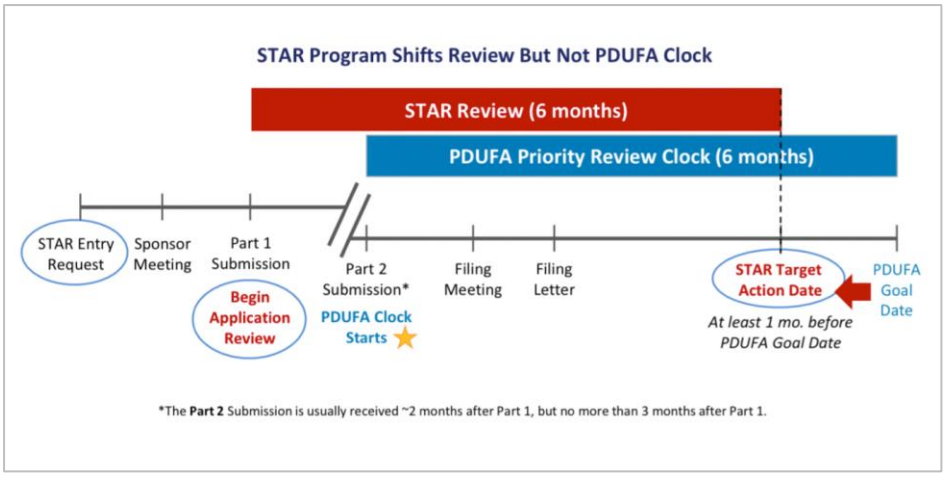
STAR is a new pilot program for certain efficacy supplements in any therapeutic area that seeks to expedite patient access to novel uses for existing therapies. It supports the initiation of review earlier than would otherwise occur and therefore potentially allows for earlier approval.

Eligibility criteria: The application is for a drug intended to treat a serious condition with an unmet medical need. To be eligible, applicants must demonstrate clinical evidence from adequate and well-controlled investigations that indicate that the drug may demonstrate substantial improvement for one or more clinically relevant endpoints over other therapies. No aspect of the submission should be likely to require a longer review time, and there should be no chemistry, manufacturing, and control (CMC) information that will require a foreign manufacturing site inspection.

Determination process: Applicant can request the consideration of an upcoming efficacy supplement to be reviewed under STAR pilot by providing the FDA with top-line trial results and proposed labelling via a (i) stand-alone STAR teleconference or (ii) type B pre-sNDA/sBLA meeting

Submission and review timeline: If accepted into the STAR pilot, the applicant agrees to provide the complete application in two parts:

- Part 1 contains all components of the new drug application (NDA)/biologic license application (BLA) efficacy supplement (except for the final clinical study reports and the electronic common technical document [eCTD] module 2 clinical summaries) and a document providing top-line results
- Part 2 contains the final clinical study reports and eCTD module 2



Expedited review: Introduced in PDUFA V and previously applied only to NDA/BLA with priority review designation, it now also applies to an efficacy supplement in the STAR pilot program.

Rare Disease Endpoint Advancement (RDEA)

A new pilot program to advance rare disease drug development by providing a mechanism for sponsor discussions with the FDA throughout the efficacy endpoint development process. RDEA is a joint initiative of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

Eligibility criteria: The associated development program should be active and address a rare disease, with an active investigational new drug (IND) or pre-IND for the rare disease.

Submissions: The FDA will select a limited number of qualified proposals for admission into the RDEA

- FY 2023: Sponsors may submit proposals beginning in Q4, and the FDA will accept a maximum of 1 proposal
- FY 2024 –FY2027: FDA will accept up to 1 proposal per quarter with a maximum of 3 proposals per year

Transparency: The FDA will conduct up to three public workshops by the end of FY 2027 to discuss various topics related to endpoint development for rare diseases.

Disclosure element: To promote innovation and evolving science, novel endpoints developed through RDEA may be presented by the FDA, such as in guidance documents, on a public-facing website, or at public workshops as case studies. These will include the period prior to the FDA's approval for the drug studied in the trial.

Advancing Real-World Evidence (RWE) Program

A pilot program that seeks to improve the quality and acceptability of RWE-based approaches to support new intended labelling claims, such as the approval of new indications of approved medical products, or to satisfy post-approval study requirements. The program includes annual reporting on pilot submissions, a public workshop or meeting, and updates to existing RWE-related guidance.

Impacts of agile regulatory pathways from a Canadian perspective

What are the implications of an increasing agile regulatory pathway for HTA and Payer decision making?

HTA agency perspective
Suzanne McGurn, *CEO, CADTH*

Lessons learned
During COVID-19, there needed to be a high level of communication between the industry and regulators, the value proposition of having a dialogue with the industry and harnessing data and information earlier to accelerate the overall time required for getting products into the market was critical. A lot of thoughtful work had already been being contemplated by the Canadian regulator prior to COVID and they were able to rapidly adapt to make the regulatory environment more agile and responsive. However there were important learnings about the need to cascade more clearly changes that were being made to other parts of the system (e.g.,HTA, payors), not just with the industry. There is also an opportunity going forward to continue to find new sustainable ways to work collaboratively on the communication and relationships between industry, regulators and other parts of the pharmaceutical access process. Finally there were learnings about the risks and benefits of accelerated procurements, which were necessary during a period of high pubic expectation, high health system demand, and often high uncertainty of effectiveness of product. This was not unique to Canada, in some cases governments acquired large quantities of products, perhaps more than they were able to utilize or were appropriate to utilize once additional information became available. On reflection, there is an opportunity to pull the HTA perspective and the payer earlier into these types of procurement processes to ensure alignment along the whole system including those who make the decision about what they are going to fund or how a product will be implemented within a jurisdiction.

Evidence impacts
When interpreting the use and value of globally collected evidence, there has never been an exact threshold. Hence, any change to the perceived standard of admissible evidence—as was the case during the pandemic—must be evaluated for long term implications both for quality and sustainability of process. The Canadian Agency for Drugs and Technologies in Health (CADTH) tried to respond to rolling reviews which are being implemented by some regulators, as well as doing their own living reviews on COVID-related topics. There was value found in these efforts however understanding what, and how to normalize in a non-pandemic world remains an active discussion. . However, some questions remain. Most importantly, is there an overarching value for these acceleration efforts for the primary users of HTA, the payer?

Future directions
As health technology assessment (HTA) bodies, we need to remind ourselves as we are considering how to re-shape our work or organizations about of what are our explicit values? For example, do we value oncology, rare diseases, or Alzheimer's over other conditions? If so, the choices for future activities that stem from priorities should be based on explicit values that make sense to the organization, partner organizations and all stakeholders. Another area of change that has been observed is that as part of the HTA or in follow-up to a reimbursement review we are increasingly being asked to reflect on,or provide guidance on, implementation considerations in a way that we have not before. As an example, in addition to clinical effectiveness and cost-effectiveness which are commonly understood to be part of an HTA assessment, new considerations such as, human resources implications or system readiness (e.g. access to infusion clinics) may need to be included in future work in recognition of a world where we may not have as many health human resources. We need to be very thoughtful about wholistic assessment of new and emerging products, especially given the high-touch healthcare systems demands.

Response of payers to agile regulatory pathways

What are the implications of an increasing agile regulatory pathway for HTA and Payer decision making?

Payer perspective

Jessica Daw, *Vice President, Pharmacy, Sentara Health Plans, USA*

The COVID-19 pandemic offered several challenges for payers. From the perspective of how we make decisions as payers, in the USA, Pharmacy and Therapeutics (P&T) Committees can sit within a Health Plan or the Health Plan can use the pharmacy benefit manager (PBM's) P&T Committee to review the evidence and make a coverage decision. The committee is made up of pharmacists and physicians and varies in size.

The P&T drug evaluation process starts with a pipeline review of the natural history of disease/burden, clinical efficacy, place in therapy, patient outcomes, and competitor identification. Then, the initial review of guidelines, pivotal trials for efficacy, safety, cost/budget impact, and class utilisation is carried out when the drug is FDA approved. Once the drug is reviewed for placement on the formulary, the ongoing decision of coverage is made by considering real-world evidence, additional financial analyses, physician feedback, comparative effectiveness, and utilisation management.

What constitutes meaningful or optimal evidence for review? Budget impact, cost-effectiveness, and comparative effectiveness are important, as are patient-reported outcomes and quality of life. We also depend upon the availability of real-world evidence, physician feedback and input, clinical trials, peer-reviewed literature, systematic reviews, and clinical guidelines.

During COVID-19, very little of this evidence was considered in the payer's decision due to the emergency use authorisations (EUAs) in place for the health crisis. For the first time in the USA, payers did not cover the costs of vaccination—the government did. The costs of administration were still covered by the payers; before 15th March 2021, it cost $28.39 for a single dose and—in series—$16.94 for the initial dose and $28.39 for the final dose. However, after 15th March 2021, the administration cost was $40 for each dose in a series.

These were additional costs to the healthcare system that had to be taken into consideration in the long term. Payers looked to use real-world evidence and post-market data to validate the EUA approval and determine coverage long term. There were some drugs for which the EUA was revoked, like hydroxychloroquine and some monoclonal antibodies. In this fast-moving process, it was helpful to have the FDA ensure an endpoint for every product and vaccine treatment that was approved. The questions that were useful were—Did it get full FDA approval? Should we still be using this medication?

One of the other questions that needed to be addressed was how much evidence was needed for approval. In this case, because it was a public health emergency, there were exceptions being made to make these approvals.

Even though payers make population-level decisions, they still receive individual requests from patients. If there is a fair amount of support in the literature or compendia (such as Micromedex DrugDex, AHFS, Clinical Pharmacology), coverage can be provided to that patient. Again, even though there are pathways where the evidence might not be ideal, coverage is being provided for patients when they need these medications.

It could be helpful to examine what worked in the EUA process during COVID-19 to see which lessons can be applied to accelerated approval. Then, we might need to prioritise some of these accelerated approvals and further support the process with the evidence needed. The pathways we

have within the USA show us that we still provide coverage for patients even if the evidence is not ideal.

Section 3: Breakout discussions

Breakout discussion A

Enhanced communication developed in the pandemic between sponsors and agencies during development: how sustainable are the processes and what should be retained?	
Chair	**Dr Brian O'Rourke**, *Chair, CIRS HTA Steering Committee*
Rapporteur	**Erin Greene**, *Senior Manager, Global Regulatory Policy & Intelligence, Pfizer, USA*

Background

A quick response was expected from regulatory and health technology assessment (HTA) authorities in terms of practices and processes during the COVID-19 pandemic. To communicate more effectively, agility and mindset changes were required on the part of both sponsors and agencies. This was achieved by establishing processes on virtual and other digital mediums to provide guidance on emerging scientific issues. Particularly, the provisioning of scientific evidence, regulatory compliance during the development of vaccines and therapeutics, guidance during clinical trials and evidence generation, and clarification of acceptable endpoints were important expected outcomes.

These enhancements were applied at all levels, from individual developers to the entire industry, including industry trade associations. In the HTA space, agencies such as The National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) performed the rapid publication of summaries and guidelines to convey regulatory requirements and—at the same time—set thresholds for safety and efficacy.

An important aspect of enhanced communication entailed ensuring transparency in knowledge sharing and combating misinformation, which was achieved through open and clear communication, risk management, and prompt decision making. HTA agencies in the UK, Australia, and Canada, as well as organisations like the International Coalition of Medicines Regulatory Authorities (ICMRA), demonstrated these virtues by sharing experiences and best practices.

The values and lessons in enhanced communication could well be extended to other products. Focusing on the experience of the last two years can help identify the drivers for the sustainability of this concept. This breakout session was aimed at understanding and identifying these values, as follows:

- **Discuss what models of communication were utilised during the pandemic to support drug development** and enhance dialogue between sponsors and agencies; what are some of the key learnings that may be referenceable in the future?
- **Identify the areas that need to be embedded for future health emergencies and recommend 2–3 areas** that could be retained for non-health emergency medicines and be more widely utilised in a sustainable manner.
- **What are the challenges and changes that need to be made** to ensure fit-for-purpose systems?

Discussion results

Q1. How would companies and agencies like to see communication between sponsors and agencies during development evolve post the pandemic: what has worked well and what lessons should be considered for utilisation with non-pandemic medicines (e.g., oncology)? Please consider both regulatory and HTA perspectives.

Areas of communication	What worked well?	What did not work well? Can the idea be explored further?
Sponsor-specific scientific evidence	• Broad-based assessment reports • Continued structured conversation • Building in diverse patient voices in development programs • Appropriate use of existing pathways and development of additional pathways	• Inefficient utilisation of some existing pathways • **Multiple sign-offs required** in the Certificate of Pharmaceutical Product (CPP) • Unstructured engagement: **Can be fixed through better pipeline conversations**
Communications	• Rapid, early, and repeated dialogue between drug sponsors and other stakeholders • Personal communication • Involvement of senior management in discussions	• **Proactive thinking** • Inconsistency in terms of initial and actual processes • **Continued use of smart sheets and visual presentations** • Involvement of political leaders in communications • Uncertainty management, especially when some countries remained silent
Transparency	• Transparency in decision making and registration processes	• **Transparency down to all stakeholders**
Guidelines on general requirements	• Broad guidelines	
Evidence generation guidelines	• Using appropriate pathways to support registrations and dialogue on novel areas for all stakeholders • Bite-sized guidance • Leaning on other regulatory guidelines	• Guidance on data, thresholds, and prioritisation • Challenges in some countries regarding Q&A guidance and web standards
Coordinated or collaborative cross-stakeholder communications	• Global harmonisation between stakeholders • Collaboration between international regulators and stakeholders	• **Aligning the consensus on prioritisation**

Role in tackling misinformation	• Transparent communications to the public (patients and other stakeholders)	• **Communicating with the public** • **Combatting the spread of misinformation**
Virtual communications/new work environment	• Broader engagement on virtual mediums • IT requirements	• Face-to-face, informal communications and deep dive sessions still needed • New and rapid ways of internal communications needed

Q2. Of the items identified above that should be retained and used for non-pandemic medicines, what needs to change (activities/frameworks/capacity/prioritisation/therapy areas/collaborations) to ensure that the enhanced communication which has occurred during the pandemic can remain fit for purpose and sustainable post-pandemic? Please consider both regulatory and HTA perspectives.

Areas of communication	What needs to change?
Sponsor-specific scientific evidence	• Replace multiple sign-offs with electronic signatures ○ A mix of structured and unstructured conversations instead of only unstructured engagement
Communications	• Proactive thought
Transparency	• Broadening transparency to all stakeholders
Coordinated or collaborative cross-stakeholder communications	• Consensus and collaboration to refine prioritisation

In summary, several procedures were found to have worked well and contributed to facilitating the development process. The Syndicate recommended extending the use of assessment reports to the review of other types of critical products; using structured pathways for iterative communication amongst stakeholders, especially when contentious or difficult topics arise; ensuring the use of existing facilitated pathways and seeking to develop new pathways in response to specific needs; and ensuring transparency in decision making processes and documenting the outcomes.

Q3. Recommend future research projects for CIRS and other groups to undertake in this area: what should be considered to support the improve current activities? Please identify up to 2–3 recommendations

1. Assess the clinical/surrogate outcomes
   - What is considered meaningful?
   - What is the acceptability among stakeholders?
   - What are the risks and benefits?
2. Identify frameworks for prioritisation
3. Manage uncertainty by using tools for grading and communicating uncertainty

Breakout discussion B

What changes to clinical trial design and conduct during the pandemic could be embedded in future decision making?	
Chair	**Fabio Bisordi,** *Global Head International Regulatory Policy, F.Hoffmann-La Roche, Switzerland*
Rapporteur	**Dr Rebecca Lumsden,** *Head of Regulatory Science & Policy EU/AMEE, Sanofi, UK*

Background

Globally, the COVID-19 pandemic delayed, disrupted, or even halted the conduct of clinical trials. Companies and agencies, on the other hand, were looking at ways to conduct quality trials and utilise research resources. However, a large number of trials were underpowered due to containment measures imposed across the world. The situation necessitated a rethink of the traditional ways of conducting trials.

The pandemic brought forth the development of new ways of conducting clinical trials. Moreover, companies and agencies continuously evaluated ways of improving the development of medicines.

Future drug development could benefit from the application of measures that expedited the development of COVID-19 treatments, across both clinical and regulatory settings. The Modifications, innovations, and improvements in trial population dynamics and patient-centric drug development can be explored further.

Previously identified areas for improvement include:

A. Simplification of trial design: common protocols, control arms, platform and basket trial designs, adaptive methods, and use of embedded or registry-based trials
B. Integration of decentralised approaches: virtual monitoring of clinical trial sites, optimising monitoring capabilities, and virtual clinical follow-up visits
C. Rigorous use of real-world data

Going ahead, can these learnings improve the quality of clinical trials and reduce redundancies? Which areas can help improve the routine conduct of clinical trials? Which of these lessons could be applied to non-COVID-19 treatments?

This syndicate discussion was aimed at addressing these questions. The key objectives outlined for this session were to:

- **Discuss the key areas** in which the conduct and design of clinical trials changed during the pandemic: what worked and what did not?
- **Identify which changes/activities/frameworks should be adopted/embedded** into clinical trial design and conduct such that they enable sustainable change and improve regulatory and HTA decision making.
- **What are the challenges and changes** that need to be made to ensure it is fit for purpose?

Discussion results

Q1. Discuss key areas in which the conduct and design of clinical trials changed during the pandemic; what worked and what did not? Please consider both regulatory and HTA perspectives.

The syndicate identified trial design, conduct, data sources, analysis, population, and role of collaboration during drug development as the key areas for the discussion. While these areas suffered due to the pandemic, the full extent of their impact can only be fully understood when phase 2 or 3 trials are included in dossier submissions.

Clinical trial areas	What worked well?	What did not work well? (Idea could be evolved)	Should this be retained post-pandemic for non-pandemic medicines
Design (use of adaptive designs, basket trials)	Increase in the number of basket studies (e.g., SOLIDARITY, RECOVERY, and PANDEMIC trials)	• Industry studies remained traditional • Many studies were repurposed, lacked design, and were underpowered and overlapping	Yes
Conduct (decentralised, virtual aspects)	Novel approaches like telemedicine, remote monitoring, virtual recruitment, remote sampling, eConsent, and mobile nurses	• Unvalidated technologies • High levels of uncertainty about regulatory acceptability	Yes
Data sources (registry or real-world data utilisation)	Observational studies after post-emergency use authorisation (EUA) were beneficial	• Real-world evidence could not be used for initial B/R discussion or EUA • Could be used to inform clinical trial designs (natural history, secondary databases vs. primary collection)	Yes Rapid sequential observational studies could support the addition of new indications or subpopulations, reduce uncertainties for earlier approvals, and inform research
Analysis (predictive modelling)	-	-	Linked to clinical trial design

Population (diversity of study population, representativeness)	Efforts aimed at ensuring diversity	• Underserved gaps identified
		  ○ Big/diverse populations: noise, slower recruitment, and increased flexibilities from reviewers
		  ○ Smaller populations: cleaner data and potential early approval
			Yes

		• Fundamental conflict between personalised medicines and increased diversity • Different meanings of diversity globally (e.g., E17 versus FDA guidance in US patients)	
Role of collaboration across stakeholders	• Data exchange between regulators • Regulator–sponsor dialogue • Transparency • Increased reliance • Partial alignment on study design and endpoints • Cross-organisation collaboration (e.g., WHO/ICMRA)	• Challenging for HTA/payers • Absence of clinical academics in collaborations • Repurposing of patients in studies	Yes

Q2. Of the items identified above that should be retained and used for non-pandemic medicines, identify what changes/activities/frameworks etc. should be adopted/embedded into clinical trial design and conduct such that they enable a sustainable change.

Clinical trial areas	Aspects to be retained	Challenges in their implementation	Changes required for their use and sustainability
Design	Use of adaptive designs and basket trials	• Lack of acceptance by payors/HTA beyond oncology • Global regulator acceptance • Duplication of studies (risk aversion to dropping randomised controlled trials) • Safety aspects difficult with historical data • Infrastructure to deliver basket studies in pandemic/non-pandemic situations • Willingness of companies to participate	• *Establish earlier joint advice* • *ICH must consider immortal trail designs and a dedicated expert working group (EWG) for validating data quality and source* • *ICMRA must continue high-level dialogue on real-world evidence (RWE) policies*
Conduct	Decentralised, virtual trials Use in wider clinical populations	• Risk aversion mindset • Higher costs • Operational challenges • IT infrastructure • Cross-border studies	• *Earlier advice on decentralised clinical trials from agencies*

		• Ethical acceptability • Perceived as a higher barrier both in companies and HCPs due to a compliance mindset	• *Use novel endpoints and data capture methods* • *Establish proof of data integrity with decentralised clinical trials (DCTs)* • *Develop risk-based approaches to deliver DCTs based on insights from contract research organisations (CRO)*
Data sources	Acceptance of RWE for informed decision making (encompassing both safety and efficacy data)	• Acceptance of registry-based randomised trials • Acceptability of efficacy/safety from registry studies; registry-based randomised trial. • Next step – non-randomised registry studies to demonstrate efficacy • Case studies needed – libraries, methodologies – ultimate novel endpoints • Strengthen existing databases – aligning data standards both nationally and internationally, e.g., Big Data TF, Critical Path, HTL7/HL7/Phire, CDISC	• *Conduct non-randomised registry studies to demonstrate their efficacy* • *Case studies needed to establish acceptance* • *Existing collaborations – data quality,* • *FDA – Oncology Center for RWE, Digital Health CoE* • *Ensure prospective data collection* • *Capture in ICH – beyond E6/M14* • *Political will to strengthen and align data standards – can't be driven by Regulators alone; cross-stakeholder dialogue and collaboration is critical*
Analysis	Predictive modelling	• Use of AI tools and natural language processing (NLP) to capture data	• *Incorporate changes in clinical trial design*
Role of collaboration across stakeholders			• *Continue broad engagement opportunities between stakeholders through CIRS meetings* • *Include patients and clinical academics in drug development dialogue*

Infodemic: challenges related to misinformation and trust in the system	Transparency in decision making Combatting the spread of misinformation	• Restoring confidence in medicine development and approval	• *Maintain some communication tools developed during the pandemic* • *Ensure communication and collaboration with multiple stakeholders, including patients and underserved populations*

This Syndicate reflected that many of the tools used during the pandemic had already been in place in some form, but their use was catalysed by the pandemic. For example, activities that worked well were the use of basket studies that spanned healthcare systems; the expanded use of telemedicine, virtual recruitment and remote sampling; and the use of post-EUA observational studies. Cross-organisational data exchange and communication were seen as paramount in aligning study needs (e.g. endpoints, enrolment diversity), and the use of RWE to support these outcomes was an invaluable asset.

Q3. Recommend future research projects for CIRS and other groups to undertake in this area: what should be considered to support the improve current activities. Please identify up to 2–3 recommendations Also consider identifying who you believe should be the actors for the recommendations; for example, CIRS, pharmaceutical companies, regulatory agencies, and Centres of Excellence.

1. Include sponsor, regulator, and HTA perspectives in future CIRS surveys on products registered based on the data collected during the pandemic.
2. Conduct workshops on decentralised clinical trials (DCTs) to identify:
    - Obstacles, challenges, and recommendations in DCT delivery based on learnings
    - New skillsets required for DCT delivery and how to integrate digital health (DCT convergence)
    - Patient insights on DCT versus randomised controlled trials
3. Address the concerns on representativeness, diversity, misinformation, and rebuilding trust in drug development and involvement of patients across the full drug discovery pathway

Breakout discussion C

Which regulatory and HTA process and operation efficiencies identified or utilised during the pandemic can be applied in the future?	
Chair	**Dr John Lim,** *Executive Director, Centre of Regulatory Excellence (CoRE), Duke-NUS Medical School and Senior Advisor, Ministry of Health, Singapore*
Rapporteur	**Dr Brenda Huneycutt,** Director, Global Regulatory Policy, Merck & Co, UK

Background

The COVID-19 pandemic also warranted a relook at process redundancies, operational inefficiencies, and rigidities to facilitate the provisioning of medications to patients. A number of these changes helped deliver flexibility and improve process outcomes. These regulatory, operational, and process efficiencies were pivotal in bringing about the development and availability of new medicines.

Learning from these improvements can further inspire permanent improvements in drug development, reviews, and reimbursement practices and processes in the face of unforeseen public health emergencies (PHE) in the future. Some of the prominent changes include modifications to the internal decision making within companies and agencies; the use of digital documents like inspection reports and electronic certificates of pharmaceutical products (eCPPs); use of other digital technologies for communication; and innovations in regulatory processes like rolling reviews and the utilisation of reliance mechanisms.

The majority opinion is to retain these changes, and this necessitates identifying the most value-adding and sustainable changes.

This breakout session was aimed at the range of operational efficiencies or flexibilities that were rolled into agencies and companies. In this context, the objectives of this breakout were to:

- **Discuss regulatory and HTA processes and operational efficiencies** utilised by agencies and companies to build in flexibilities and/or remove/reduce redundancies in the development review and reimbursement process.
- **Identify operational efficiencies utilised during the pandemic** that can be applied in the future for non-public health emergency therapeutics.
- **Assess the challenges and changes** that need to be made to ensure fit-for-purpose systems.

Discussion results

Q1. Which regulatory and HTA process and operational efficiencies utilised by agencies and companies to build in flexibilities and/or remove/reduce redundancies in the development, review and reimbursement process worked well?

Areas for consideration	What worked well?	What did not work well?	Should it be retained?
Decision making process (both internal and external)	• Enhanced engagement	• Difficulty in getting public input when speed and agility were necessary	*Yes*

	• Regulatory connections with the public helped raise health awareness and literacy	• Regulators were often targeted • Regulators' time was consumed in responding to misinformation	
Review practices and processes (rolling or reliance reviews)	• Reliance or facilitated pathways improved the efficiency of processes • Bridging studies expedited processes in India	• Facilitated registrations do not necessarily mean equal access • Lack of COVID-19 vaccine trials in emerging economic countries made them feel left out • Trials were not conducted in populations with a high incidence of HIV, malaria, TB, and malnutrition	*Yes*
Utilisation of digital technology to enable the continuation of activities	• Virtual meetings reduced unnecessary accompanying hassles (no VISAs required, no impact on environment, no travel, real-time participation in own language with the help of simultaneous translation)	• Virtual encounters eliminated the subtle benefits accrued from face-to-face meetings (like relationship building) • Technical shortcomings like the lack of recording sharing	*Yes, in some circumstances*
Procurement	• Conditional basis for agreements based on regulator and HTA agreement	• Rushed procurements, especially by governments even before regulatory approval, often undertaken due to political pressure • Inconsistencies in the actions of governments, regulators, and HTA • Clinician disagreement on the use of vaccines • Ethics of placebo trials and fast-paced gathering of real-world data	*Yes, but with implementation considerations*

Q2. Of the items identified above that should be retained and used for non-pandemic medicines, identify which changes/activities/frameworks should be adopted/embedded into regulatory and HTA operational efficiencies such that they enable sustainable change.

Operational efficiencies	Aspects to be retained	What are the biggest challenges (real or perceived) to enable this to occur?	Changes that need to be put in place to ensure this is fit for purpose and sustainable
Decision making processes and practices within companies and agencies	• Flexibility to ensure increased dialogue • Bring people across the spectrum to discussions • Openness to do things differently • Retain public trust and maintain engagement	• Resource limitations (staffing communications department) • Investments in processes and capabilities • Public leaning on mis/disinformation • Treading the line between simplicity and technicality of information	• *-Moving beyond regulator involvement to a more inclusive alignment with national health priorities and jurisdictions* • *Championing and risk-taking by upper leadership* • *Need for additional resources, cultural changes, and capacity building* • *Patient engagement and listening to the patient's voice as a critical component of product development*
Review practices and processes (e.g., use of rolling or reliance reviews and expedited pathways)	• Collaboration between regulators • Transparency	• Sharing information like assessment reports • Product access in the absence of sponsors	• *Clarity in terms of information sharing (trade secrets, etc.)*
Utilisation of digital technology to enable the continuation of activities (e.g., virtual meetings and inspections)	• Virtual meetings can be retained as an option with face-to-face and hybrid models	• Challenges with hybrid meetings	• *Develop meeting etiquettes for hybrid mode (video mode off, ensure screen presence)*
Utilisation of digital documentation: decentralised trials	• Hybrid approach while retaining some traditional traits (e.g., 1st doctor visit at the clinic*)*	• Nomenclature (e.g., DCT trial in China refers to government trials) • Cultural characteristics of a population	• *Continuous monitoring* • *Factor in the changes taking place in the healthcare system*

		• Ensuring comfort/ease of study participants • Differential approach for participants based on their preferences	
HTA vaccine system		• How to move a vaccine from government procurement to the HTA system • - Deciding payment modules (when does the government pay and when individuals pay)	• *Creating an opportunity for population-based contingent payments* • *(Companies may find it unfair if the WHO decides strain choices)*

This Syndicate recognized the value of engaging the public, especially as regulators became the public advocates to raise important issues about healthcare during the pandemic. Using reliance authorization pathways and other facilitated pathways improved process efficiency and also opened organizations to the benefits of using these approaches. Because so many of the issues during the pandemic had international impact, the use of virtual meeting technologies found a ready audience amongst drug developers and regulators. Digital technologies allowed the real-time collection of data and rapid measurement of the observations. Further, Procurement Agreements conditional on regulator and HTA agreements proliferated and accelerated access to important therapeutics. All of these activities built flexibility into the process while maintaining public engagement and confidence.

Q3. Recommend future research projects for CIRS and other groups to undertake in this area: what should be considered to support the improve current activities? Please identify up to 2–3 recommendations. Please also consider identifying who you believe should be the actors for the recommendations; for example, CIRS, pharmaceutical companies, regulatory agencies, and Centres of Excellence.

Recommendations for CIRS and other groups:

1. Conduct another CIRS workshop with regulators, HTAs, patient organisations, and industries to identify areas requiring continued agility and prioritise and sequence the future course of action.
2. Create action-oriented plans and outline the elementary steps to move forward.
3. Conduct a SWOT analysis to identify what worked and what did not; identify the reasons for failure or success.
4. Explore issues with the workforce: identify the global and country-level investments in terms of people and capabilities.

Has or should the development review and HTA assessment for priority treatments change(ed)?

New ways of working to enable the development review and reimbursement of innovative medicines: Has or should the development review and HTA assessment for priority treatments change(ed)?

Regulatory perspective

Finnuala Lonsdale, *Director of Human Products Authorisation and Registration, Health Products Regulatory Agency, Ireland*

It is generally accepted that the COVID-19 pandemic had a far-reaching effect on regulatory processes. However, on the whole, it seems to have accelerated some existing trends while delaying others. Industry leaders now have to decide which of these changes to retain. However, implementation in the late-pandemic era has become difficult because COVID-19 profoundly affected human resources, and not merely systems and processes.

Ecosystem thinking and other COVID-19-induced changes

At this stage of the pandemic, regulation has become more collaborative than ever before. There are now more parallel health technology and regulatory assessments and a need for regulators to engage more with health care systems. These new ways of working require individuals who are effective communicators. Many regulators and assessors, however, do not fit the bill. So, regulatory agencies have been left with the difficult choice of hiring new regulators or providing alliance management training to existing staff.

The greater need for collaboration is also apparent in the process of giving health advice. Nowadays, regulators often have to give joint scientific advice with health technology assessment (HTA) agencies.

New evidence types and expedited approval

Several new types of evidence in model-based drug design have remained in consideration for a long time. The pandemic has brought some of these new options to the fore and onto the regulators' table. These include:

- Surrogate endpoints
- Pharmacometric data
- Real-world evidence (RWE)

Rolling reviews were a necessary innovation during the pandemic and helped to fast-track drug development. However, their widespread use may be neither sustainable nor effective in the long run. The Health Products Regulatory Authority (HPRA) had to commit 42% of its workforce for close to 3 months to complete one rolling review, which proved debilitating. Most small regulators like HPRA may not be able to afford the human resources required to conduct rolling reviews on a regular basis.

Increased efficiency and Increased use of derogations

There are inefficiencies in the regulatory mechanism that need urgent correction. In the Irish context, some of the chemistry manufacturing and controls (CMC) labelling-related inefficiencies are particularly troubling. There needs to be a careful analysis of the system to determine which of these are valuable to the drug development process and which of these are barriers.

Some measures to reduce inefficiencies are:

- Increased use of common packaging
- Common labelling
- Removing the bureaucratic barriers to accepting variations

The use of derogations can be useful in some contexts, especially in shortage situations. Ireland had to solve some of the Brexit-related shortages by derogating from European rules. However, this entails a lot of work.

Increased transparency and digital transformation

The has been a greater push towards sharing data, enabling the public scrutiny of trials, and performance reporting and benchmarking since the pandemic. However, this too requires regulators to learn new skills and build more capabilities.

While digital technologies in healthcare, including system integration and data analytics, are making rapid gains, regulators have not been able to use them optimally. Many a time, agencies find it impossible to utilise artificial intelligence data as they lack the required technical know-how.

Barriers to change

The effective implementation of regulatory changes often requires geopolitical intent. Regulators need to have hard conversations at the political level about what can be achieved realistically. There are many factors that may prove to be barriers to regulatory reform, such as:

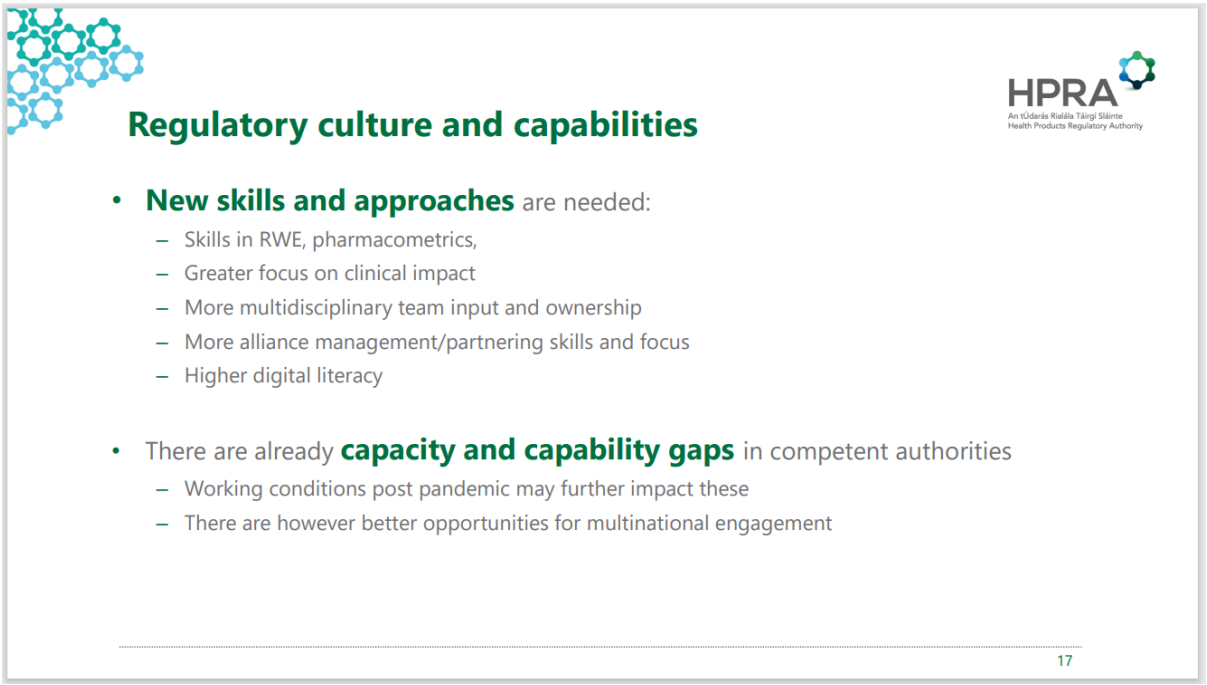
- Wider geopolitical considerations
- Balance between the nation-state and regional accountabilities
- Organisational silos
- Culture and capability

Building regulatory capabilities and a common vision

Regulators need to adapt to prepare for the post-pandemic age. However, this cannot be done unless the current capability gaps are properly addressed. Before regulators can affect change, they need to build sufficient capabilities. Some crucial skills and approaches in this respect are:

- Skills in RWE and pharmacometrics
- Greater focus on clinical impact
- More multidisciplinary team input and ownership
- More alliance management/partnering skills and focus
- Higher digital literacy

Regulatory agencies have to engage with the changing landscape and approach culture, capacity, and capability anew. With realistic goals and a common vision to drive change, regulators can achieve sustainable progress in drug regulation.



Drug development approaches: learnings and improvements

New ways of working to enable the development review and reimbursement of innovative medicines: Has or should the development review and HTA assessment for priority treatments change(ed)?

Company perspective
Ginny Beakes-Read, *Executive Director, GRR&D Policy, Amgen, USA*
Several new ways to collect data emerged during the COVID-19 pandemic. However, more data did not automatically yield better evidence. It is important that as we explore new virtual ways of collecting and analysing data, we do not forget about legal and regulatory standards of evidence. After all, the patient is the most important stakeholder and their data need to be used effectively.

Experience from the pandemic
One of the more fortunate changes that the COVID-19 pandemic brought about was the improved understanding and awareness of clinical trials among the public. In the post-pandemic era, this gives regulators the opportunity to engage with people at a deeper level than before.
The pandemic also saw the use of several new tools to reach participants. This challenged traditional ways of working and forced regulators to reconsider assumptions. The pandemic also spurred discussion on the role of participants in clinical trials.

The way forward
Going forward, there is a need to make trial protocols more flexible. While designing flexible protocols, regulators have to manage patient risk, as well as data integrity. Agencies are currently trying to figure out how best to balance the needs of regulators with the needs of patients.
The pandemic has given fresh impetus to clinical trial diversity. In the past, it has been difficult for regulators to reach out to rural communities and ensure equal participation from diverse communities. In the future, regulators need to find ways of improving representation from underserved communities.
Regulators have been exploring new ways of getting input from patients. The use of digital tools to assess novel endpoints and for the passive collection of data will help agencies get a better sense of patients' needs and perspectives.

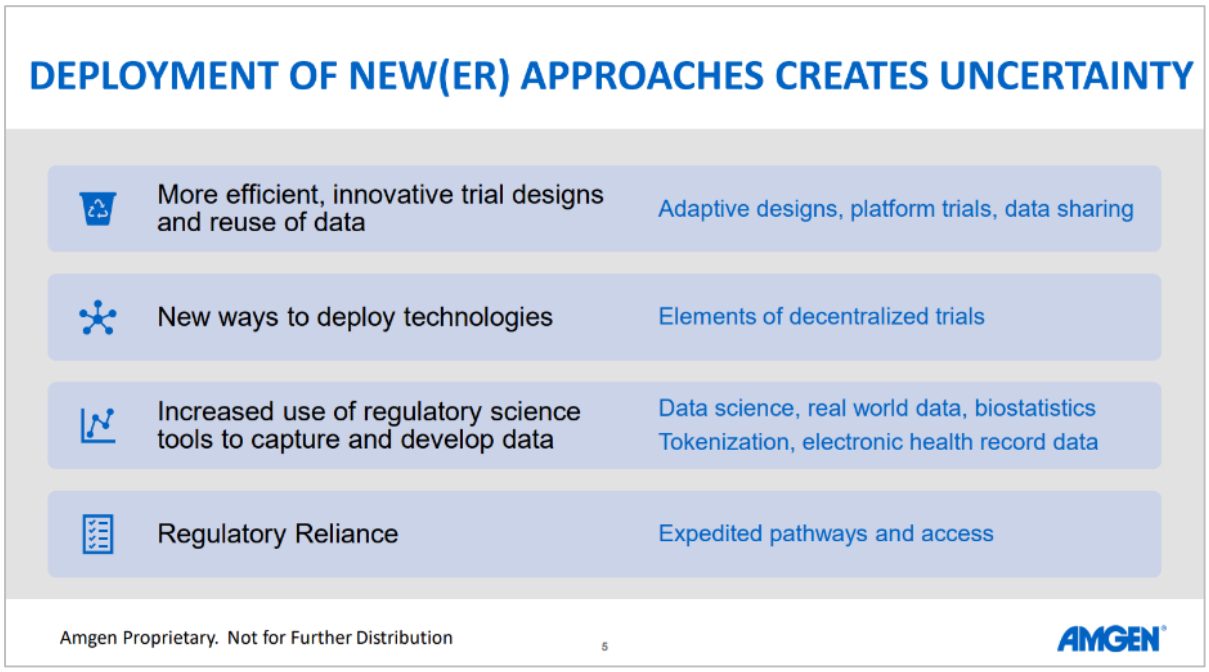
A new level of uncertainty
The use of novel trial designs, regulatory science tools, and aspects of decentralised trials has raised the level of uncertainty that regulators have to contend with. While new approaches are definitely adding value, agencies need time to adapt to new technologies and utilise them optimally. Regulators are still adjusting to many new approaches in the regulatory system, such as:

- Adaptive designs, platform trials, and data sharing
- Elements of decentralised trials
- Data science, real-world data, biostatistics, tokenization, and electronic health record data
- Expedited pathways and access

Unmet needs in development
Patients with serious illness have felt their needs are being ignored due to the increased focus on COVID-19. This presents several challenges to managing risks versus benefits.
To address limitations in drug development for serious illnesses, agencies need to improve engagement with stakeholders across the board and ensure timely interactions.

Ways to address uncertainty and improve the use of new tools
In the interest of bringing stakeholders together and reducing uncertainty in the system, educational grants and workshops need to be leveraged. Some of the existing multi-stakeholder programs like the Reagen-Udall Foundation Evidence Accelerator and FDA Standard Core Clinical Outcome Assessment (COA) Grants can be helpful in this regard.
Like multi-stakeholder interaction, peer–peer interaction also needs a push. This can be achieved through regulators-only groups like the International Coalition of Medicines Regulatory Authorities (ICMRA) clusters and initiatives/consortia like the Medicines Development Modernization Initiative, Duke-Margolis Health Policy Center, and Harvard Multi-Regional Clinical Trial Center. Overall, better

communication among stakeholders and among peers can help embed new technologies/approaches within regulation and ensure they do not lead to more uncertainty.



Joint clinical assessment in the EU

New ways of working to enable the development review and reimbursement of innovative medicines: Has or should the development review and HTA assessment for priority treatments change(ed)?

HTA perspective
Finn Borlum Kristensen, *Professor of Health Economics and HTA, University of Southern Denmark*

In late 2020, a group of eight institutions involved with the European Network for Health Technology Assessment (EUnetHTA) decided to do COVID-19 rolling reviews by applying EUnetHTA's rapid collaborative review methods of systematic search, review, and synthesis of all available evidence and put them on EUnetHTA's public website. Altogether, there were more than 20 regularly updated reviews published in the following year.

As has been highlighted in a recent article [1], EUnetHTA proved capable of tight cooperation for a coordinated work and a quick response, showing flexibility in restructuring its products without jeopardizing their quality and trustworthiness. However, while timeliness could be dealt with by partners' collaboration and the rapid/rolling reviews' initiative, the lack of robust underlying clinical study data compromised the endeavour of providing conclusive scientific evidence. Given the overload of bad quality primary studies and the lack of coordination within the scientific community, uncertainty could not be avoided.

It is thus prudent to know the limitations of accelerated assessments aiming at meeting the challenge to reduce redundancies without compromising review quality.

The path to joint clinical assessment
The call for joint action in health technology assessment (HTA) in the EU started more than a decade ago. The road to sustainable HTA cooperation was long and arduous However, the proximate legislative steps leading to joint clinical assessment involving the European Commission, member states and the EU parliament would not have been possible without EUnetHTA.
The continued engagement of individuals and institutions in EUnetHTA and stakeholder involvement was instrumental in providing the necessary impetus to get the joint assessments going. EUnetHTA showed that some of the tools necessary that were either internationally available or developed by the network were sufficient to manage joint cross-border work.
Member state agencies are now preparing for the joint clinical assessments slated to start in 2025. All 27 member states and some countries outside the EU will be involved.

Possible future course
Joint clinical assessments will likely focus on the cutting edge of innovation: New cancer drugs and advanced therapies are possible candidates followed by other medicinal products in 2028.
There are quite a few challenges that need to be met before getting the next phase of European HTA off the ground. EUnetHTA is now working on methodological guidelines and national HTA institutions and the European Commission are charting the course for future assessments. This will additionally need to muster the necessary IT, administrative, and technical know-how, and ensure coordination between HTA and regulatory agencies.
The EUnetHTA-21 Methodological Guidance addresses several important aspects of clinical assessments like the choice of comparator, simple scoping of the questions, PICO (Population, Intervention, Comparator(s), Outcomes), and the applicability of evidence.

National HTA reports and benchmarking

The proposed future joint assessments entail-parallel processes, many of which will be happening at the EU level. To ensure that policymakers at the national level can stay informed and follow up on recommendations, timely HTA reports will be vital. Also, extending benchmarking from regulatory agencies to HTA agencies can be valuable in the long run.

Now that permanent HTA cooperation is well within sight, the EU needs to ensure close coordination between regulatory and HTA agencies and between policy at the EU and state levels.

Reference

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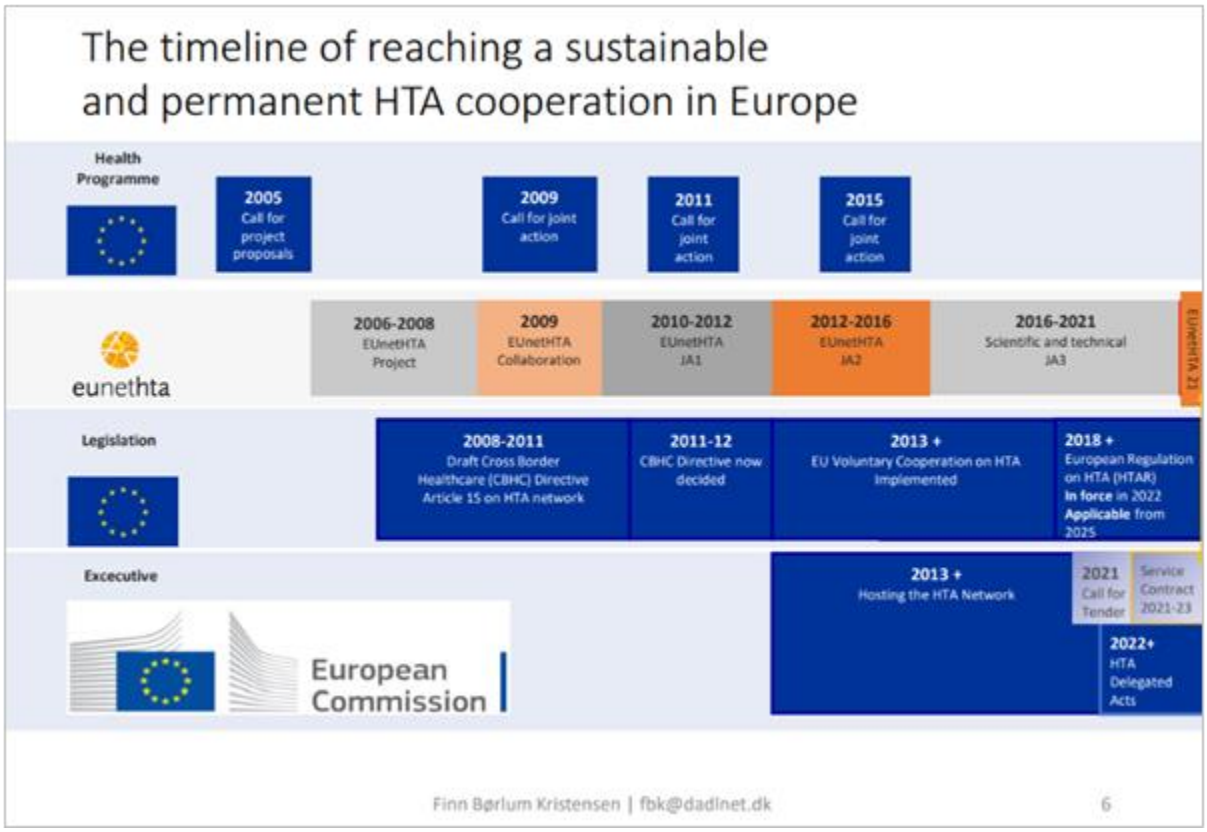

Cost of healthcare in the post-pandemic era

New ways of working to enable the development review and reimbursement of innovative medicines: Has or should the development review and HTA assessment for priority treatments change(ed)?

Payer perspective

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When COVID-19 hit, there was a considerable fall in the use of non-critical care, which caused all sorts of issues for payers. Hospitals suffered from a loss of business, and patients with non-serious conditions found it challenging to obtain the care they needed. There was a push for disinvestment from some quarters, and drug shortages continued to worsen during the pandemic.

Emergency care of patients with COVID-19 suffered too. Doctors were trying to adapt to the shortages by developing new combinations of therapies, and at times, drugs were being used off-label.

Fallout from the pandemic

At this current stage of the pandemic, patients are having to deal with the direct effects of COVID-19 and the high cost of therapies for other illnesses. For instance, Long COVID remains unaddressed because proper therapies have not yet been developed, even as patients are having to pay for investigational treatment. The silence on what actually works as therapy or how these patients need to be categorised is deafening.

Patients are curious as to what their total spending is going to be and if they are getting value for their money. Therefore, the interest among payers in Horizon Scanning to help address this question has increased.

At the moment, there seems to be some disagreement as to what reasonable endpoints in clinical trials need to be. The endpoints that patients want and payers want may be far removed from what regulators want. Thankfully, the pandemic has broken certain barriers to communication between these parties. Hence, we may yet see some consensuses emerge.

The road ahead

Payers are looking forward to some very highly priced cell/gene therapies in the near future. These new therapies promise great value for money. They are going to be real gamechangers with sickle cell anaemia, haemophilia, and some neonatal diseases.

Commercial payers, Medicaid payers, Medicare payers, and single-system European payers, all have to address dire cost problems. They also believe that these problems can escalate further.

Consequently, payers now want to be involved with the pre-authorisation process. This interest can be attributed to the need to ascertain value for money, predictability, and total spending. Payers seem to be ready to pay based on evidence and new data. Moreover, they are more connected with patients and are employing digital tools to aggressively manage the health of their populations. It is heartening to see some of these new approaches. Sometimes patients need external motivation to act in their own interest.