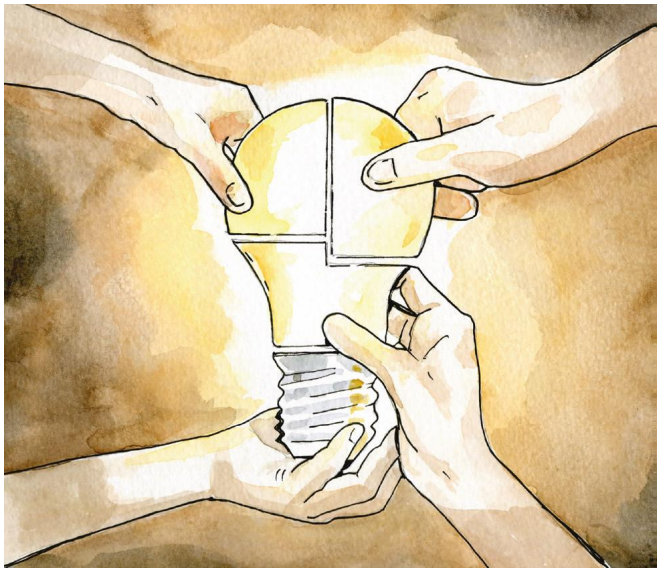

Re-imagining medicines regulatory models: implementing fit-for-purpose sustainable activities for patient access

8-9th December 2020

Workshop in the memory of

Professor Sir Alasdair Breckenridge

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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

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Tribute to Professor Sir Alasdair Breckenridge

Professor Sir Alasdair Breckenridge, Chair of CIRS SAC 2013-2019

Professor Sir Alasdair Breckenridge died, aged 82, on the 12th of December 2019 after a short illness. I first got to know and work with Alasdair in 1969, while I was a lecturer in clinical pharmacology at the Cardiothoracic Institute, when he had just been appointed as Consultant and Senior Lecturer at the Royal Postgraduate Medical School in London at the young age of 32. So early on in his career he had already made a significant contribution to medicine where he established himself as an expert in the field of hypertension.

Just five years later in 1974 he moved to the University of Liverpool to become Head of the Department of Clinical Pharmacology, which he transformed into an internationally recognised research institution. Over a period of 50 years Alasdair's research contributions were extensive with many publications in prestigious journals, chairing and speaking at meetings around the world, during which time he received many awards too numerous to mention. He claimed that his work in Liverpool was his greatest achievement.

I may disagree with that, for in 1984 he joined the Committee on Safety of Medicines (CSM) and became its chairman in 1994. It was therefore appropriate that he should have been awarded the CBE in that same year, with a knighthood some 10 years later, for his outstanding contributions to medicine. In 2003 he was appointed as the inaugural chairman of the board of the Medicines and Healthcare Products Regulatory Agency (MHRA), where he combined his vision and expertise to the area of regulatory science.

I can say without any hesitation that he was a giant in his field, physician, academic, medicines regulator and clinical pharmacologist. It has been a privilege to have known and worked for him and his contribution to CIRS has had a major impact and significantly influenced what the organisation has achieved to date. Alasdair has left us a legacy on which I know we can build.

Professor Stuart Walker, Founder of CIRS

Section 1: Executive Summary

Background to the workshop

As the regulatory landscape changes to meet new challenges, such as increasingly sophisticated medical innovations, fundamental questions are being raised: what is the role of a 'modern' regulator today? Does the regulatory paradigm need to be reconstructed to meet future demands? These questions need to be addressed if regulators are to remain relevant as well as being part of the solution for the sustainable development and review of innovative medicines.

These questions were actively confronted from a practical standpoint in 2020 with the COVID-19 pandemic. Regulatory and Health Technology Assessment (HTA) systems were, and continue to be, challenged in all areas to support the pandemic response. There has been increased stakeholder dialogue to identify where flexibilities are possible and can be enacted within an agency's legal framework. These have covered areas such as: supply chain; conduct and reporting of clinical trials; manufacturing, inspection and quality audits; authorisation review processes; and post-authorisation activities.

The pandemic has created both opportunities and challenges for new ways of working and accelerating the assessment of medicines, both in clinical trials and approval settings. This has been supported by the increased availability and rapid turnaround of scientific advice and identification and reduction of redundancies in review systems. In addition, the situation has resulted in increased collaborations between regulators across jurisdictions on both the technical and policy fronts, as well as within regulatory and HTA agencies.

The question that was addressed in this workshop was: is the time right to re-imagine medicines regulatory models? Can we incorporate the lessons learned to date, not just from the extensive experience of both agencies and companies, but also from the changes instigated during this pandemic, to minimise non-value adding activities or adapt the regulatory model?

The workshop was held in memory of world-leading regulatory expert, Professor Sir Alasdair Breckenridge, who had challenged CIRS prior to his death in December 2019 to consider the topic, "Are medicines regulatory models fit for purpose today?" The overall aim of th workshop was to outline what should be considered to make the regulatory framework more robust and sustainable.

Workshop objectives

- Discuss current regulatory models and whether the regulatory paradigm for development and review needs to evolve to meet current and evolving needs.
- Identify opportunities and challenges to re-imagine the regulatory assessment process:
    - Potential areas for change that have been exposed by the pandemic
    - Traditional areas of activity the pandemic has exposed and that can be adapted flexibly; which of these can form the basis of a sustainable model(s) across all products and therapy areas post-pandemic?
    - Activities that have increased or have been accelerated by the pandemic
- Make recommendations on activities that should be considered to evolve a sustainable, fit-for-purpose model(s) for the development, review and access of new medicines.

Venue

This workshop was held virtually over two days: 8-9th December 2020.

Key points from presentations

Session 1: Current regulatory models: do they meet the evolving needs of 21st century medicines?

Professor Stuart Walker, *Founder, CIRS,* and **Professor John Lim**, *Executive Director, Centre of Regulatory Excellence (CoRE), Singapore*, opened the workshop by reflecting on the distinguished regulatory career of Professor Sir Alasdair Breckenridge, who had chaired both CIRS' and CoRE's advisory boards. Prior to his death in December 2019, Prof Sir Breckenridge had challenged CIRS to consider the question "Are medicines regulatory models fit for purpose today?", which inspired the topic of this workshop.

Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency (EMA)*, spoke about how drug regulation has adapted to the changing nature of products, data and expectations, however, its fundamental principles remain the same in that benefits must be shown to outweigh harms and economic considerations should not influence regulatory decision making. While it may not be time to reframe the regulatory model, a more complex, multifaceted world needs a new degree of flexibility in relation to clinical evidence standards; flexible notion of drug and target population; better methods for evidence synthesis and decision making; and communication on knowns and (unavoidable) unknowns.

Dr Khair ElZarrad, *Deputy Director, Office of Medical Policy, Center for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA),* described how regulators face a rapidly evolving ecosystem with an advancing evidence generation paradigm, increasingly digital world, use of artificial intelligence (AI) for therapeutic development and innovative trial designs. To move forward, the regulatory community must ensure shared understanding; collaboration and engagement; workforce development; continuous learning and fast implementation; an agile regulatory framework; and that the 'right' questions are asked.

Meindert Boysen, *Deputy Chief Executive and Director of the Centre for Health Technology Evaluation, The National Institute for Health and Care Excellence (NICE), UK,* spoke about the new Innovative Licensing and Access Pathway (ILAP), which, building on experiences from the COVID-19 pandemic, brings together the Medicines & Healthcare products Regulatory Agency (MHRA), NICE, NHS England and the Scottish Medicines Consortium in a collaborative lifecycle approach that will help to reduce time to market for innovative medicines. To ensure successful multi-stakeholder collaboration in future, organisations must ensure scientific and planning information is shared freely and effectively. Downstream implications of earlier licensing also need to be understood and a common taxonomy for uncertainty agreed.

Dr David Jefferys, *Senior Vice President, Eisai, UK,* gave an overview of learnings from the COVID-19 pandemic such as the use of rolling reviews, remote trial monitoring and electronic certification. Wider environmental changes that present opportunities include changes in the delivery of healthcare, new emphasis on public health and better societal understanding of drug development. Going forward, we must embed agilities identified during the pandemic into the new normal, encourage the regulator to be an enabler of new technologies and promote co-creation of new policies and approaches.

Session 2: Accelerating change and enabling flexibility for early access – what will become a new way of working?

Dr Max Wegner, *Senior Vice President, Head of Regulatory Affairs, Bayer, Germany,* described how the COVID-19 pandemic has demonstrated that high regulatory standards and speed are not incompatible. Collaborative steps have been taken to maximise the efficiency of clinical trials, harmonise regulatory processes and utilise innovative digital technologies. The efficiency and flexibility realised could prove

beneficial well beyond the pandemic, but this will only be possible if the same sense of urgency is maintained. More focus also needs to be given to maturing Real World Evidence (RWE) and building a cloud-based system for submission/review.

Dr Martin O'Kane, *Unit Manager, Clinical Trials Unit, Licensing Division, MHRA, UK,* spoke about how MHRA has moved from reacting to the COVID 19 pandemic, to providing support for recovery and resilience and encouraging new 'standard' ways of working. Going forward MHRA will take an integrated approach to support innovation in design through continued engagement with industry, charities, patients and research bodies. The agency has developed a regulatory toolkit composed of required components (tools that ensure regulatory compliance) as well as those that can be selected individually to support a bespoke development programme that reflects a lifecycle approach to evidence generation.

Dr Nikolai Brun, *Director of Division, Medical Evaluation and Biostatistics, Danish Medicines Agency,* described how the data landscape has evolved, giving us vast volumes of data that have the potential to contribute significantly to the way the benefits and risks of medicines are assessed over their entire lifecycle. To move forward and fully realise this potential, the regulatory community must address the currently limited capacity and capability to access and analyse these large, heterogeneous and unstructured data sets.

Dr Virginia Acha, *Associate Vice President, Global Regulatory Policy, MSD, UK,* spoke about how the pandemic has accelerated existing trends for digital technologies, which have shaped regulatory activities in the areas of clinical research, telematics and electronic information. In future, greater productivity gains may be unlocked through digital breakthroughs involving machine learning and AI. Furthermore, quantum computing platforms could also further expand AI's potential, maybe even helping to predict and prevent the next pandemic.

Session 3: Accelerating change and enabling flexibility for early access – what will become a new way of working? Continued

Dr Peter Arlett, *Head of Data Analytics and Methods Taskforce, EMA,* spoke about how the COVID-19 regulatory response has been a "sandbox" for experimentation, demonstrating that regulators can act as innovators. Although there is a need for further convergence between regulators, between regulators and other stakeholders, and between different regulatory domains, regulation should remain focused on patient and public health.

Andrew Emmett, *FDA Liaison & Head of US Regulatory Policy, Pfizer, USA,* described how industry, regulators and the wider research community can learn and apply durable lessons from the COVID-19 pandemic. Focus should be given to building digitally resilient clinical trial systems; enhancing platforms for secure data sharing to enable collaboration, work sharing and reliance; and streamlining the development and review of therapies for severely debilitating or life-threatening diseases.

Dr Jillian Fuhs, *Advisor, Global Regulatory Affairs North America, Eli Lilly, USA,* spoke about scientific dialogue and interactions between industry and regulators during the COVID-19 pandemic. This has brought about opportunities for change that are widely applicable and high impact, such as the creation of a global platform for real time data and insight sharing; development of a central electronic repository for submitted documents; enhanced iterative scientific advice and communications; continued leveraging of digital technologies; and transparency and clear guidance on how best to leverage these tools.

Pat Furlong, *Founding President and CEO, Parent Project Muscular Dystrophy (PPMD), USA,* gave a patient perspective on the opportunities and challenges that have arisen from the COVID-19 pandemic. There have been learnings around the use of telemedicine; real-world evidence; data sharing; innovation in clinical trials; validating video capture as an outcome measure; and wearables. Application of these

learnings, while maintaining the same sense of urgency as for COVID-19, could be greatly beneficial for drug development for rare debilitating diseases like Duchenne muscular dystrophy.

Session 4: Reimagining international partnerships – collaborations and convergence supporting global needs

Dr Theresa Mullin, *Associate Director for Strategic Initiatives, CDER, FDA, USA*, spoke about how the COVID-19 pandemic has catalysed regulatory collaboration and information sharing and highlighted the need for agility for both regulators and manufacturers. Opportunities for further coordination and convergence have been identified, and the harmonisation work that is required could perhaps be led by the International Coalition of Medicines Regulatory Authorities (ICMRA), working closely with the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Dr Samvel Azatyan, *Team Lead, Regulatory Convergence and Networks, World Health Organisation (WHO)* described how timely access to medical products is a continuous challenge that has become even more important to address with the COVID-19 pandemic. To generate quality national decisions and avoid duplication, regulators globally must collaborate and take into consideration the information available from other regulatory authorities. Focus should be given to the practical implementation of various accelerated pathways and regulatory flexibility should become a 'norm', rather than an exception only used in public health crises.

Maria Cristina Mota Pina, *Regulatory Policy Director for the Emerging Markets, Abbvie, USA,* gave an overview of collaborations between regulators as well as how industry engages with its stakeholders. The COVID-19 pandemic has created an opportunity to implement stronger frameworks for international collaboration that go beyond managing a crisis. As well as continuing to use existing regulatory convergence and harmonisation platforms like ICH, WHO and ICMRA, the use of digital collaborative tools, for example, for regulatory submissions, should be explored and a roadmap for the future developed.

Dr Claus Bolte, *Head of Sector Marketing Authorisation, Swissmedic,* spoke about how regulators globally are faced with common challenges and so can benefit from working together and leveraging regulatory decisions. This is a stepwise approach, based on standards but also requiring trust of the quality of decisions as well as networks for collaboration. While reliance could be beneficial for all regulatory systems, work sharing may be better suited to more mature systems and pre-qualification to less mature systems.

Dr Murray Lumpkin, *Deputy Director, Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA,* closed the speaker sessions by sharing his view of key issues within the regulatory system that need to be addressed to ensure a sustainable quality healthcare system. In addition to marketing authorisations, there are other aspects of the regulatory system that should be reimagined: substandard and falsified products; electronic labelling; manufacturing variations; post authorisation infrastructure; regionalisation of regulation; confidentiality laws; and the impact of conditional authorisations.

Outputs from breakout discussions

A) Clinical trials during the pandemic – how does this reframe the thinking for undertaking clinical trials post-pandemic?

The breakout group focusing on clinical trials discussed practices that arose or were accelerated by the pandemic and were then challenged to identify up to five areas that it believed were critical and should continue post-pandemic:

1. **Stronger interactions** between sponsors-agencies as well as stakeholders within each country
2. **Remote monitoring**
3. **Regulatory flexibility** e.g. using a risk-based approach for source data verification
4. **International collaboration** e.g. ICMRA meetings, multi-sponsor trials
5. **Resource prioritisation** e.g. mechanisms within each country to enable rapid set up of trials.

Topics for further exploration:

- Optimal use of facilitated regulatory pathways and how to enhance them
- Optimal use of digital tools/wearables e.g. 24-hour monitoring
- How co-development (multiple sponsors) and co-creation (agency-sponsor) can continue to drive innovation to address unmet needs
- Need for in-depth cases studies on COVID-19 trials – how can learnings be translated to non-COVID trials?
- Use of social media/technology for trial recruitment - currently no clear guidance

B) Use of digital technologies to accelerate development and review – how can these be built on to enable increased efficiency and effectiveness throughout the lifecycle?

The breakout group on digital technologies discussed the impact of several digital tools and activities during the pandemic and was challenged to identify up to three critical areas that should be retained post-pandemic:

1. Enablers of virtual or decentralised clinical trials and associated tools, including **electronic Patient Reported Outcomes, telehealth, apps and site monitoring**
2. Use of apps (especially for the collection of safety data), **digital tools, wearables, devices with digital software** for pre/post authorisation utilisation
3. **Common digital infrastructure** and platforms for collaboration and work-sharing during the review, including Cloud submissions

Topics for further exploration:

- Inconsistency in digital practices
- Qualification, guidance and expertise to accommodate rate of change to innovation
- Ability of trials sites and investigators to utilise digital tools

Outputs from breakout discussions (continued)

C) Patient engagement – future opportunities to engage both in development and regulatory decision making

The breakout group examining patient engagement highlighted a major opportunity in the use of virtual/remote technology as an engagement tool. However, it was noted that virtual meetings cannot easily facilitate the networking and personal interactions that occur in face-to-face meetings, which can offer important opportunities for drug developers and regulators to learn from patients (and vice-versa) in a less formal manner. It will be important to build on the learnings from virtual meetings and expand the patient engagement toolbox after the pandemic.

Topics for further exploration:

- The group concluded that significant progress has been made in relation to patient engagement in development and regulatory assessment over the last decade and policy continues to move in the right direction.
- However, the pandemic has highlighted the challenge of adapting patient engagement strategies and the collection of patient-reported data to expedited procedures and timelines – do new strategies need to be considered?

D) Collaboration and knowledge sharing between stakeholders for improved interactions for facing healthcare challenges – what does the future roadmap look like?

The breakout group focusing on collaboration discussed practices that arose or were accelerated by the pandemic and were then challenged to select four areas that it believed were critical and should continue post-pandemic:

- Digital technologies
- Co-creation (sponsor-agency collaboration during development and use of rolling reviews)
- Information sharing
- Rapid scientific advice and assessment.

Topics for further exploration:

- An independent review to determine the most appropriate use of rolling reviews e.g. for public health emergencies, when linked to a classification of unmet need.
- An independent benchmarking study to determine appropriate use of new scientific advice and assessment pathways and which worked best.
- Investigate the impact of confidentiality laws on reliance.
- Alignment of politicians with scientific bodies to balance access demands with understanding of good regulatory practices.
- Maintain the evolving role of ICMRA as well as other international/regional collaborations such as the International Pharmaceutical Regulators Programme (IPRP) and Pan-American Health Organisation (PAHO).

Workshop Programme

8th December 2020

Session 1: Current regulatory models: do they meet the evolving needs of 21st century medicines?	
CIRS welcome and introduction	**Prof Stuart Walker,** *Founder, CIRS*
Professor Sir Alasdair Breckenridge – personal reflections	**Prof Stuart Walker,** *Founder, CIRS* **Prof John Lim,** *Executive Director, Centre of Regulatory Excellence (CoRE), Singapore*
Session Chair introduction	**Adj Prof John Skerritt,** *Deputy Secretary for Health, Products Regulation, Department of Health, Australia*
Reframing the regulatory model – is it time to challenge the anchors that have evolved over time?	**Prof Dr Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency (EMA)*
Are medicines regulatory and HTA models fit-for-purpose to support the development and an efficient review/access process?	
Regulatory agency perspective **HTA perspective** **Company perspective**	**Dr Khair ElZarrad**, *Deputy Director, Office of Medical Policy, CDER, FDA* **Meindert Boysen,** *Deputy Chief Executive and Director of the Centre for Health Technology Evaluation, NICE, UK* **Dr David Jefferys**, *Senior Vice President, Eisai, UK*
Session 2: Accelerating change and enabling flexibility for early access – what will become a new way of working?	
Session Chair introduction	**Dr Joseph Scheeren,** *President and CEO, Critical Path Institute, USA*
Accelerating changes to clinical development: what are the new opportunities and which ones do regulators, HTAs and industry want to evolve and why?	
Company perspective **Agency perspective**	**Dr Max Wegner,** *Senior VP, Head of Regulatory Affairs, Bayer, Germany* **Dr Martin O'Kane,** *Unit Manager, Clinical Trials Unit, Licensing Division, MHRA, UK*
Increasing the use of RWD and RWE pre- and post-approval to support regulatory decision making – Is there a growing acceptance of its use?	**Dr Nikolai Brun,** *Director of Division, Medical Evaluation and Biostatistics, Danish Medicines Agency*
What digital technologies are helping to increase operational efficiencies in the regulatory space, and that companies hope will become part of the new normal?	**Virginia Acha**, *Associate VP, Global Regulatory Policy, MSD, UK*

Session 3: Accelerating change and enabling flexibility for early access – what will become a new way of working? Continued	
Session Chair introduction	**Dr J Patrick Stewart**, *Director General, Therapeutic Products Directorate, Health Canada*
Adapting the medicines review framework pre- and post-approval - what flexibilities have been identified and what are the opportunities for and barriers against these being applied more widely across products for un-met medical need	
Agency perspective **Company perspective**	**Peter Arlett,** *Head of Data Analytics and Methods Taskforce, EMA* **Andrew Emmett**, *FDA Liaison & Head of U.S. Regulatory Policy, Pfizer, USA*
Scientific dialogue and interactions during development - what new opportunities have been identified and are these sustainable to being more widely applicable?	
Company perspective **Patient perspective**	**Dr Jillian Fuhs**, *Advisor, Global Regulatory Affairs North America, Eli Lilly, USA* **Pat Furlong,** *Founding President and CEO, Parent Project Muscular Dystrophy (PPMD), USA*
Accelerated regulatory approvals, risk sharing and sustainable access – What are the implications for access recommendations, and will this lead to increased use of a lifecycle approach to access?	**Dr Clifford Goodman,** *Senior Vice President, The Lewin Group, USA*

9th December 2020

Session 4: Re-imagining international partnerships – collaborations and convergence supporting global needs	
CIRS welcome and introduction to Day 2	**Dr Lawrence Liberti,** *Head, Regulatory Collaborations, CIRS*
Session Chair introduction	**Lorraine Nolan,** *Chief Executive, Health Products Regulatory Authority, Ireland*
International collaborations on policy and technical issues - is this just for pandemics or a roadmap for future global collaborations to enable sharing of expertise and knowledge?	
Agency perspective **World Health Organisation (WHO) perspective** **Company perspective**	**Dr Theresa Mullin,** Associate Director for Strategic Initiatives, Center for Drug Evaluation and Research, FDA, USA **Samvel Azatyan**, *Team Lead, Regulatory Convergence and Networks, WHO* **Maria Cristina Mota Pina,** *Regulatory Policy Director for the Emerging Markets, Abbvie, USA*

Leveraging comparable agency decisions – In what situations is this the right way forward?	**Dr Claus Bolte,** *Head of Sector Marketing Authorisation, Swissmedic*
Future thinking – Reimagining the regulatory model - What are the questions we should be asking of the regulatory systems but are not?	**Dr Murray Lumpkin,** *Deputy Director, Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA*
Session 5: Breakout Discussions	
Introduction to breakout discussions	**Dr Neil McAuslane,** *Director, CIRS*
Breakout A: Clinical trials during the pandemic – How does this reframe the thinking for undertaking clinical trials post-pandemic?	**Chair: Prof Dr Ton de Boer**, *Chairman, Medicines Evaluation Board, The Netherlands* **Rapporteurs: Prof Sam Salek,** *Head, Regulatory Science Programme, University of Hertfordshire, UK* **Amelie Sylven,** *Senior Regulatory Affairs Manager, Abbvie, Switzerland*
Breakout B: Use of digital technologies to accelerate development and review: How can these be built on to enable increased efficiency and effectiveness throughout the lifecycle?	**Chair: Dr Alison Bond,** *Director, EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen, UK* **Rapporteur: Dr Sannie Chong,** *Asia Pacific Technical Regulatory Policy, Roche, Singapore*
Breakout C: Patient engagement – Future opportunities to engage both in development and regulatory decision making	**Chair: Dr Mathieu Boudes,** *Project Coordinator, IMI project PARADIGM* **Rapporteur: Dr Bettina Doepner,** *Global Lead Regulatory Intelligence and Policy, Director, CSL Behring, Germany*
Breakout D: Collaboration and knowledge sharing between stakeholders for improved interactions for facing healthcare challenges. What does the future road map look like?	**Chair: Dr Thomas Lonngren,** *Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden* **Rapporteur: Stephen Fawbert,** *Director, Global Regulatory Policy EMEA, MSD, UK*
Panel discussion with Breakout Chairs – Policy/action considerations	

Section 2: Presentations

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Reframing the regulatory model – is it time to challenge the anchors that have evolved over time?

Prof Dr Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency (EMA)*

The fundamental elements of drug regulation have not changed over time; patient-relevant benefit must still be demonstrated and expected benefits must outweigh expected harms. Regulatory decisions continue to be grounded in science and are taken to the exclusion of economic and other considerations.

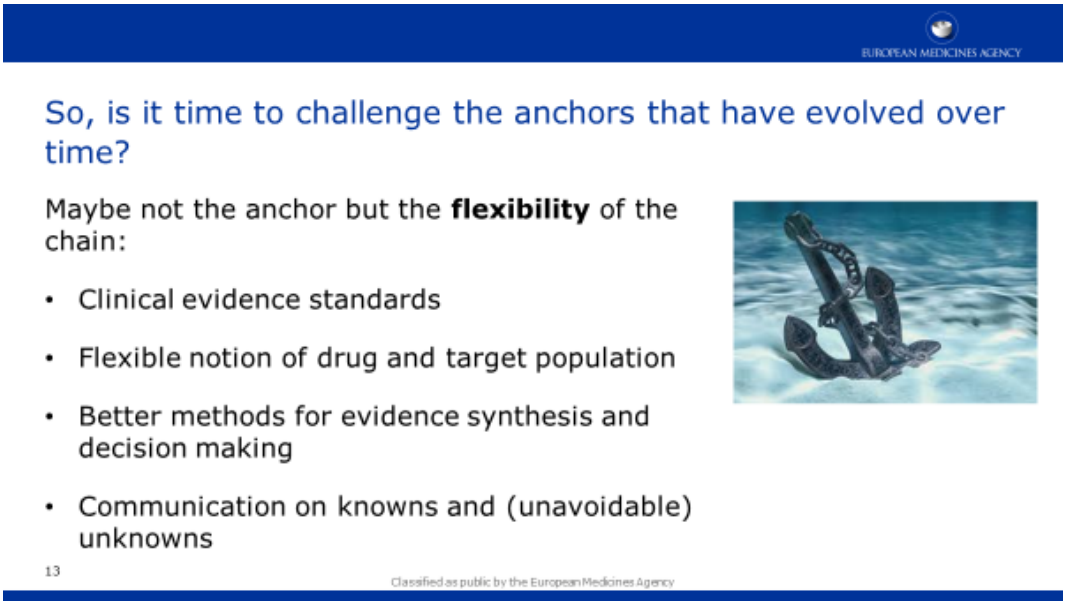
Nevertheless, the products regulators are authorising today are very different to 20th century 'statin-type' drugs, which were usually chemicals and relatively homogeneous in their drug-target interactions. Between 2018-2019, the EMA approved 73 products containing a new active substance, 39 of which were chemicals, 29 biologicals and five cell/gene therapies. In addition, 28 of the 73 products (~40%) were for rare diseases. This trend towards complex biologicals, cell/gene therapies and rare disease drugs is expected to accelerate; by 2025, 10–20 cell and gene therapy products will be approved each year [1].

The changing nature of drug products has consequences for evidence generation. Target populations are getting smaller (n=1 at the extreme) and extrapolation of efficacy from one subpopulation to the next is impossible in some cases. The definition of 'drug' is becoming more fluid, for example, some antisense oligonucleotides tailored to individual patients could be described as one archetypal drug, a drug class, or a multitude of different, individualised drugs. Some drugs' properties may also shift over time as a result of improvements of production processes, as has been seen with cell therapies.

The nature of data is also changing in that there are new data sources available, such as e-health records, insurance claims, wearables, apps etc, and new analytics methods using artificial intelligence. Expectations about data have changed too; while the Scandinavian Simvastin Survival Study (4S) was seen as a breakthrough for evidence-based medicine in the 1990s, it did not answer many important questions related to optimal dose, treatment time etc.

Drug developers now face an ever-growing matrix of informational needs from multiple stakeholders, which cannot all be addressed by a randomised controlled trial. Although real-world data will help as an additional or even alternative evidence base, there will still be situations where 'unavoidable uncertainty' has to be accepted, for example, with small effect sizes in small target populations.

While it may not be time to reframe the regulatory model, a new degree of flexibility is needed to cope with this more complex, multifaceted world of drug development. The future of clinical evidence standards will be a combination of randomised and non-randomised methods, drawing on a variety of data sources (prospectively or retrospectively collected) with prolonged patient follow-up (including post-authorisation). Regulators need to adapt to these changing evidence standards, embrace the flexible notion of drug and target population, find better methods for evidence synthesis and decision making and learn to communicate the 'knowns' and (unavoidable) 'unknowns'.



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[1] Eichler, H et al. (2021), Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. Clin Pharmacol Ther. Accessed on 18th February 2021 at: https://doi.org/10.1002/cpt.2083

Agile regulatory ecosystem in the age of exponential technologies:

Are medicines regulatory and HTA models fit-for-purpose to support the development of an efficient review/access process?

Regulatory agency perspective

Dr Khair ElZarrad, *Deputy Director, Office of Medical Policy, CDER, FDA*

The regulatory ecosystem is faced with an advancing evidence generation paradigm that is harnessing the potential of real-world data (RWD). RWD are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources, such as pharmacy dispensations, insurance claims, digital sensors, lab results, electronic health records, registries and hospital records. Data does not necessarily mean evidence; analytical tools and methods as well as various clinical study designs are used to turn RWD into real-world evidence (RWE), which informs on the usage and potential benefits or risks of a medical product.

Key considerations for the FDA's RWE Program framework include whether the RWD are fit for use; whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question; and whether the study conducted meets FDA regulatory requirements [1]. While there are many opportunities in utilising RWD, there are still challenges with linkages, interoperability, how to make sense of unstructured data, identifying and managing bias, identifying missing data and trend detection.

Innovative trial designs can help to overcome the inefficiencies of traditional development models and thus reduce costs. For example, decentralised trials may collect data virtually using remote or direct-to-patient methods, rather than collecting it via intermediaries at a research site. Artificial intelligence (AI) is also being used to address suboptimal patient selection and recruitment, as well as to aid patient retention and adherence.

Although AI has great potential to make advances from early development right through to post-market stages, it is important that the complexities of using AI are understood. Algorithms predict the most likely outcome/decision based on input data, not necessarily the accurate answer, meaning AI may produce unconventional 'solutions' that are not expected. Regulations, transparency and documentation on the use of AI will be crucial going forward.

The COVID-19 pandemic accelerated changes and activities that were already happening, such as decentralised clinical trials, and encouraged a practice of continuous learning. Lessons learned from the pandemic include leveraging existing healthcare infrastructure, conducting remote assessment and monitoring, identifying critical processes and prioritising them, leveraging technology and innovations to ensure trial integrity and effective communication.

In summary, we face a rapidly evolving regulatory ecosystem with an advancing evidence generation paradigm, increasingly digital world, use of artificial intelligence for therapeutic development and innovative trial designs. To move forward, we must ensure shared understanding (through transparency, validation, benchmarking, best practices etc.); collaboration and engagement; workforce development; continuous learning and fast implementation; an agile regulatory framework; and that the right questions are being asked.

Considerations for a sustainable regulatory ecosystem

- Can our current regulatory frameworks handle rapidly evolving innovations?
- Can our regulation and policy development processes keep up with rapidly evolving innovations?
- What should be the parameters for transparency?
- What are the needed validation & benchmarking approaches?
- What will an effective work force & work processes look like?
  - ❑ Attracting talents
  - ❑ Team work and/or multidisciplinary expertise
- What are the ethical implications?
  - ❑ Considerations for IRBs & DSMBs
  - ❑ Informed consent
  - ❑ Data privacy
  - ❑ What about the human-machine interface?
- How best to develop new norms, shared understandings, and ultimately standards?
  - ❑ Early engagement with regulatory agencies
  - ❑ Establishing effective collaborations and engagements

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[1] FDA (2018) Framework for FDA's Real-World Evidence Program. Accessed on 19th February 2021 at: https://www.fda.gov/media/120060/download

Are medicines regulatory and HTA models fit-for-purpose to support the development of an efficient review/access process?

HTA agency perspective

Meindert Boysen, *Deputy Chief Executive and Director of the Centre for Health Technology Evaluation, NICE, UK*

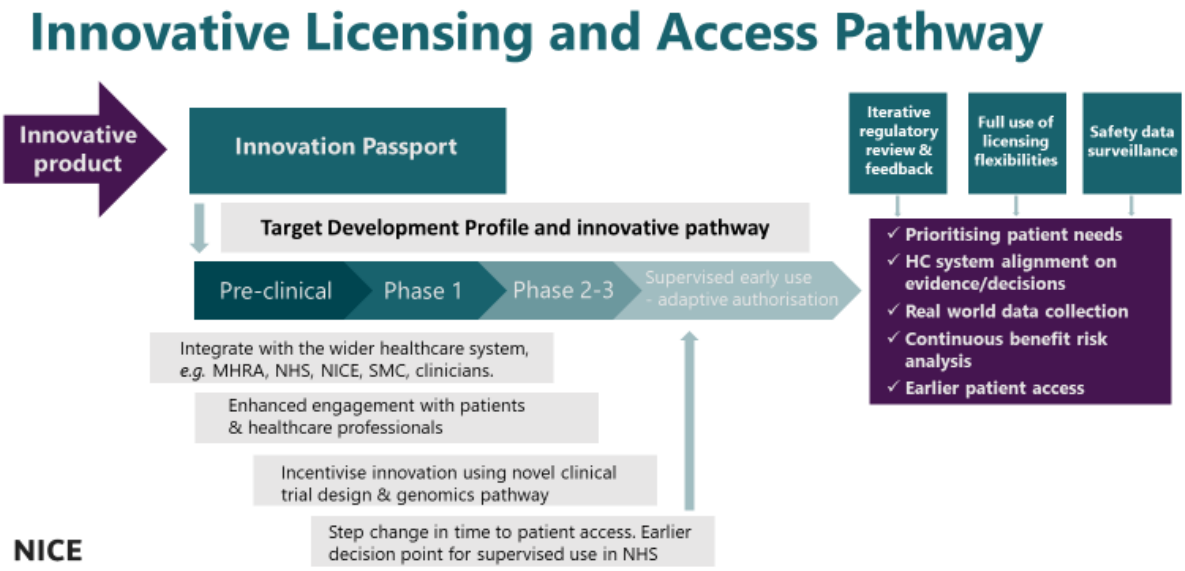
NICE's work focuses on three main areas: the guideline ecosystem, developing best practice recommendations and advice for frontline practitioners; the life sciences ecosystem, evaluating technologies to determine funding decisions and new procedures to assess safety; and the information ecosystem, providing a wide portfolio of evidence-based information and advice. NICE has an important role in innovation by acting as facilitator between NHS England and industry, using robust methodology to evaluate technologies and produce guidelines, and working with partners to support the adoption of innovative care.

At the beginning of the COVID-19 pandemic, there were questions over whether HTA bodies had a role to play, but it soon became apparent that rapid guideline development was an area they could assist with. NICE has developed briefings on the safety and efficacy of COVID-19 treatments and provided a single point of access to a suite of NICE COVID-19 rapid guidelines and NHS-developed specialty guides on its website. It continues to be a key part of the infrastructure responding to COVID-19 and meets weekly with the MHRA, NHS England and NHS Improvement (NHSE&I) and the National Institute for Health Research (NIHR) as part of the RAPID C-19 initiative, which aims to get treatments for COVID-19 to NHS patients quickly and safely. The RAPID C-19 decision-making process is not sequential but involves all the collaborative partners. NICE, working closely with NIHR, coordinates horizon scanning activities and the process for identifying the most promising candidate medicines.

The new Innovative Licensing and Access Pathway (ILAP) aims to develop a frictionless pathway to the timely availability of effective and safe medicines through collaboration to align UK health partner systems (see below). Building on experiences from the COVID-19 pandemic, this pathway brings together MHRA, NICE, NHSE&I and Scottish Medicines Consortium in a collaborative lifecycle approach that will help to reduce time to market for innovative medicines. Key benefits of the ILAP are a new medicines designation (Innovation Passport), development of a roadmap for designated products (Target Development Profile) and a toolkit of support options to facilitate timely R&D, regulation and access. Nevertheless, there are challenges to such an innovative approach to licensing and access including: increased complexity of downstream HTA and commissioning processes; methodological challenges, such as the quantification and presentation of uncertainty; policy challenges to ensuring safe and financially sustainable early access, and capability and capacity challenges in the design, commissioning and interpretation of real-world evidence studies.

Sequential approaches to regulation and HTA are now redundant as they are too slow and do not give enough 'touch' points between the two stakeholders. The pandemic has raised questions over the effectiveness of parallel regulatory-HTA approaches, as they do not facilitate collaboration between the two stakeholders. The best way forward may be to facilitate concurrent considerations of regulatory and HTA, where both stakeholders actively collaborate and there are several touch points.

To ensure successful multi-stakeholder collaboration in future, we must ensure scientific and planning information is shared freely and effectively between organisations. Downstream implications of earlier licensing need to be understood, a common taxonomy for uncertainty agreed, and risks for key stakeholders adequately managed. Shared stakeholder interest in new forms of data, evidence and standards should provide a fertile ground for continued partnership to support new technologies.



Are medicines regulatory and HTA models fit-for-purpose to support the development of an efficient review/access process?

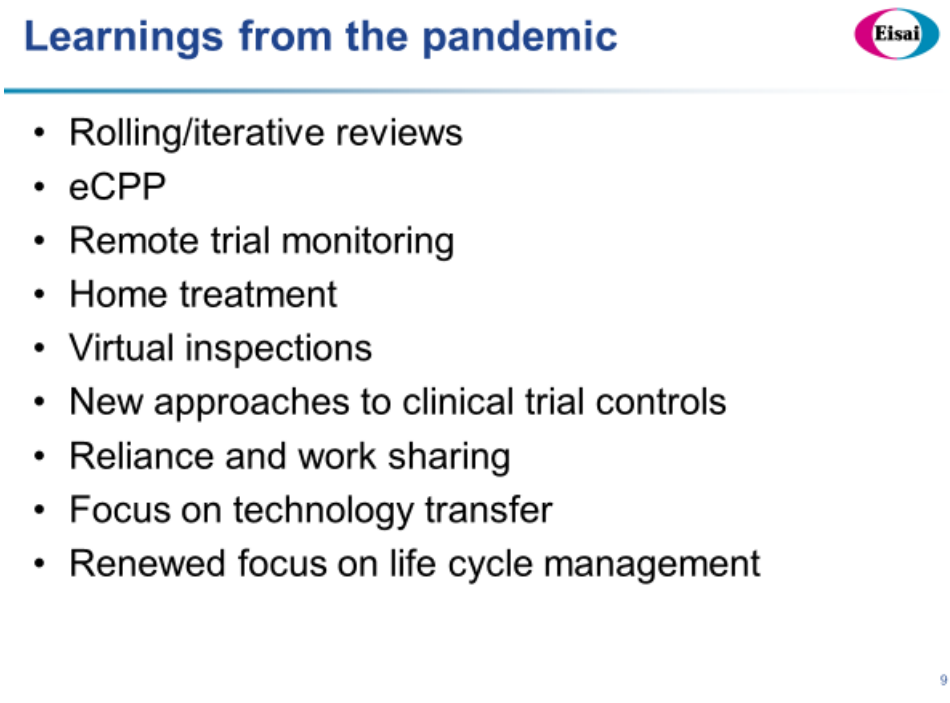
Industry perspective

Dr David Jefferys, *Senior Vice President, Global Regulatory, Government Relations, Corporate Affairs and Patient Safety, Eisai, UK*

During the COVID-19 pandemic, regulators and industry closely collaborated on an emergency response to maintain clinical trials and make vital preparations for vaccines and treatments. Regulatory agilities were identified, and a new co-creative environment was established, where both stakeholders worked jointly to pull products through development. Regulators offered support at all stages and became an enabler of technology as well as a promoter of public health. National, regional and international dialogues allowed best practices to be shared and regulatory agilities evaluated. Organisations like the World Health Organisation and International Coalition of Medicines Regulatory Authorities (ICMRA) played a key role in facilitating these discussions, as well as trade associations, patient groups and professional bodies.

The pandemic has presented several learnings for the life science sector, including the use of rolling reviews, remote trial monitoring, home treatment, electronic Certificate of Pharmaceutical Product (eCPP), virtual inspections, new approaches to clinical trial controls, reliance and work sharing, focus on technology transfer and renewed focus on life cycle management. Some of the wider environmental changes that have occurred are changes to the delivery of healthcare, acceleration of digital medicine, innovative approaches to diagnostics and new emphasis on public health. In addition, the pandemic has helped to improve societal understanding of drug development, which has not only created opportunities for industry and regulators to engage with the public and media, but also raised challenges related to trust, transparency and equity in healthcare.

To move forward and build on the learnings of the pandemic, we must find a way to fix the identified regulatory agilities into the new normal. Regulators should be encouraged to be an enabler of new technologies and promote co-creation of new policies and approaches.



New approaches to regulatory innovation emerging during the crucible of COVID-19

Accelerating changes to clinical development: what are the new opportunities?

Industry perspective

Dr Max Wegner, *Senior Vice President, Head of Regulatory Affairs, Bayer, Germany*

Urgency in responding to COVID-19 has led to new, efficient ways of regulatory innovation in relation to performance, speed, adaptability and collaboration. Regulatory professionals around the world have embraced home working, which has somewhat unexpectedly boosted productivity and facilitated teamwork and collaboration. The use of virtual platforms has allowed businesses to continue 'as usual', though it is important to recognise the loss of personal interactions, such as impromptu 'water cooler' conversations, which help to foster creativity, strengthen working relationships, and boost morale [1].

The COVID-19 pandemic prompted many regulatory agencies to introduce accelerated reviews of research proposals; at least a quarter of the world's regulatory agencies have issued guidance expediting standard review and approval processes. Despite these new agilities, the mission of regulatory agencies to promote and protect public health remains unchanged.

The use of mobile tools and digital technologies, including video technologies, have become more sophisticated, collaborative and accepted. The pandemic has prompted an increase in the use of decentralised trial models, telemedicine, measurements of endpoints with digital tools and direct shipments of study medicines to patients. It is important to learn from these experiences and leverage these technologies in a post-COVID-19 setting, which may allow more diverse participation in trials as well as real-time data collection.

Real World Data (RWD) and Real World Evidence (RWE) can help in the fight against COVID-19 and support regulatory approvals, provided there are appropriate data sources and methods for surveillance and analysis. However, the use of RWE in drug development is still maturing; recent learnings from high-profile studies of COVID-19 therapies (some of which were retracted) highlight the challenges with the use of RWE. Nevertheless, its utility in helping to identify and select study participants remains for more efficient and potentially safer clinically studies. There is a need for regulatory agencies, Health Technology Assessment (HTA) bodies and industry to come together to standardise datasets, data capture and data analysis.

New approaches to digital and electronic regulatory submissions and reporting could become more mainstream in future; all data could reside in the Cloud and be more readily exchanged between and among regulatory agencies across different geographies. The use of 'wet' signatures could be discarded, and electronic Common Technical Documents (eCTDs) be more broadly adopted. It may be possible empower more sophisticated analyses across disparate studies, applications and reviews and to facilitate global regulatory reviews simultaneously by enhancing support and capabilities for increasingly larger datasets. However, data integrity, security and protection must be ensured to allow acceptance of a Cloud-based approach.

Collaboration has been essential in the response to COVID-19. The International Coalition of Medicines Regulatory Authorities (ICMRA) has facilitated international collaboration between regulatory agencies, supporting regulatory convergence and flexibility, while pharmaceutical companies have shared perspectives and experiences through the Charles Forum [2].

In summary, the COVID-19 pandemic has demonstrated that high regulatory standards and speed are compatible. Collaborative steps have been taken to maximise the efficiency of clinical trials, harmonise

regulatory processes and utilise innovative digital technologies. The efficiency and flexibility realised could prove beneficial well beyond the pandemic, but this will only be possible if the same sense of urgency is maintained.

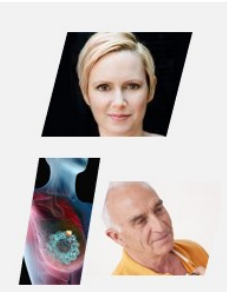
Learning New Ways of Working…

The use of mobile tools and digital technologies, including video technologies, have become more sophisticated, collaborative, and accepted! How can we leverage this ?

Decentralized clinical trials/ hybrid study approaches

Increased use of telemedicine

Use of digital tools in development to measure endpoints



Direct shipment of study medicines to patient homes

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Accelerating changes to clinical development: what are the new opportunities?

Regulatory agency perspective

Dr Martin O'Kane, *Clinical Trials Unit Manager, MHRA, UK*

As part of its initial response to the COVID-19 pandemic, MHRA set up a dedicated assessment team for COVID-19 trials, which offered expedited trial review and an optional informal pre-assessment process prior to the formal submission. In addition, an independent expert advisory group reviewed all Clinical Trial Authorisation (CTA) applications for COVID-19. Building on existing relationships, MHRA worked closely with ethics services and the NHS Health Research Authority to put in place a joint output on protocols for COVID-19 trials, which helped to reduce the risk of iterations.

Although there was a large drop in the number of non-COVID-19 trials assessed by MHRA from March – June 2020, this is now recovering to pre-pandemic levels. The average approval time for COVID-19 trials between January – August 2020 was nine days, which was greatly expedited compared to statutory timelines (30 days for initial assessment, 60 days for final decision). This expedited approval time was a collaborative effort between MHRA and sponsors, who often responded to the agency's questions within a matter of hours.

The MHRA Clinical Trials Unit has been tracking novel trial applications since January 2018 with the aim to support the use of these designs to increase trial efficiency. During 2020, there was a significant increase in the number of applications with novel trial designs, such as platform and umbrella trials. Collaboration across UK healthcare partners and infrastructure played a crucial role in the RECOVERY trial, which recruited approximately 1000 patients from 132 hospitals in 15 days.

During the pandemic, MHRA has identified where flexibilities in the regulation of medicines and medical devices may be possible, with a view to supporting the healthcare products supply chain and wider COVID-19 response. For clinical trials many of these flexibilities already existed but were rarely used, despite their regulatory acceptance and the availability of guidance. MHRA is consulting with its stakeholders to better understand why these flexibilities were not used prior to the pandemic and explore how they could become more embedded in normal practice.

MHRA is also looking to embed its new ways of working; for example, the pre-assessment service will be offered to sponsors of designated clinical trials to assist with finalisation of their key documentation for application for a CTA. The Clinical Trials Unit assessment team will provide feedback on the documentation in an expedited timeframe to facilitate document finalisation and internal sign offs prior to the project entering the critical path. This will greatly improve the chance of the application receiving a CTA without additional requests for further information at the time of the formal submission.

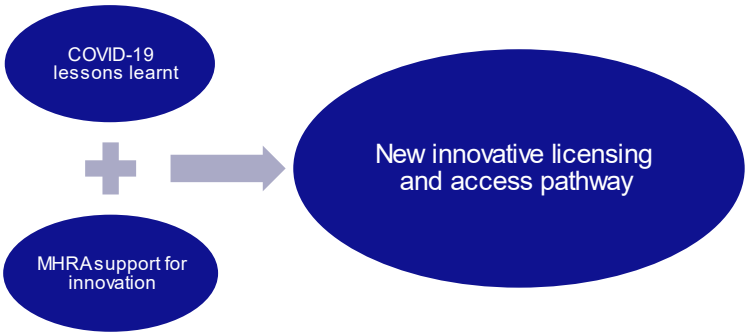
MHRA has launched a new ambitious route to approval called the Innovative Licensing and Access Pathway (ILAP), which aims to deliver efficient and timely development of medicines and earlier patient access. ILAP offers a new medicine designation called the Innovation Passport, which links to the development of a roadmap to patient access. This roadmap – called the Target Development Profile – is tailored to the needs of each innovative product, utilising tools from a toolkit and providing a platform for sustained collaboration between multiple stakeholders, including NICE, the Scottish Medicines Consortium and NHS. The regulatory toolkit is intended to drive efficiencies in the development programme, supporting data generation and evidence requirements. Tools being developed include novel clinical trial methodologies and design support, assisted trial recruitment using the Clinical Practice Research Datalink, and continuous benefit-risk assessments that integrate real word evidence.

In summary, MHRA have moved from reacting to the pandemic to providing support for recovery and resilience and encouraging new 'standard' ways of working. Going forward, MHRA will take an integrated

approach to support innovation in design through continued engagement with industry, charities, patients and research bodies. The agency has developed a regulatory toolkit composed of required components (tools that ensure regulatory compliance) as well as those that can be selected individually to support a bespoke development programme that reflects a lifecycle approach to evidence generation.

Moving Forward

- There is new experience and lessons learnt from COVID -19
- Use of existing but underused regulatory approaches were accelerated
- Existing and ongoing MHRA support for innovation eg novel trial design



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Increasing use of real world data (RWD) and real world evidence (RWE) pre- and post-approval to support regulatory decision making – is there a growing acceptance of its use?

Dr Nikolai Brun, *Chief Medical Officer, Danish Medicines Agency and Joint Chair, HMA-EMA Big Data Steering Group*

The data landscape has changed with the evolution of genomics, proteomics, imaging, behaviouromics, clinical data, wearables and social media data. These advances are driving digitisation of large volumes of research and clinical data, commonly termed 'big data', which may offer novel insights but the acceptability of such insights as evidence for regulatory decision-making is uncertain.

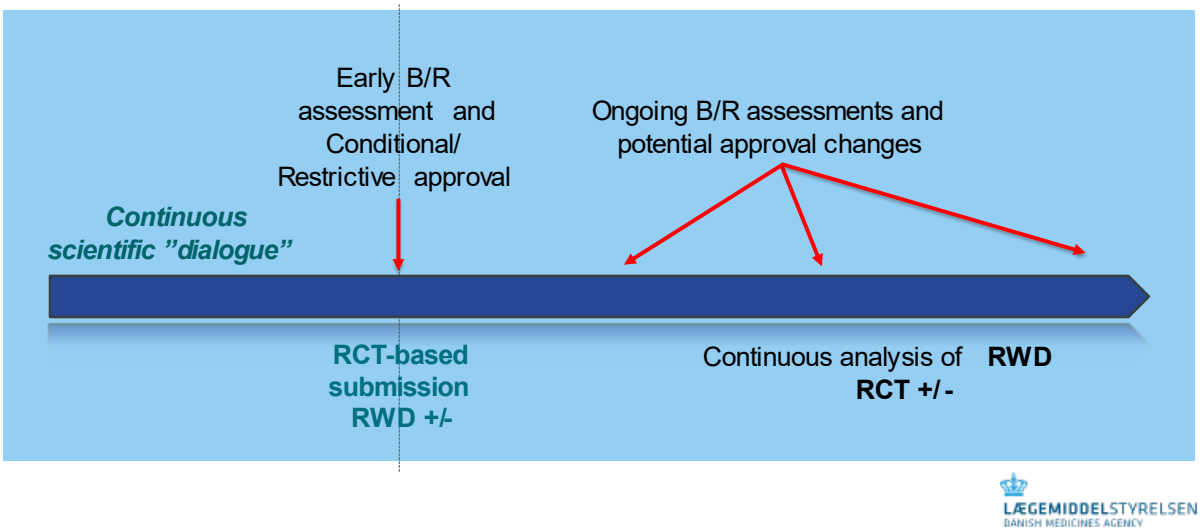
Currently, the regulatory paradigm utilises structured data sets from clinical trials, preferably randomised controlled trials (RCTs) to eliminate bias. Post-approval surveillance, which makes use of less structured datasets, is largely focused on pharmacovigilance rather than real world effectiveness. In addition, there is a lack of coverage for post-approval surveillance so adverse events are likely to be under reported.

In future, the regulatory paradigm may shift towards continuous scientific dialogue and earlier benefit-risk assessments, resulting in more conditional/restrictive approvals (see below). Regulatory submissions are likely to remain focused on RCTs but may also be supplemented with RWD. There would need to be agreement on a plan for continuous RWD analysis, not just for the reporting of adverse events but also for real world effectiveness. This would be of greater benefit to patients as well as industry and regulators.

The Heads of Medicine Agencies (HMA)-EMA Joint Big Data Task Force was formed to describe the big data landscape and identify opportunities for improvement for the EU regulatory system to ensure it has the capability and capacity to guide, analyse and interpret these data [1]. Priority recommendations from the Task Force include delivering a sustainable platform to access and analyse healthcare data from across the EU (called the Data Analysis Real World Interrogation Network (DARWIN)), enhancing data quality and representativeness, upskilling employees, building analytics capacity, and engaging with international initiatives on big data [2].

In summary, the data landscape has evolved, giving us vast volumes of data that have the potential to contribute significantly to the way the benefits and risks of medicines are assessed over their entire lifecycle. To move forward and fully realise this potential, the regulatory community must address the currently limited capacity and capability to access and analyse these large, heterogeneous and unstructured data sets.

Future Regulatory Paradigm?



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The pandemic accelerator - what digital technologies are helping to increase operational efficiencies in the regulatory space, and that companies hope will become part of the new normal?

Dr Virginia Acha, *Lead, Global Regulatory Policy, MSD*

The COVID-19 pandemic has accelerated existing trends for digital technologies that were able to support working during the pandemic and working to resolve the pandemic. These were applied at all stages of the medicines lifecycle for both COVID-19 and non-COVID-19 vaccines and treatments. Regulatory activities have been shaped by these digital solutions, particularly in the areas of clinical research, telematics and electronic information.

Socially distanced clinical research

Clinical research was greatly impacted by the pandemic from the outset, as healthcare settings were restricted and overwhelmed, and healthcare professionals were redeployed to COVID-19 care. Trial participants were not regularly able to travel safely and there was a risk of disruption to investigational medicinal products and other supplies as well as data integrity. Collaboration between industry and regulatory agencies helped to identify flexibilities that made use of available digital options such as remote monitoring and informed consent, direct to patient supply and remote source data verification. However, there are issues remaining related to data integrity and validity, trial site readiness for digital technologies and global variability.

Telematics and digital certification

Global interdependencies and collaboration took on an enhanced role during the pandemic, which facilitated agreement on the use of electronic Certificates of Pharmaceutical Product (eCPPs), remote inspections and extended Good Manufacturing Practice (GMP) certificates. There was also renewed emphasis on reliance during the pandemic, as it offered a solution to reducing the workload on regulators. However, not all countries were prepared to take advantage of these tools

Social distancing and restrictions on travel accelerated the global use of telematics such as virtual meetings, electronic submission of documents and electronic review systems. Where regulators had the infrastructure, capability and security measures to rely on these telematics, delays and backlogs were reduced.

Flexibility through electronic information

Electronic information offers the flexibility to tailor the provision to the needs of the user, for example, for the patient, carer, healthcare professional and wider public, as well as for different languages, cultures and abilities. Electronic information can also provide flexibility for supply to move where it is needed.

While the value of electronic information is generally agreed, there are questions over how it should balance with (or even replace) printed materials. Urgency in response to COVID-19 has shifted the balance in favour of more electronic formats, though there is still a need for an aligned approach with appropriate standards and security. Nevertheless, a legacy of acceptance amongst stakeholders may be possible, as the pandemic has clearly demonstrated the benefits of electronic information.

Progress made and direction indicated

Survey research conducted by European Federation of Pharmaceutical Industries and Associations (EFPIA), Vaccines Europe and Medicines for Europe highlighted the value of digital tools and support to meet the challenges of the pandemic. The survey showed that digital technology had provided flexibility and increased productivity in clinical research, regulatory operations, supply chain and pharmacovigilance (see below). Opportunities were identified in relation to Cloud computing, Blockchain technology and use of Artificial Intelligence (AI).

In future, greater productivity gains may be unlocked through digital breakthroughs involving machine learning and AI. Furthermore, quantum computing platforms could also further expand AI's potential, maybe even helping to predict and prevent the next pandemic.

Progress made and direction indicated

- Recent survey research conducted by EFPIA, Vaccines Europe and Medicines for Europe **recognised the value of digital tools and support** to meet the pandemic challenges.
- Digital tech provides **flexibility and increased productivity**:
  - Clinical research: patient access, novel metrics / patient-relevant measures, data controls
  - Regulatory operations: submissions, data review, certification, e-labelling
    - **Cloud computing** as a next step
  - Supply chain: stock control, testing controls, security
    - **Blockchain** as an opportunity
  - Safety and pharmacovigilance: reporting, enhanced signal detection and validation
    - **Artificial Intelligence** in signal detection and processing

Pr Proprietary

MSD 6

Reimagining medicines regulatory models

Adapting the medicines review framework pre- and post-approval - what flexibilities have been identified and what are the opportunities for and barriers against these being applied more widely across products for unmet medical need?

Regulatory agency perspective

Dr Peter Arlett, *Head, Data Analytics and Methods Task Force, EMA and Co-chair, HMA-EMA Big Data Steering Group*

Medicines regulation is for the good of patients and society and covers different steps in the lifecycle of medicines as well as different facets e.g. manufacturing, clinical, on-market use. At its best, regulation converts data to evidence to decisions and produces outputs such as evidence generation plans, authorisations and product information. In this way regulation enables patients to access medicines that address their needs and optimises the safe and effective use of products on the market. However, regulators are faced with a world that is changing in terms of diseases, products, evidence, companies and regulations. Other considerations include the distinction between public and private sectors, which can sometimes be blurred in medicines research, and that there will always be 'goodies and baddies', so some regulations are essential to deal with those who are non-compliant and less informed or less motivated than others.

To evoke change, regulators need political support, a legal mandate and resources. Other key enablers of change include transparency, good governance e.g. for public-private-partnerships, access to good data; work across disciplines; clear vision; and an experimental approach where regulators are ready to try, fail, learn etc. A public health crisis like the COVID-19 pandemic is also a driver for change. The regulatory response to COVID-19 has been a "sandbox for experimentation" and many lessons have been learned including the need for large, well-designed clinical trials; that real world evidence (RWE) can contribute to decision making but good data and methods are essential; and that it is possible to develop vaccines to accelerated timelines (when there is urgency and resource).

In terms of what changes should be implemented in future medicines regulatory models, there needs to be further convergence internationally, between regulatory domains (drug, device, digital etc) and between stakeholders e.g. through one development plan common across regulators and down-stream decision-makers including HTA bodies. In addition, the impact of major decisions on products (both authorisation and restriction of products) should be routinely monitored using RWE. Other concepts that could be discussed and considered in future regulatory models include:

- Is there a role for a supra-national or even a global regulator?
- Is there a role for regulators to act as innovation generators i.e. providing a hub for experimentation on regulatory science and process?
- Is there a role for regulators to act as consultants i.e. supporting academics/companies to make good choices?
- Is there a role for regulators as service providers i.e. with a unique position of knowledge and access to data and evidence?
- Should data and knowledge available to regulators be made a common resource for common good?
- Could regulatory outputs/information be designed to enable choice by patients i.e. by being more user friendly, focussing on information provision more than rules?

Nevertheless, there are aspects of regulation that must remain unchanged, such as the key focus on patient and public health. Clinical trials should remain a foundation of evidence generation, but with other approaches complementing this evidence base. Regulation should also continue to oversee the lifecycle of the product, whilst being risk proportionate.

In summary, to reimagine medicines regulatory models, we must recognise the purpose of medicines regulation and the changing environment that regulators are faced with. The COVID-19 pandemic has demonstrated that regulators can act as innovators experimenting in regulatory science, but there is still a need for further convergence between regulators, between regulators and other stakeholders, and between different regulatory domains.

EUROPEAN MEDICINES AGENCY

What will (should?) change

- Convergence between regulatory domains (drug, device, digital)
- Convergence internationally
- Convergence between stakeholders: one common development plan
- Impact of products and major decisions should be routinely monitored (RWE)

COVID-19 lessons learned and the 'new normal': Pfizer perspectives on adapting the medicines review framework pre- and post-approval

Adapting the medicines review framework pre- and post-approval - what flexibilities have been identified and what are the opportunities for and barriers against these being applied more widely across products for unmet medical need?

Industry perspective

Andrew Emmett, *FDA Liaison & Head of US Regulatory Policy, Pfizer, USA*

The COVID-19 pandemic has pressure tested regulatory systems like never before, as regulators and industry rapidly deploy innovative regulatory strategies to combat COVID-19 and sustain the integrity of clinical trials. There are opportunities for industry and regulators to learn from this crisis and proactively consider which of those learnings could be adopted permanently to help create a more efficient and patient-centric regulatory environment.

One such opportunity highlighted by the pandemic is the development of digitally resilient clinical trial systems, for example making use of telehealth, virtual monitoring, flexible sample collection, direct-to-patient delivery and apps/sensors/wearables. Decentralised clinical trials represent a spectrum of alternatives for how, when and where patients can participate in a trial, ranging from a single digital interaction to never coming to a trial site. Value drivers for decentralised trials include faster trial recruitment and retention; increased geographic reach, accessibility and population diversity; reduced participant burden; increased participant satisfaction; improved protocol adherence and enhanced representation of real-world elements. However, not all studies are suited to decentralised designs, so it is important to develop a framework that allows sponsors to choose between decentralised or traditional designs.

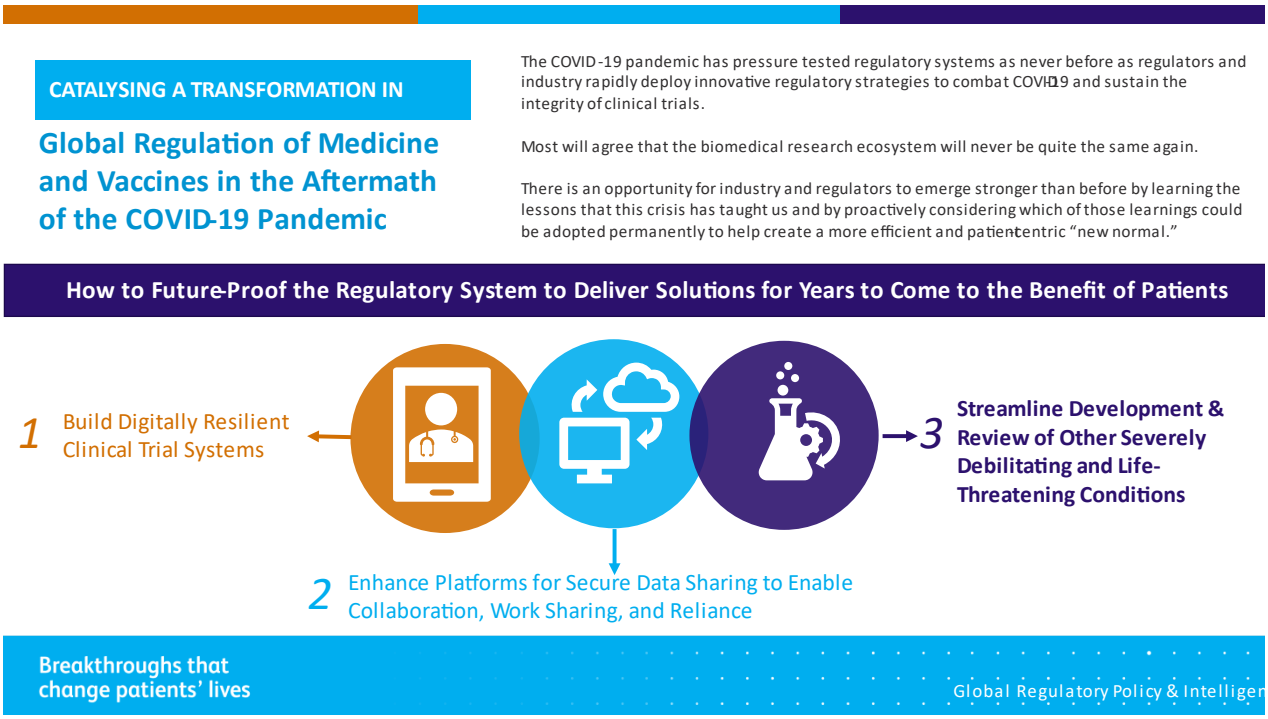
Advancements in health information technology and data science are creating novel opportunities to generate insights and evidence from real-world data sources, such as electronic health records, claims data, registries, and wearables. Databases and research methodologies used to collect and analyse these data have become more sophisticated, as healthcare researchers are gaining access to new, previously unavailable data. While the COVID-19 pandemic has pushed regulators to become more comfortable with leveraging real-world evidence (RWE) in their decision making, further progress is needed to validate RWE strategies for regulatory use, define the appropriate contexts-of-use, and articulate regulatory policies for use of RWE globally.

The breadth and depth of the collaboration between regulators and industry during the pandemic has highlighted the need for enhanced secure data platforms for regulatory data exchange and decision making. This would help to accelerate global capacity for regulatory submissions and facilitate real-time review, global collaboration and reliance, which will be important for addressing submission backlogs. In the long term, use of these platforms may evolve into a digitally-based ecosystem where multiple stakeholders can access the data they need and can leverage innovative drug development tools and data, such as RWE and artificial intelligence-based machine learning.

During the pandemic, the level of collaboration, urgency, and scientific ingenuity has helped to advance biomedical innovations in record time, for example through parallel scale-up, leveraging prior knowledge from platform technologies and deploying innovative clinical trial designs. This raises questions around whether the same level of urgency can and should be applied to severely debilitating or life-threatening diseases (SDLTs). However, it is important to define the scope and requirements for SDLTs; a given disease may be non-SDLT or SDLT at certain points during its trajectory, and in other instances, SDLTs may represent more severe manifestations of a condition not shared by all patients with the broader

disease. Workshops and guidance may help to clearly articulate objective criteria for SDLTs across therapeutic areas and identify conditions that warrant streamlined and flexible development plans.

In summary, there is great potential for the research community to learn and apply durable lessons from the COVID-19 pandemic. Focus should be given to building digitally resilient clinical trial systems; enhancing platforms for secure data sharing to enable collaboration, work sharing and reliance; and streamlining the development and review of therapies for SDLTs.



Scientific dialogue and interactions during development: what new opportunities have been identified and are these sustainable to be more widely applicable?

Dr Jillian Fuhs, *Advisor, Global Regulatory Affairs North America, Eli Lilly, USA*

During the COVID-19 pandemic there has been increased use of digital platforms by companies and agencies to enable increased speed and collaboration for the development and review of COVID-19 products. For example, virtual meeting platforms have facilitated real-time information sharing in a more flexible manner than previous physical meetings. In addition, there has been timely solicitation and receipt of scientific advice and guidance for industry has been published rapidly and updated in real time.

Regulatory agencies and companies have worked together during the pandemic to identify what submission packages would be available when, to then put in place a strategy for rapid submission and review. Leveraging this regulatory flexibility facilitated timely global submissions elsewhere, for example, Eli Lilly was able to repurpose its request for US Emergency Use Authorisation (EUA) for baricitinib for other countries. Regulatory agencies have also applied risk-based decision-making criteria to the acceptance of innovative clinical evidence generation such as adaptive trial designs.

Based on these learnings and experiences, there are opportunities that can be implemented post-pandemic. Central electronic access for submitted documents and harmonised requirements amongst agencies would be beneficial to avoid duplication and improve transparency. This could go one step further by developing a Cloud-based platform where multiple stakeholders in different regions can share real-time data and insights. There is also an opportunity for flexible and iterative regulatory advice along the development continuum, which integrates greater access to specialised input (paediatrics, drug-device combinations etc) when novel approaches are proposed. Rather than creating new pathways to accelerate drug development, regulatory agencies should consider optimising existing pathways by applying them more transparently and liberally, as well as leveraging existing tools to increase early and iterative communication. In addition, risk-based decision-making criteria should be expanded to Chemistry, Manufacturing and Controls (CMC) regulatory requirements.

Regardless of which opportunities are implemented post-pandemic, our priority should be to maintain high standards for quality, safety and effectiveness. It is not sustainable to approach every drug development programme as we have for COVID-19 products, for example, the ‘24/7 work week’ should only be reserved for public health emergencies. However, certain risk-based opportunities for change should be considered for other life-threatening diseases and epidemics, such as obesity and diabetes in the US. Other opportunities for change that should be implemented as they are widely applicable and high impact are the creation of a global platform for real time data and insight sharing; development of a central electronic repository for submitted documents; enhanced iterative scientific advice and communications; continued leveraging of digital technologies; and transparency and clear guidance on how best to leverage these tools.

What new opportunities may exist?

- Central electronic access to submitted documents and harmonized requirements
- Global platform to share real -time data and insights
- Flexible and iterative regulatory advice along the development continuum, which integrates greater access to specialized input (e.g., pediatrics, drug - device combinations) when novel approaches are proposed
- Expand risk-based decision-making criteria to CMC regulatory requirements
- Transparently apply existing accelerated pathways more liberally and leverage the existing tools to increase early and iterative communication

Patient perspective of the pandemic: benefits and challenges

Pat Furlong, *President and CEO, Parent Project Muscular Dystrophy (PPMD), USA*

The COVID-19 pandemic has had an impact on all stakeholders involved in drug development from industry to patients to regulatory agencies. A number of changes have been implemented to accelerate COVID-19 development programmes and relieve pressures on healthcare systems, some of which could greatly benefit diseases other than COVID-19 if continued and evolved post-pandemic.

One such change has been in telemedicine; the pandemic has enabled more widespread access to telemedicine, which can be greatly beneficial for patients (particularly for paediatric and disabled patients) as it reduces the burden of travel. For example, for families living with the rare muscle-wasting disease, Duchenne muscular dystrophy, travel to specialist clinical centres can be tiring and costly, and visits may become more frequent and burdensome as the condition progresses. The pandemic has also accelerated innovations in clinical trials, such as the use of master protocols, where multiple drugs are investigated using one protocol with only one common placebo control. This may be a more efficient and inclusive approach for rare diseases like Duchenne with small recruitment populations.

Increasing evidence shows that assessments done by trained caregivers in a trial participant's own setting allows for a more habitual functional assessment than assessments done in an artificial environment with strange assessors. For example, home video capture has been explored as an outcome measure to quantify the progression of Duchenne with greater sensitivity and reliability than traditional measures performed in the clinic. After watching training videos that standardised video capture procedures, caregivers recorded their children performing specific tasks in the home environment using a mobile app. The videos were then quality controlled and watched by trained physical therapists serving as central reporters who scored each activity using a validated scorecard.

Wearables have great potential in capturing outcomes that matter to patients, though it is important that they meet the requirements of and are accepted by regulatory agencies. Furthermore, wearables need to be actually 'wearable' for patients, for example, for boys with Duchenne muscular dystrophy, this may mean being the right colour, size and/or style.

Parent Project Muscular Dystrophy (PPMD) has published white papers and several studies that give insight into the expectations of families living with Duchenne, including information about benefit expectations and risk tolerance relating to Duchenne drug development [1-2]. These have helped to inform regulatory agencies about the Duchenne patient experience and to evolve the science of patient involvement. Although significant progress has been made in promoting patient-focused drug development, it is important to understand how this will be weighted within the regulatory review process and explore how it could further evolve post-pandemic.

The PPMD Duchenne registry collects real-world data from patients with Duchenne muscular dystrophy including genetic information, patient-reported outcomes, steroid use, trial participation and clinical function assessments. The registry's rigorous data collection makes it a valuable resource for the synthesis of real-world evidence to be used in industry and regulatory decision making. It is available for trial design feasibility, targeted research, surveys, mutation-specific data, longitudinal data, targeted recruitment and post-marketing surveillance.

In summary, clinical studies need to fit into the lives of patients and families and assessment should be tasks that are meaningful to them. COVID-19 has brought about learnings around the use of telemedicine; real-world evidence; data sharing; innovation in clinical trials; validating video capture as an outcome measure; and wearables. Application of these learnings, while maintaining the same sense of urgency as for COVID-19, could be greatly beneficial for drug development for rare debilitating diseases like Duchenne muscular dystrophy.

Learnings from Sars Cov-2

- Telemedicine – continue to refine
- Real World Evidence (RWE) – what is acceptable
- Validate video capture as outcome?
- Patient Focused Drug Development (PFDD) – come full circle – understand how this will be weighted within the review process
- Innovation in clinical trials
- Data sharing – Patient Reported Outcomes, RWE
- Wearables – what is acceptable for regulatory agencies and 'wearable' for patients.

References:

[1] Hollin, IL, Peay, HL, Apkon, SD & Bridges, JF (2017), Patient-centered benefit–risk assessment in Duchenne muscular dystrophy. Muscle Nerve, 55: 626-634. https://doi.org/10.1002/mus.25411

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Accelerated regulatory approvals, risk sharing and sustainable access – what are the implications for access recommendations, and will this lead to increased use of a lifecycle approach to access?

Dr Clifford Goodman, *Senior Vice President, The Lewin Group*

Regulatory agencies around the world have established programmes to expedite drug development and regulatory review for serious conditions. The US Food and Drug Administration (FDA) offers four expedited approval programmes: Accelerated Approval, Priority Review, Fast Track and Breakthrough Therapy. Although these are distinct programmes, they share common characteristics in that they facilitate earlier approval of drugs for serious conditions and that fill an unmet medical need; offer increased engagement with the FDA; and allow for approval based on preliminary clinical evidence, such as phase 2 or single-arm trials, or on surrogate or intermediate clinical endpoints. Following an accelerated approval, confirmatory phase 4 trials are required, which then allow the FDA to either grant a traditional approval or remove the drug from the market.

Products that have accelerated regulatory approval can raise several challenges for Health Technology Assessment (HTA) agencies and payers. These approvals are often based on small sample sizes (especially for therapies for rare conditions) with insufficient follow-up meaning that the data on duration of efficacy/effectiveness and on rare and delayed adverse events is limited and there may be insufficient subgroup data or patient heterogeneity. There may also be a limited set of outcomes/endpoints and reliance on biomarkers/surrogate outcomes, which may or may not correlate well with the primary endpoints of interest. Furthermore, the comparator selected may not always be appropriate for HTA and payer decisions and the costs may be difficult to estimate based on available pre-market trials.

HTA agencies and payers are responding to these issues by adapting their requirements and processes, for example, by having different requirements for clinical submission; different requirements for economic submissions; more leniency in evidence rigour; more flexibility in economic modelling; different willingness to pay, for example, in cost per Quality Life Adjusted Year (QALY) gained thresholds; broader consideration of value; conditional approval/coverage that may require more data collection; more emphasis on patient/caregiver input; different or adjusted appraisal committees; separate formularies; and separate budgets. In addition, some HTA agencies have distinguished between therapies for rare and ultra-rare diseases and have developed separate pathways for each.

An increasing number of drug and biologic candidates for expedited regulatory review include ‘durable’ or potentially ‘curative’ gene therapies, cell therapies, and other therapies using highly innovative mechanisms of action. Many of these therapies have list prices in the range of $1 million or even higher. Uncertainties about patient response/outcomes, durability, and financial/actuarial risk to payers of some of these therapies are increasing interest in alternative payment models where the risk is shared between payer and manufacturer. These models are usually either outcomes/value-based or finance-based i.e., not linked to outcomes. Types of outcomes/value-based payment arrangements include:

- **Milestone** (or “installment” or “conditional treatment continuation”): payment when outcome targets are met at specified intervals
- **Performance-based annuity**: annual (or other time interval) payments as long as therapy continues to meet outcome targets
- **Value-based pricing**: price set on magnitude of net benefit (may be based on cost-effectiveness)
- **Regimen-based pricing**: price decreases (or manufacturer rebates payer) when a patient needs an additional therapy to improve the effectiveness of the therapy
- **Indication-specific pricing**: price varies depending on magnitude of net benefit when therapy used for different clinical purposes (could be variable value-based pricing)

Outcomes/value-based payment arrangements are likely to rely on data from registries or other sources of Real-World Data (RWD). For example, Centers for Medicare & Medicaid Services (CMS) issued conditional coverage for a transcatheter aortic valve replacement technology that required an approved registry to track the following outcomes: stroke, all-cause mortality, transient ischaemic attacks, major vascular events, acute kidney injury, repeat aortic valve procedures and quality of life.

In summary, accelerated regulatory approvals have downstream implications for payers and the HTA agencies that advise them. Payers and HTA agencies are responding to the increased uncertainty of accelerated approvals by adjusting their requirements and processes as well as considering risk-sharing agreements, such as outcomes/value-based payment arrangements.

Accelerated Regulatory Approvals Pose Challenges

Products that have accelerated regulatory approval can raise challenges from payers and the HTA organizations

- Small sample sizes, esp. for therapies for rare conditions
- Insufficient follow -up
  - limited data on duration of efficacy/effectiveness
  - limited data on rare and delayed adverse events
- Insufficient subgroup data/patient heterogeneity
- Limited set of outcomes/endpoints; reliance on biomarkers/ surrogate outcomes
- Selection of comparator
- Costs difficult to estimate based on available pre -market trials

Opportunity for harmonisation of requirements to increase regulatory and industry agility

Dr Theresa Mullin, *Associate Director for Strategic Initiatives, FDA Centre for Drug Evaluation and Research*

In March 2020, regulatory agencies around the world were confronted with the unprecedented challenge of the COVID-19 pandemic, which created a shared focus on a single, life-threatening disease with no available and proven safe and effective medicines or vaccines. This unique context introduced a greater tolerance of risk and uncertainty and a strong sense of urgency; for example, agency staff have been working at a level of intensity that is not sustainable in the long term.

The pandemic has catalysed collaboration and information sharing among regulatory agencies. The International Coalition of Medicines Regulatory Authorities (ICMRA) has acted as a key facilitator and has convened multiple technical workshops including topics such as vaccines, trial designs, therapeutics under investigation, use of observational studies and Real-World Data (RWD) etc. Since April 2020, there have been bi-weekly ICMRA teleconferences co-chaired by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), which have focused on sharing information on policies, regulatory agilities, treatments, shortages related to COVID-19; updates on other focus topics addressed by working groups and statements being prepared; and more in-depth presentation and discussion on topics of interest e.g. virtual inspections, health fraud, approaches to pharmacovigilance.

The pandemic has also had a significant impact on supply chains including manufacture of Active Pharmaceutical Ingredients (APIs) providing much of the world's pharmaceutical supply. Stay-at-home orders have affected manufacturing facility staffing and operations and regulators have not been able to travel to facilities and conduct inspections. Closed borders have disrupted the flow of normal pharmaceutical supply chains and there have been materials shortages including glass vials and stoppers for parenteral medicines, as well as surges in demand for critical care medicines already at risk of shortage before the pandemic. These issues highlighted the need for greater mutual reliance as well as greater agility for both regulators and manufacturers.

Regulators have responded to supply issues by making efforts to enable continued operations including premarket inspection in review of new drugs. Temporary guidance has been issued to amend requirements for Good Manufacturing Practices (GMPs) to enable flexible approaches to deal with disruptions in formal facility operations. The use of remote site assessments has been expanded and regulatory reliance utilising site inspection reports and other information gathered by other capable regulatory authorities has been used to enable more timely decisions.

Manufacturers have faced simultaneous surges in demand for medicines used to treat patients hospitalised with COVID-19 on every continent and have been under pressure to adjust suppliers, processes, systems and operations to overcome disruptions and strengthen the supervision and the resilience of the supply chain. This has put a spotlight on the critical importance of post-approval changes (PACs) to rapidly respond to new issues and integrate new experience and information to improve drug quality and availability. Depending on the changes to be made and how many countries a drug is marketed in, manufacturers may have to apply for tens or even hundreds of PACs, which can be challenging to coordinate.

Regulators must work with manufacturers to build capability for pharmaceutical quality knowledge management, which may require:

- **Harmonisation of standards for unique identifiers** for facilities, products, marketing application holders and marketing authorisation applications.
- **Harmonisation of structure and content of facility inspection reports** to support a common structured electronic format that is more readily accessed and analysed.
- **Further structuring and standardisation for industry submissions** of Chemistry, Manufacturing and Controls (CMC) information in Module 2 and 3 of the electronic Common Technical Document (eCTD).
- **Harmonisation of standards and approaches to regulatory review and assessment of CMC information** including assessment of pharmaceutical quality system effectiveness for PACs.
- **Secure and sharable storage of data** related to facility inspections and sponsor application information to enable greater reliance among regulators under mutual recognition agreements.

In summary, the COVID-19 pandemic has catalysed regulatory collaboration and information sharing and highlighted the need for agility for both regulators and manufacturers. Opportunities for further coordination and convergence have been identified, and the harmonisation work that is required could perhaps be led by ICMRA, working closely with the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

International collaborations on policy and technical issues - is this just for pandemics or a roadmap for future global collaborations to enable sharing of expertise and knowledge?

Dr Samvel Azatyan, *Team Lead, Regulatory Convergence and Networks Team, Regulation and Safety Unit, World Health Organisation (WHO)*

Medical products regulation is faced with challenges related to globalisation of markets; increased sophistication of health technologies; rapid evolution of regulatory science; increasing complexity of supply chains; transparency and growing public expectations. There is currently a lack of clear vision and understanding in the setting up of regulatory systems that are able to manage all regulatory functions in one national setting. International cooperation is important to ensure local access to safe, effective and quality products and to make the best use of available resources and expertise, avoid duplication and concentrate regulatory efforts and resources where they are needed most.

About a third of National Regulatory Authorities (NRAs) have limited or no capacity to perform core regulatory functions. There is a regulatory capacity gap between low- and high-income countries in terms of human and financial resources, effective performance of regulatory functions, expertise available for fulfilling regulatory functions, availability of proper systematic training for regulators and applying quality management principles. WHO efforts to address this gap and facilitate good quality regulatory decisions globally include promoting good governance and transparency through Good Regulatory Practices; promoting and facilitating regulatory system strengthening, such as through its global benchmarking process; supporting regulatory workforce development via a global regulatory curriculum; promoting regulatory cooperation, convergence and harmonisation; promoting work sharing and reliance; and facilitating accelerated products introduction into countries through various pathways.

Reliance is defined as the act whereby a regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions, assessments and information of others. As the level of reliance increases, the efficiency of regulation increases, which thereby improves access to quality-assured, effective, and safe medical products. The WHO has set out principles and recommendations for Good Reliance Practices in a guideline that has recently been adopted by the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP). Examples of pathways/initiatives based on reliance include the WHO Prequalification collaborative registration procedure, the ‘Stringent Regulatory Authority’ collaborative registration procedure and regional networks such as the African Medicines Regulatory Harmonisation initiative, Association of South East Asian Nations (ASEAN) project to Strengthen the Implementation of ASEAN Harmonised Requirements (SIAHR), Caribbean Regulatory System and others.

During the COVID-19 pandemic, the WHO has been working with many stakeholders to accelerate research, ensure manufacturing capacity, facilitate regulatory coordination and collaboration, and support policies and delivery channels. The Access to COVID-19 Tools (ACT) Accelerator launched on 24th April 2020 with the aim to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines. ACT is a joint effort between WHO and other global health actors, private sector partners and other stakeholders to accelerate development and availability of new COVID-19 tools; accelerate equitable global access to safe, quality, effective, and affordable COVID-19 diagnostics, therapeutics and vaccines; and ensure that in the fight against COVID-19, no one is left behind.

The WHO has also partnered with the Italian and Japanese regulatory agencies to analyse regulatory agilities/flexibilities that have been implemented in the context of COVID-19 in a broad spectrum of regulatory activities. This analysis showed that most regulatory agilities were aiming to facilitate

production and access to COVID-19 medical products and that clinical trials oversight and marketing authorisation/approval were the most targeted regulatory functions/activities across the different product types. In addition, there was an increase in the implementation of registration pathways through reliance and mutual recognition for COVID-19 products, and remote monitoring and virtual inspections were important in continuing to provide regulatory services for clinical trials, manufacturing etc.

In summary, timely access to medical products is a continuous challenge that has become even more important to address with the COVID-19 pandemic. To generate quality national decisions and avoid duplication, regulators globally must collaborate and take into consideration the information available from other regulatory authorities. Focus should be given to the practical implementation of various accelerated pathways and regulatory flexibility should become a 'norm', rather than an exception only used in public health crises.

Timely access to medical products– never-ending challenge

- Today's reality and demand:
  - Regulatory flexibility (agility) should become a "norm" and not the exemption;
  - Focus should be on the practical implementation of various accelerated pathways (fast-track, etc.) – **country readiness**;
  - To generate quality national decisions regulators globally MUST collaborate and MUST take into consideration the information available from other regulatory authorities;
  - Not using the outputs and outcomes from other (better resourced) regulatory authorities would only mean lost opportunity, duplication of efforts, increased regulatory burden and waste of scarce resources;
  - At time of a pandemic this would cost many lives which otherwise could have been saved.

World Health Organization

Re-imagining Medicines Regulatory Models: Implementing fit-for -purpose sustainable activities for patient access. 8-9 December 2020

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International collaborations on policy and technical issues - is this just for pandemics or a roadmap for future global collaborations to enable sharing of expertise and knowledge?

Maria Cristina Mota Pina, *Director, Regulatory Policy, Abbvie, USA*

International collaborations and work-sharing arrangements have been evolving over recent years and investment in these is now paying off with the COVID-19 pandemic. During crises it is even more evident that the world is interconnected; with globalisation and people mobility, it is clear that no country can work in isolation and that global issues require global solutions.

Regulators are working together through various collaborations, such as the International Medical Device Regulators Forum (IMDRF), the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The World Health Organisation (WHO) has a key role in communicating and coordinating among member states and supporting regulatory alignment and convergence. Regulatory reliance is a key enabler in expediting approvals globally and work-sharing initiatives such as Project Orbis and the ACCESS Consortium are demonstrating new, more efficient ways to conducting medicine regulation.

Industry is also willing to collaborate and to not work in isolation; there are multiple international trade groups that engage on a wide range of advocacy issues and present an aligned industry view. Industry participates in forums with regulators such as through ICH and Asia-Pacific Economic Cooperation, and has engaged with other stakeholders such as the WHO, World Bank and the Bill and Melinda Gates Foundation. TransCelerate and the Charles Forum are examples of industry collaborations that share the same goal in how to better engage, collaborate and be a partner in developing faster and better medical products.

ICMRA has been supporting regulatory agencies with initiatives on communication, crisis management, innovation, pharmacoviglance, supply chain integrity, antimicrobial resistance and reliance. During the COVID-19 pandemic, ICMRA has demonstrated its leadership by issuing multiple statements and hosting frequent meetings and workshops to facilitate collaboration and information sharing among regulatory agencies. Industry must continue to engage with ICMRA to share experience and develop solutions, which will support an even more robust framework and preparedness for future crises.

There is an opportunity to capture learnings from the experience in collaborating during the pandemic to implement stronger frameworks for international collaboration that go beyond managing a crisis. To further realise these benefits to patients, we need to continue advancing these learnings, including the use of digital technology to facilitate interaction and collaboration. For example, can we extend further to collaborative platforms for regulatory submissions? Cloud-based systems have the potential to accelerate and streamline the regulatory review and enhance regulatory decision-making, encompassing parallel regulatory review and reliance. However, there is a need for a roadmap for the future, which could consider international collaborations and use of platforms to support regulatory agilities and good communication between regulators and industry.

In summary, public health emergencies trigger regulatory agencies and industry to identify opportunities to innovate and be more agile to keep business continuity and develop new medicines in new and transformative ways. Using existing regulatory convergence and harmonisation platforms like ICH, WHO and ICMRA, will continue to support coordination and international collaboration. While some of the agilities identified during the COVID-19 pandemic have the potential to become permanent solutions, the use of digital tools has the potential to transform international collaborations.

Aspirations for the future

- The pandemic revealed that perceived barriers to collaboration could be overcome, to allow collaboration in a very agile way
- Opportunity to capture learnings from the experience in collaborating during the pandemic to build upon the lessons learned and implement stronger frameworks, for international collaboration, beyond managing a pandemic
- To further realize these benefits to patients, we need to continue advancing these learnings, including the use of digital technology to facilitate interaction and collaboration

Leveraging comparable agency decisions – in what situations is this the right way forward?

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

Regulators around the world are faced with common challenges and so can benefit from working together and leveraging regulatory decisions. This includes societal challenges, such as COVID-19, uncertainties in benefit-risk decisions, empowered patients and the 'legal lag' of trying to catch up with innovation, as well as technical challenges related to precision medicine, Advanced Therapy Medicinal Products (ATMPs), new facilitated (expedited) licensing pathways and new trial designs. In addition, there can be ongoing challenges with healthcare budgets, Health Technology Assessment (HTA) and cost-benefit analyses and evolving digital technologies such as artificial intelligence and machine learning.

Trust is the foundation to leveraging regulatory decisions; this is built through harmonisation and convergence, for example, by implementing Standard Operating Procedures (SOPs), familiar processes and templates, and by adhering to international requirements and guidelines. Once confidence has been built, regulatory agencies can operationalise reliance and work-sharing models to benefit from shared workload whilst maintaining autonomous decision making. Recognition models, where the decision of a regulator or other trusted institution is accepted by another, are often viewed as the 'highest' level of reliance and may be based on a mutual agreement or treaty between the organisations involved.

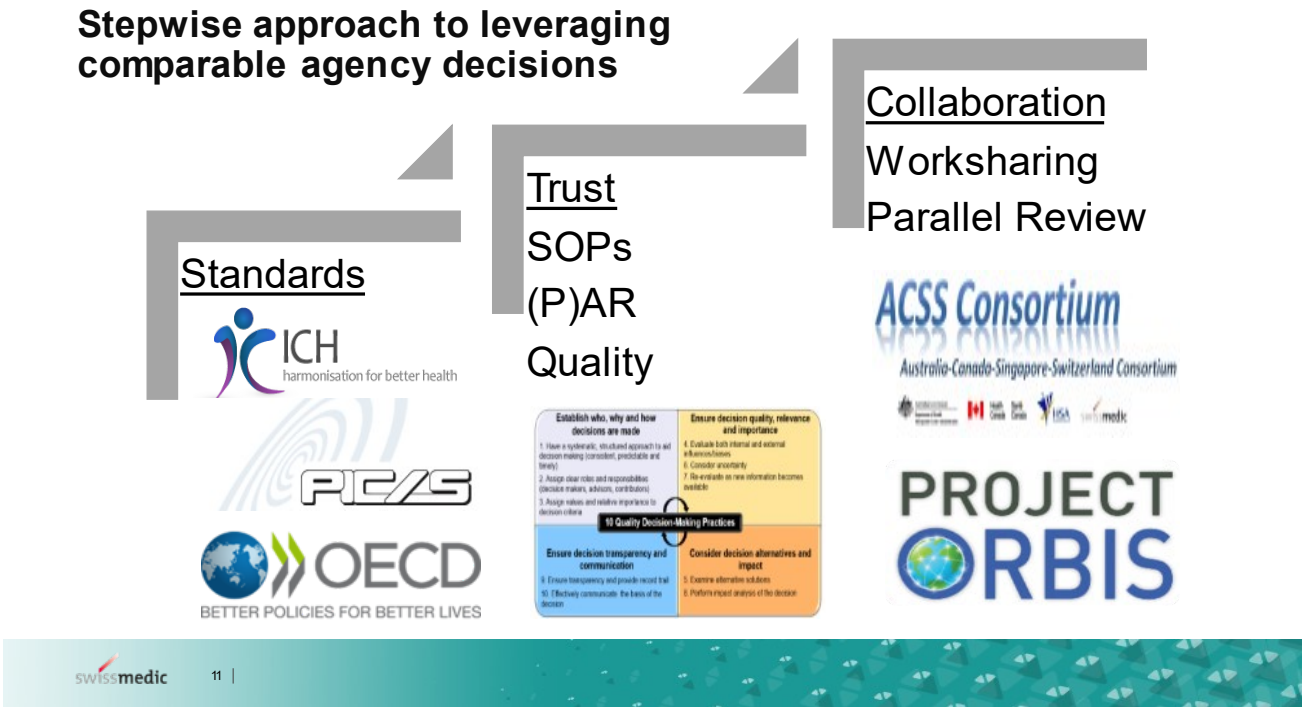
The ability to leverage regulatory decisions evolved in a stepwise fashion, beginning with national regulators who formed networks across regions, such as those in Europe under the European Medicines Agency (EMA), as well as agencies in Australia, Canada, Singapore, Switzerland and UK working together under the ACCESS Consortium. Global networks of regulatory agencies include the International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organisation (WHO).

When operationalising reliance, agencies need to make use of an integration model in combination with a collaboration model. The integration model is based on trust of formal processes, methodologies, standards etc, while the collaboration model is more improvisational and highly dependent on deep expertise across multiple functions; for this reason, collaborative working is important for more complex products. However, it is not enough for agencies to simply rely on these operating models; these concepts must also be firmly documented and implemented in their strategic goals. For example, Swissmedic's 2019-2022 strategy includes objectives on international standards (working with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)), work sharing (through ACCESS and Project Orbis) and regulatory system strengthening in low- and middle-income countries (working with the WHO).

Comparable agencies can be identified through ICH membership and/or referring to the WHO Global Benchmarking Tool (GBT), which defines maturity levels of regulatory agencies (level 1 being lowest maturity, 4 being highest). The GBT also helps to identify agencies who have legal provisions or regulations that allow recognition or reliance (see sub-indicator MA01.08). It is important that regulatory agencies are transparent about the criteria they use to identify comparable agencies and that they document this in the public domain.

Some methods of leveraging regulatory decisions may be better suited to some regulatory agencies than others. For example, WHO pre-qualification (PQ) is mainly relevant to GBT level 1 & 2 agencies, whereas work sharing largely applies to GBT level 3 & 4 agencies, as it requires some expertise to coordinate. Parallel review also requires some resource to ensure processes run smoothly so may only be suited to GBT level 4 agencies. Although various reliance procedures could be used by all regulatory agencies, regardless of maturity, it seems that GBT level 1-3 agencies might benefit the most.

In summary, standards, trust and collaboration are key to leveraging comparable agency decisions. This is a stepwise approach, based on standards but also requiring trust of the quality of decisions as well as networks for collaboration (see below). While reliance could be beneficial for all regulatory systems, work sharing may be better suited to more mature systems and pre-qualification to less mature systems.



Future thinking: reimagining the regulatory model – what are the questions we should be asking of regulatory systems but are not?

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

To reimagine regulatory models, we must consider the wider context of the healthcare system. Medical product regulation is only one part of ensuring a quality health care system; having quality practitioners as well as quality facilities are equally important. The regulatory authority is key to ensuring quality health care products and must add value to the healthcare system to be valued by it. In addition to marketing authorisations and other routine lifecycle regulatory milestones, such as clinical trial authorisations, there are other aspects of the regulatory system that should be reimagined: substandard and falsified products; electronic labelling; manufacturing variations; post authorisation infrastructure; regionalisation of regulation; confidentiality laws; and the impact of conditional authorisations.

Substandard and falsified products

Substandard and falsified products are a major public health problem in much of the world. Even in high-income countries, it has been reported that it is equally profitable and less risky to engage in falsifying medical products rather than engaging in illicit trafficking of controlled substances, particularly with the rise of direct internet purchasing. This problem will potentially be exacerbated by the increasing political emphasis on local manufacturing in some countries (to create jobs etc), without adequate local regulatory oversight of manufacturing to assure that products produced meet international quality standards.

Technologies such as international barcoding could help address this issue, though it is important that these technologies meet the needs of all countries and their healthcare and economic systems. Regulation must demonstrate its value not only for public health but also for economic health. Quality should be incentivised, and procurement processes changed to focus on treatment with quality medicines, not just treating patients with the cheapest medicines. However, it is also important that products are only considered medicines if they work and if they are accessible at the patient level without bankrupting the patient. Without systems in place to assure product quality and to assure access to such quality medicines, the public health problem of substandard and falsified medicines will not go away.

Electronic labelling

In many parts of the world, professional and patient leaflets are not updated quickly, or at all, when changes are made to approved labelling/leaflets. This defeats the purpose of providing current, actionable information about a product to practitioners and patients, meaning they are not aware of how to use it most effectively and safely. Often this lack of updating is simply due to the logistics of trying to print new labels in multiple languages and formats and then to have them inserted into medicines that are already in the field.

Paper requirements should be substituted with electronic labelling, which could be available in the cloud or elsewhere through barcodes or other technologies. This would alleviate the issue of printing in multiple languages and allow for more accessible formats, for example, audio copies for those who are blind or illiterate. In addition, this would help with inventory management as products could be sent across boundaries without having to be relabelled. The required infrastructure for electronic labelling should be feasible with the evolution of smart phone technology, however, we must start investing in this area for it to ever become a reality.

Manufacturing variations

With increasing numbers of authorised products, variations are a huge amount of work for companies and regulators. Non-synchronous authorisations of variations – especially manufacturing changes – is one of the major causes of shortages and stockouts in many parts of the world.

For products being authorised via a reliance mechanism, one could imagine a system where manufacturing variations, once authorised by the reference agency, would be communicated to all countries in which the variation applies, and which relied on the reference agency for the initial authorisation. Rather than the current 'opt in' approach, the reliant agency would have to 'opt out' of the authorisation within a certain period of time or the authorisation would take effect automatically. This would arguably require changes in legislation or regulation, but such an approach could relieve companies and agencies of much needless work and would help assure that the lack of a variation submission and/or authorisation would no longer be a cause for a stockout locally.

Post-authorisation infrastructure for continuous learning

Increasing numbers of products are being initially authorised via facilitated pathways, often with requirements for post-approval studies to ensure continuous learning and re-evaluations of benefit-risk. However, much of the world does not have the infrastructure to implement such post-authorisation requirements i.e., studies, limited distribution, mandatory reporting schemes etc. Will this lead to inequity in access and/or unsafe or ineffective use of the product in certain areas? Going forward, it will be important to invest in this infrastructure, if there are going to be more and more accelerated/conditional/ emergency authorisations with requisite follow-up. Without this infrastructure, patients in such countries will either be denied timely access through these accelerated pathways, or will have access but without the requisite safety/distribution/follow-up required to assure the most effective and safe use of the product.

Increase in regionalisation of regulation

Regulation is increasingly being regionalised; this is being driven by a need to pool regulatory resources in the clinical trials, marketing authorisation and pharmacovigilance arenas, as well as to increase attractiveness to developers by increasing the size of the market to which a regulatory decision applies. How do we define what the community wants from these regionalisation efforts? For example, how should fees and workforces be managed, and how should it be linked to procurement (like pre-qualification) so that it has added value versus individual national authorisations? Within these regional networks, national agencies still have the key role, particularly those in 'anchor' countries that have expertise and resources; how can these be successfully transferred to other agencies in the network?

Confidentiality laws

With an increasing emphasis on reliance-based regulatory pathways and reducing redundancy, it is important that access to full regulatory work products (scientific assessments, inspections reports, laboratory testing reports) is increased. Agencies must also have access to the data they need to assure that the product coming to their country is the same version of the product assessed by the agency upon which it wishes to rely when making its own decision. However, confidentiality laws are a significant barrier to achieving this, as agencies are restricted both in what they can share and what they can receive. Are our 20th century confidentiality laws no longer fit for purpose in our globalised, interconnected 21st century world? Do we need a complete reassessment of our confidentiality laws? This is necessary to allow reliance pathways to reach their full potential.

Impact of conditional authorisations

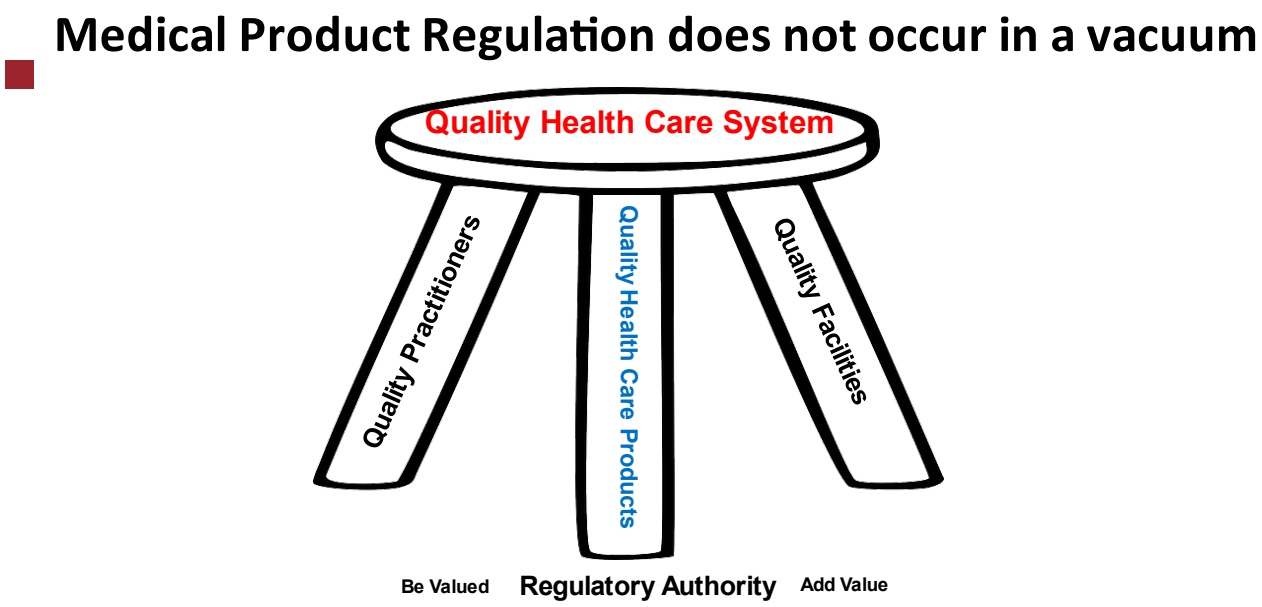
There is increasing pressure to authorise products for unmet medical needs on less than comprehensive data sets under various emergency and/or conditional/accelerated approvals. But what does this mean for the wider health ecosystem for example in terms of conditional liability and conditional reimbursement? Like regulatory processes, these too must be more agile and evolve with the increased knowledge we gain over time with each product.

Marketing authorisations

There is a fundamental question around whether establishing an individual product's benefit-risk profile is still the only fit for purpose goal of a product development and regulatory assessment ecosystem. Why would one expend regulatory resources assessing a product that cannot demonstrate its value to the health care system or that no one is willing to buy? Is having a regulatory agency assessing benefit-risk and an HTA agency assessing value a redundancy when it comes to safety and efficacy? Is it a waste of regulatory resources to assess a product that then is found not to add value or be of an acceptable value by an HTA or procurement agency?

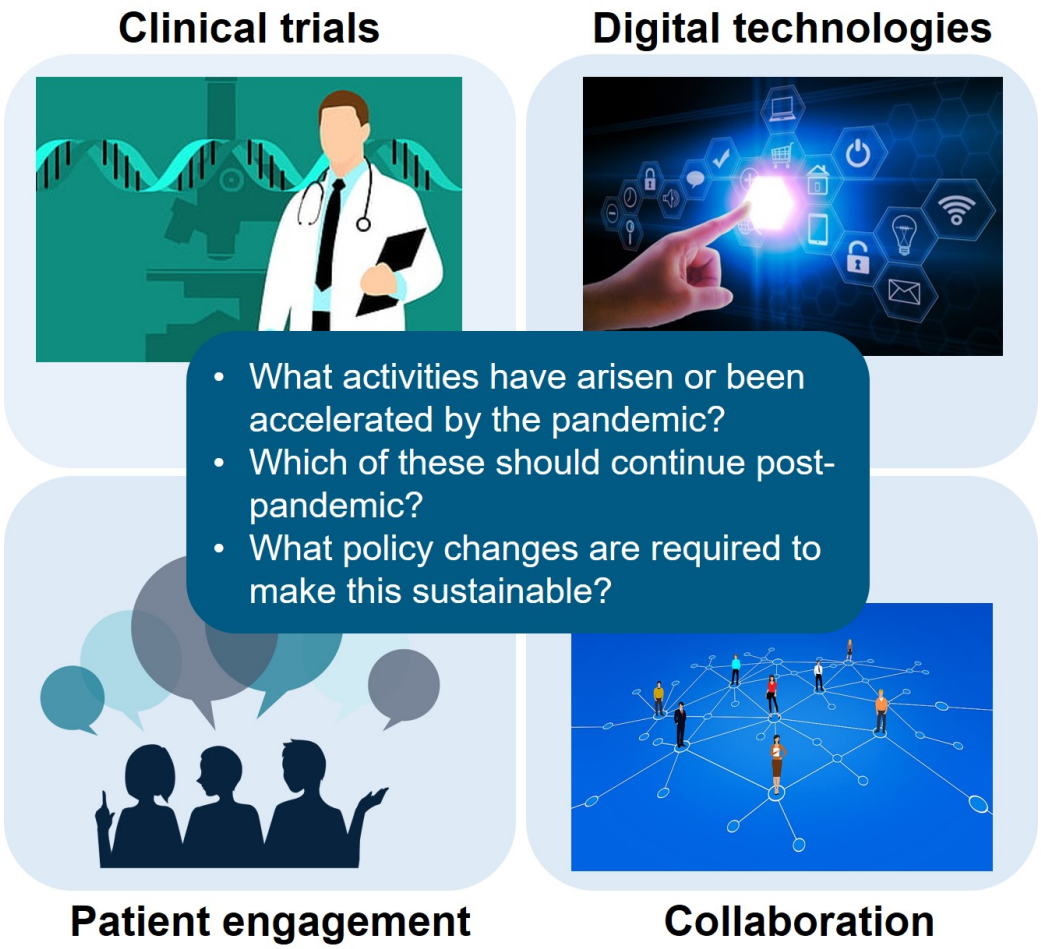
Perhaps we could consider a future regulatory ecosystem for marketing authorisation that requires positive outcomes from two systems (either linked or separate systems):

1. One system assesses and assures quality of products entering the market and the equivalence of various versions of those products
2. The other system assesses the safety, efficacy and public health value of the product to the healthcare system.



Section 3: Breakout discussions

A key objective of this workshop was to make recommendations on activities that should be considered to evolve a sustainable, fit-for-purpose regulatory model(s) for the development, review and access of new medicines. This was facilitated through breakout groups during which workshop participants discussed lessons learned from four areas that had to fundamentally change because of the pandemic: clinical trials, digital technologies, patient engagement and collaboration. Each breakout focused on one of these areas and discussed activities that evolved as a result of the COVID-19 pandemic as well as lessons learned that could inform future regulatory models.



Breakout A

Clinical trials during the pandemic – how does this reframe the thinking for undertaking clinical trials post-pandemic?	
Chair	**Prof Ton de Boer,** *Chairman, Medicines Evaluation Board (MEB), The Netherlands*
Rapporteurs	**Prof Sam Salek**, *Head, Regulatory Science Programme, University of Hertfordshire, UK* **Amelie Sylven,** *Senior Regulatory Affairs Manager, Abbvie, Switzerland*

Background

The COVID-19 pandemic has forced sponsors of clinical research to re-think elements of the traditional model of how clinical trials need to be conducted. Every element of the process has been impacted, from the distribution of supplies, to addressing way to ensure compliance and remote data capture. This offers an opportunity to transform the holistic approach to clinical trials. As Honig and Hirsh (2016) noted before the pandemic, an approach they termed Adaptive Biomedical Innovation (ABI) offers a "multi-stakeholder approach to product and process innovation aimed at accelerating the delivery of clinical value to patients and society. ABI offers the opportunity to transcend the fragmentation and linearity of decision-making in our current model and create a common collaborative framework that optimises the benefit and access of new medicines for patients as well as creating a more sustainable innovation ecosystem" [1].

Adapted approaches are now being put in pace for even the largest scale trials. For example, UC Irvine and dozens of other research centres had just begun enrolling participants in the AHEAD study, a global effort that will test whether an investigational drug can slow down the earliest brain changes associated with Alzheimer's disease. These remote studies will provide real life evidence for what can and cannot work poste-pandemic, even if vaccinations allow the return to non-socially distanced approaches to clinical studies.

An important opportunity is arriving with the reauthorisation of PDUFA. Industry has indicated that PDUFA VII should glean from lessons learned during the COVID-19 pandemic. There is a pressing need for FDA, and industry, to identify actions taken during the COVID-19 pandemic and evaluate their effectiveness and applicability to innovative drug development beyond the public health emergency. Industry spokesmen have indicated that they would also like to see "More predictable and timely engagement and better communication during drug development," including enhanced technological infrastructure at the agency including a flexible and scalable global framework for digital technology development, building on experience with a shift to telemedicine and digital health technologies during the pandemic. Greater support for real world evidence in regulatory decision-making can be an important way forward.

The purpose of this breakout is to examine how the pandemic has affected these aspects of development and specifically clinical trials used in the development and regulatory assessment of innovative products, and what learnings can be taken forward to a post-pandemic setting. The key considerations for discussion are:

- What are the changes that have been observed in how clinical data are collected that have arisen as a result of the pandemic?
- Which of the traditional and which of the "innovative" approaches or modifications should continue or be evolved post-pandemic?
- What are the key challenges/barriers for putting these into practice?

- What are the regulatory considerations for suggested changes and how do we ensure that they meet regulatory rigour?

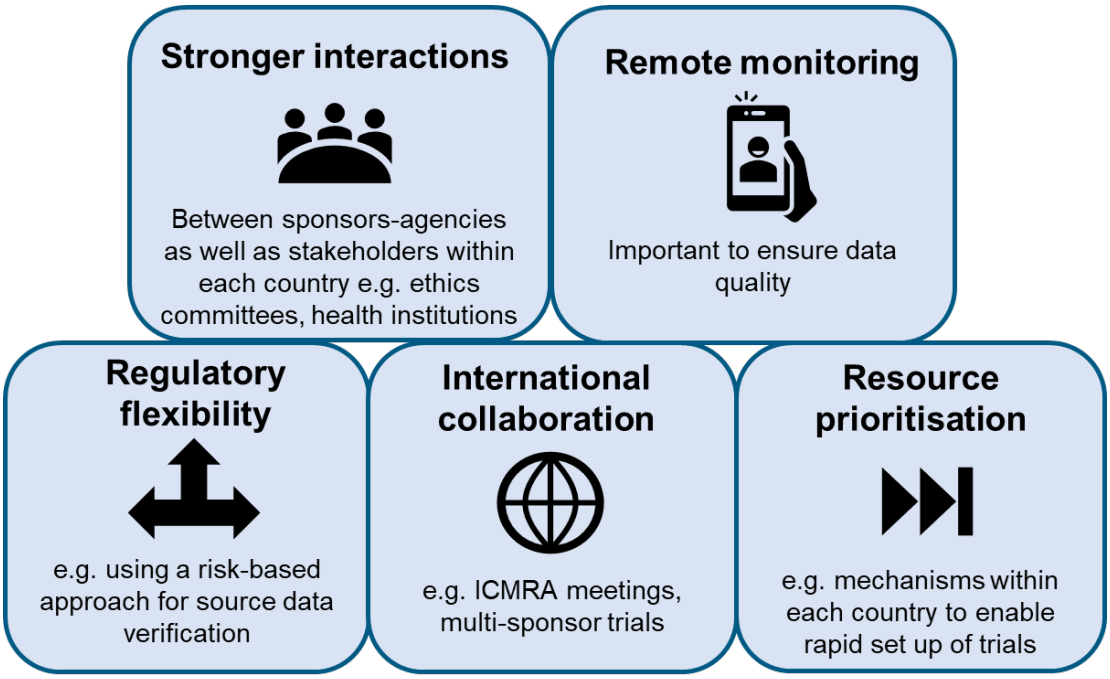
References

[1] Honig, P. and Hirsch, G. (2016), Adaptive Biomedical Innovation. Clin. Pharmacol. Ther., 100: 574-578. https://doi.org/10.1002/cpt.513

Discussion results

The breakout group focusing on clinical trials discussed practices that arose or were accelerated by the pandemic and were then challenged to identify up to five areas that it believed were critical and should continue post-pandemic.

What should continue or be evolved post pandemic?



Topics to explore further

- Optimal use of facilitated regulatory pathways and how to enhance them
- Optimal use of digital tools/wearables e.g. 24-hour monitoring
- How co-development (multiple sponsors) and co-creation (agency-sponsor) can continue to drive innovation to address unmet needs
- Need for in-depth cases studies on COVID-19 trials – how can learnings be translated to non-COVID trials?
- Use of social media/technology for trial recruitment - currently no clear guidance

Breakout B

Use of digital technologies to accelerate development and review – how can these be built on to enable increased efficiency and effectiveness throughout the lifecycle?	
Chair	**Dr Alison Bond,** *Director, EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen, UK*
Rapporteur	**Megan Klopchin,** *Consultant- Policy Research, Global Patient Outcomes & Real World Evidence, Eli Lilly and Company, USA*

Background

The COVID-19 pandemic made change unavoidable. Development and regulatory systems globally have been challenged in all areas to support the pandemic response. This has forced a regulatory rethink as agencies and companies respond to the challenges by increased flexibility, novel solutions as well as acceleration of regulatory approaches to clinical development, review and post approval activities that had previously been only theoretical, piloted or in limited use prior to the pandemic.

The use of digital technology is at the forefront of many of these required changes for companies and agencies to ensure that the development and review of new medicines could be sustained during the pandemic. In the development space this saw the increased use of existing digital tools to improve the efficiency of operations both by companies and agencies; this has included the rapid move to virtual or decentralised clinical trials and utilisation of digital technologies such as apps and wearables.

Changes have also occurred in the way other regulatory activities are now undertaken, moving to virtual onsite inspections, acceptance of electronic documentation and submissions, the potential to share data electronically and make changes in real time.

As the regulatory landscape changes to meet the challenges of today to facilitate patient access to essential therapies, several questions arise:

- What have we learned from having to amalgamate the best of the current regulatory approaches to immediately implement new fit-for-purpose approaches?
- How and where has digital helped to bridge the gap between what was previously done physically to being undertaken virtually
- Which of these activities should be retained and what are the opportunities to enhance the use of these post-COVID and which approaches can be evolved to become applicable to all medicinal products for unmet need?

This breakout is therefore being asked to build on the workshop discussions but with the lens on the use of digital technologies and changes to the regulatory model. Key points to discuss are:

- What are the new opportunities or key areas that digital technologies have had a major impact in the development, review and post approval and which ones do regulators and industry want to evolve and why?
- What digital technologies are helping to increase operational efficiencies in the regulatory space, and which ones would do companies and agencies hope to become part of the way forward?

Discussion results

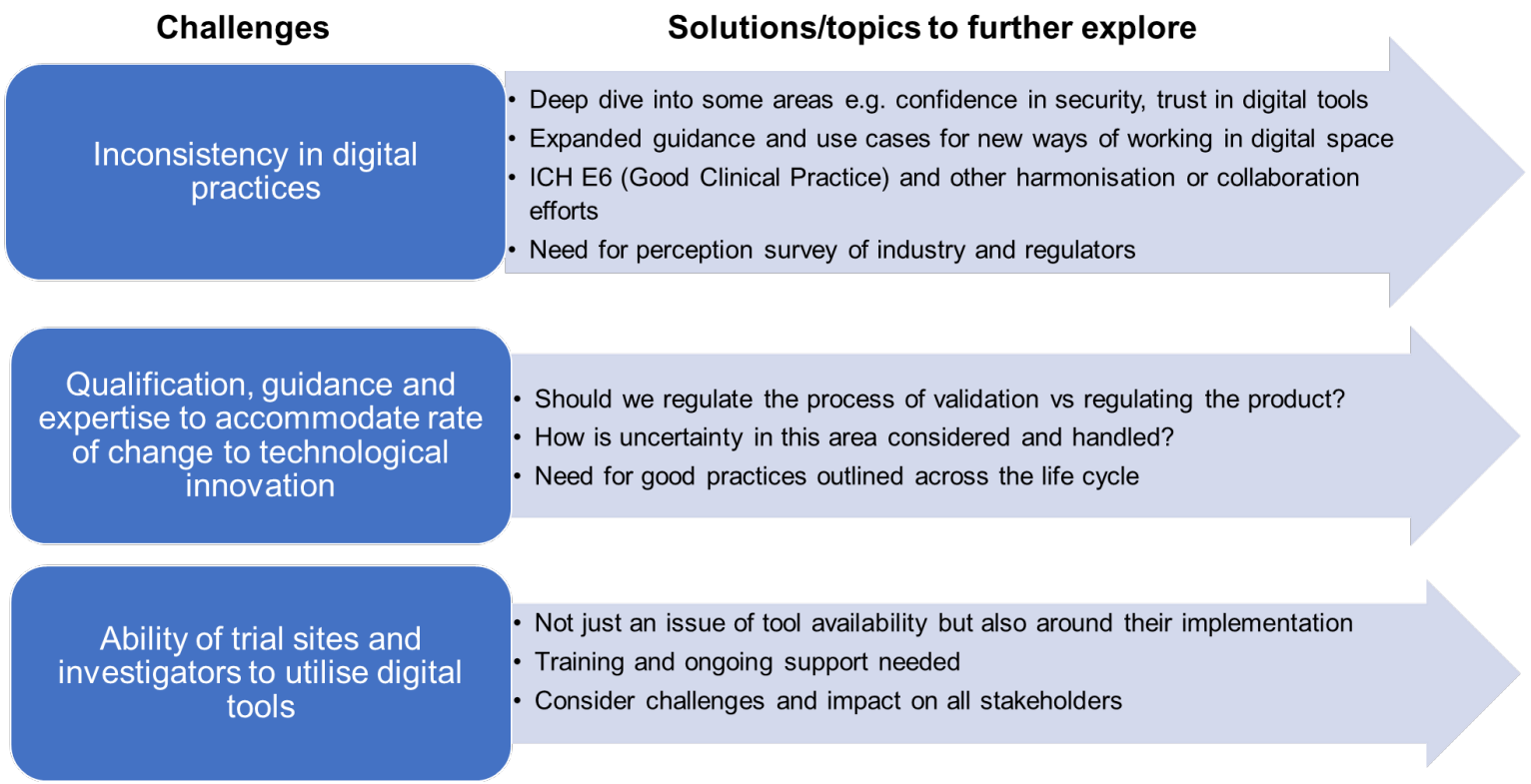
The breakout group on digital technologies discussed the impact of several digital tools and activities during the pandemic and was challenged to identify up to three critical areas that should be retained post-pandemic (see below). The group was also asked to identify up to four key challenges and their potential solutions or policy changes needed to leverage the technologies' potential (next page).

Many of the digital technologies discussed were essential in enabling decentralised clinical trials and remote inspections during the pandemic but also have value outside of a pandemic setting.

One issue that was raised during the breakout but could not be discussed in the time available was around **access to digital technologies** e.g. there may be limited participation by some groups as a result of age, geography, social-economic factors.

How have digital technologies changed the regulatory model?		
Digital technologies (activities/areas)	**Impact on medicines development, review or post approval**	**Retain post-pandemic?** (Pick up to three)
Enablers of virtual or decentralised clinical trials and associated tools, including **electronic Patient Reported Outcomes, telehealth, apps and site monitoring**	• Provides additional clarity on endpoints, conduct, and what can be remotely captured • Continuous patient monitoring to enable insights • Reducing barriers to participation in research can facilitate faster and more diverse patient recruitment • Considerations – important that data privacy is still protected in a virtual setting and aspects related to data integrity must also be considered	✓
Use of **apps** (especially for the collection of safety data), **digital tools, wearables, devices with digital software** for pre/post authorisation utilisation	• Additional clinical aspects that can be collected and examined, including new novel endpoints • Increased ability to monitor compliance and patient engagement e.g. reminders	✓
Clarity of e-consent	• Ease of consenting and ensuring the right version gets to the patient at the right time • Ability to provide information in a more easily understood way • Increased control and security around consent • Better understanding of expectations which could also help with compliance	
Algorithms for signal detection (use of machine learning/artificial intelligence) and the potential for moving data to the Cloud	• Ability to better and more quickly detect issues and signals	
Common digital infrastructure and platforms for collaboration and work-sharing during the review, including Cloud submissions	• Ease of submission and review • Opportunities for parallel review • Facilitation of regulatory processes • Reduction of duplication • Improved review efficiency • Potential for increased harmonisation and alignment • Accelerated regulatory approval and patient access	✓

What are the main regulatory challenges and potential solutions for sustaining these digital technologies post-pandemic?



Breakout C

Patient engagement – Future opportunities to engage both in development and regulatory decision making	
Chair	**Dr Mathieu Boudes**, *Project Coordinator, IMI project PARADIGM, European Patients Forum*
Rapporteur	**Dr Bettina Doepner,** *Global Lead Regulatory Intelligence and Policy, Director, CSL Behring, Germany*

Background

The COVID-19 pandemic has amplified public interest in science, research and healthcare, which could be a potential opportunity for education and engagement. However, the pace at which COVID-19 research has been pushed through suggests that public and patient input may have been bypassed in the process. It will be important to ensure that this is not carried through to regulatory assessments, which are not only about determining benefit-risk but also interpreting what this corresponds to in real life.

There has been significant progress in recent years around the science of patient input and several guidelines have been published such as the EUPATI Patient Engagement Roadmap [1], PARADIGM Toolbox [2] and FDA Patient-Focused Drug Development guidance [3]. However, questions still remain over how best to collect and submit comprehensive and representative patient experience data. This data may also change over time, so how can it be submitted throughout this continuum in a timely and meaningful manner? In addition, there may be a need to grade the quality of patient experience data in order to define the weight it has on regulatory decision-making.

While the pandemic has had a damaging impact on non-COVID-19 research, with many trials still on hold, it has also enhanced the availability and use of digital/virtual tools and platforms. Remote monitoring and telemedicine are now being used widely, but what impact has this had on gathering patient input – is it now easier to collect patient experience data? Or are patients facing COVID19-related challenges that affect their involvement?

The purpose of this breakout is to examine how the pandemic has affected patient engagement in development and regulatory assessment and what learnings can be taken forward to a post-pandemic setting. The key considerations for discussion are:

- What opportunities for patient engagement in development and regulatory assessment have arisen as a result of the pandemic?
- Which of these should continue or be evolved post-pandemic?
- What are the key challenges/barriers for putting these into practice?

Definitions used in this breakout

The FDA definition of patient engagement is “activities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA’s public health mission. Such activities may include testimony at Advisory Committee meetings, submission to a regulations.gov public docket, meetings attended by patients, FDA, and other stakeholders, other correspondence with FDA, interactions through social media, and interactions with or information from patient representatives or patient advocates.”

References

[1] Geissler, J., Ryll, B., di Priolo, S. L., & Uhlenhopp, M. (2017). Improving Patient Involvement in Medicines Research and Development:: A Practical Roadmap. Therapeutic Innovation & Regulatory Science, 51(5), 612–619. https://doi.org/10.1177/2168479017706405

[2] https://imi-paradigm.eu/petoolbox/

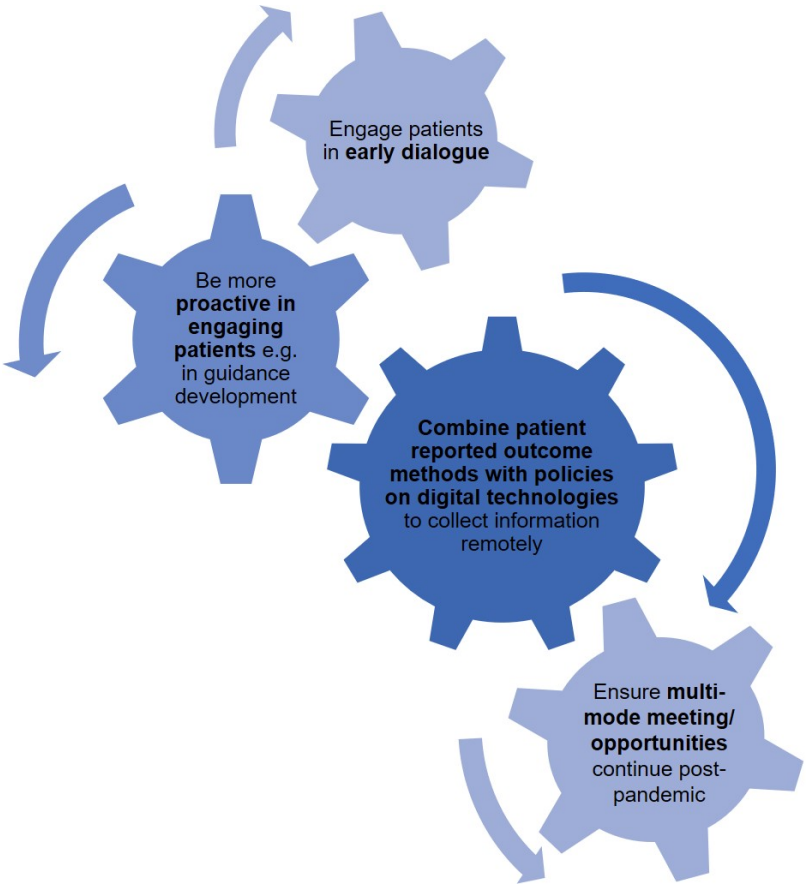
[3] https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Discussion results

What activities have arisen or been accelerated by the pandemic?

The breakout group examining patient engagement highlighted a major opportunity in the use of virtual/remote technology as an engagement tool. The use of virtual meeting platforms increased significantly during the pandemic, making it easier to accommodate multi-stakeholder meetings including patients. These meetings were organised more quickly, more frequently and included more people, potentially reaching patients who had not engaged before. However, it was noted that virtual meetings cannot easily facilitate the networking and personal interactions that occur in face-to-face meetings, which can offer important opportunities for drug developers and regulators to learn from patients (and vice-versa) in a less formal manner. It will be important to build on the learnings from virtual meetings and expand the patient engagement toolbox after the pandemic.

How could patient engagement be evolved post-pandemic?



Topics to explore further

Significant progress has been made in relation to patient engagement in development and regulatory assessment over the last decade and policy continues to move in the right direction. However, the pandemic has highlighted the challenge of adapting patient engagement strategies and the collection of patient-reported data to expedited procedures and timelines – do new strategies need to be considered?

Other issues for consideration

Issues that were raised during the breakout but could not be discussed in the time available were:

- Challenges faced by patient organisations during the pandemic e.g. funding
- Different roles of patient organisations vs. individual patients
- Questions of bias (independency when done remotely) and data security
- Enabling patients / patient groups to help in the collection of real-world data
- Challenge to build public trust in the vaccines being developed.

Breakout D

Collaboration and knowledge sharing between stakeholders for improved interactions for facing healthcare challenges – what does the future roadmap look like?	
Chair	**Dr Thomas Lonngren,** *Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden*
Rapporteur	**Stephen Fawbert,** *Director, Global Regulatory Policy EMEA, MSD, UK*

Background

The COVID-19 pandemic has challenged the current regulatory paradigm and promoted coordination across stakeholders, both at the technical and policy level, to facilitate timely availability of vaccines/treatments globally. This has been enabled by agencies working together, such as a continuation of the long-standing collaboration between EMA and FDA, and organisations such as ICMRA and the WHO. In addition, this has been facilitated through collaboration at industry level, such as through the "Solidarity trial", demonstrating that much can be achieved by companies coming together early in the development process. The evolution and creation of novel networks has emphasised that no single organisation is sufficiently resourced to face the pandemic alone and that working together can help get rid of divergences, remove duplication and address unmet medical need globally in a timely manner.

As stakeholders continue to re-imagine the regulatory landscape, including any lessons learned from the pandemic, it is of importance to review the current approaches to collaboration and knowledge sharing between stakeholders. The objective should be to determine which types of collaboration should be continued even without the pandemic setting, recognising that others may need to be reserved for emergency situations only. In addition, it would be of interest to discuss what additional approaches are still lacking and should be put in place to further facilitate sharing of information and resources.

The three key areas of greatest interest for collaboration and convergence are to ensure: 1) common direction for policy areas and regulatory science priorities; 2) common technical standards through information and work-sharing; 3) knowledge sharing through different stages of the regulatory review through the use of reliance and recognition. The ultimate aim would be to ensure a sustainable cooperation model for all therapy areas for the future.

The key considerations for discussion from this breakout are:

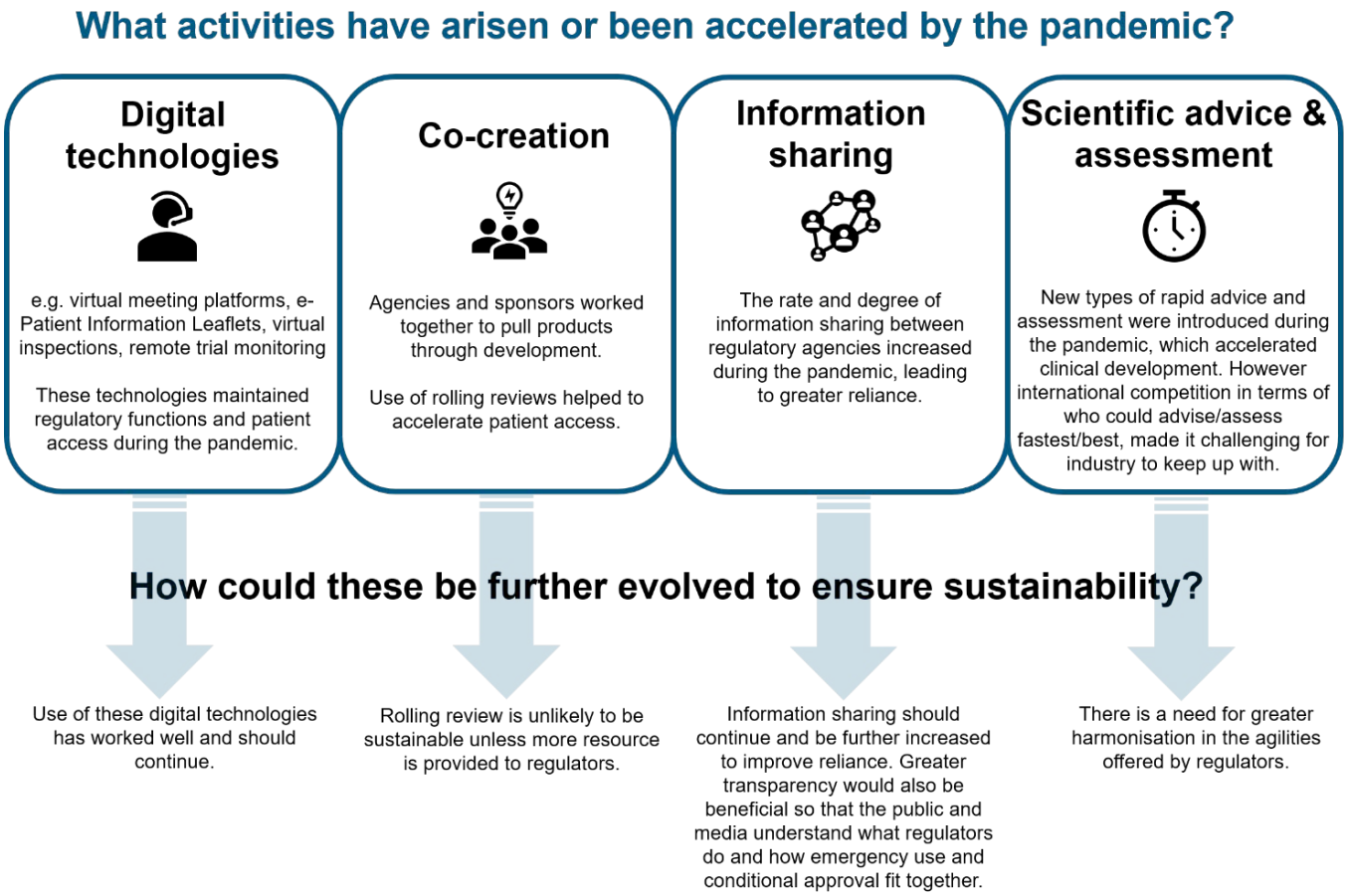
- Does the current regulatory paradigm allow for efficient collaboration and knowledge sharing between stakeholders to ensure timely access to medicines globally?
- What are the most important new interactions that were created or accelerated by the pandemic and should stay? What is their value and how could it be further evolved?
- What are the gaps in current interactions (highlighted by pandemic) that need to be brought forward – what hasn't been tried yet and what next steps could be proposed?
- What would a sustainable roadmap for the future look like to ensure interactions and collaborations add value? What are the three key success factors?

Discussion results

The breakout group examining collaboration and knowledge sharing highlighted the roles of important collaborations during the pandemic, such as the Access to COVID-19 Tools (ACT) accelerator and Africa Vaccine Regulatory Forum (AVAREF), as well as key organisations including the World Health Organisation (WHO) and International Coalition of Medicines Regulatory Authorities (ICMRA).

ICMRA played a more prominent role in bringing global regulatory agencies together to align on policy approaches and regulatory flexibility during the pandemic. However, it was noted that ICMRA could do more to increase its transparency, for example by improving its website to include information on its decision-making processes and criteria for membership.

The development of guidelines during the pandemic was also discussed; the length of time required to approve new guidelines through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) made it difficult to use this mechanism during the pandemic, however, ICH clearly plays a vital role in this area.



What gaps in current interactions were highlighted by the pandemic?			
Gap in current interactions	**Key stakeholders involved**	**Barriers to addressing gap**	**Solutions and next steps**
Connectivity gap in information sharing between all the international bodies	Companies, WHO, Low- and Middle-Income Countries (LMICs)	Confidentiality agreements for LMICs to obtain information from stringent authorities	**Global cloud** so that information can be uploaded to one place with access permissions.
Ensuring that LMIC receives same product	LMIC regulators, Marketing Authorisation Holders	Which version of products are coming to the LMIC?	**Need transparency on version** e.g. follow model where the manufacturer has to certify which version they are sending.
Greater use of reliance models for post-marketing commitments	ICMRA pharmacovigilance vaccines subgroup, Companies, ICH	Length of time to agree new guideline	Ensure global alignment on how to react to adverse reactions to vaccines. **Greater reliance** in the post approval space. ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management) should help leading authorities in this space – how can LMICs have the confidence to rely on their decisions?

Topics/projects to further explore

- An independent review to determine the most appropriate use of rolling reviews e.g. for public health emergencies, when linked to a classification of unmet need.
- An independent benchmarking study to determine appropriate use of new scientific advice and assessment pathways and which worked best.
- Investigate the impact of confidentiality laws on reliance.
- Alignment of politicians with scientific bodies to balance access demands with understanding of good regulatory practices.
- Maintain the evolving role of ICMRA as well as other international/regional collaborations such as the International Pharmaceutical Regulators Programme (IPRP) and Pan-American Health Organisation (PAHO).

Appendix: Workshop attendees

Regulatory agencies		
Denize Ainbinder	*Head of Drug Registration Department*	*Ministry of Health, Israel*
Peter Arlett	*Head of Data Analytics and Methods Taskforce*	*European Medicines Agency*
Nathalie Bere	*Patient Engagement*	*European Medicines Agency*
Prof Dr Ton de Boer	*Chairman*	*Medicines Evaluation Board, The Netherlands*
Dr Claus Bolte	*Head of Sector Marketing Authorisation*	*Swissmedic*
Dr Nihan Burul Bozkurt	*Head of Clinical Trials Department*	*Turkish Medicines and Medical Devices Agency*
Dr Nikolai Brun	*Director of Division, Medical Evaluation and Biostatistics*	*Danish Medicines Agency*
Patricia Carmona	*Head of Registration of Pharmaceutical Products*	*Instituto de Salud Pública, Chile*
Prof Hans-Geog Eichler	*Senior Medical Officer*	*European Medicines Agency*
Khair ElZarrad	*Deputy Director, Office of Medical Policy, Center for Drug Evaluation and Research*	*Food and Drug Administration, USA*
Oguzhan Koyuncu	*Head of the Marketing Authorisation for Medicine Department*	*Turkish Medicines and Medical Devices Agency*
Carole Légaré	*Director, Office of Clinical Trials, Therapeutic Products Directorate*	*Health Canada*
Dr Thomas Lonngren	*Former Executive Director* *Independent Strategy Advisor*	*EMA* *PharmaExec Consulting Filial SE, Sweden*
Dr Theresa Mullin	*Director, Office of Strategic Programs, Center for Drug Evaluation and Research*	*Food and Drug Administration, USA*
Lorraine Nolan	*Chief Executive*	*Health Products Regulatory Authority, Ireland*
Dr Martin O'Kane	*Unit Manager, Clinical Trials Unit, Licensing Division*	*Medicines and Healthcare products Regulatory Agency, UK*
Robert Peterson	*Former Director General, Therapeutic Products Directorate*	*Health Canada*
Susan Robertson	*Senior Medical Advisor, Office of Risk Management, Therapeutic Products Directorate*	*Health Canada*
Barbara Sabourin	*Former Director General, Therapeutic Products Directorate*	*Health Canada*
Dr Tomas Salmonson	*Former Chair* *Partner*	*CHMP, EMA* *Consilium Salmonson & Hemmings, Sweden*
Adj Prof John Skerritt	*Deputy Secretary for Health, Products Regulation*	*Department of Health, Australia*
Evelyn Soo	*Director, Bureau of Gastroenterology, Infection and Viral Diseases*	*Health Canada*
Dr Patrick Stewart	*Director General*	*Therapeutic Products Directorate, Health Canada*

HTA agencies		
Luc Boileau	*President and CEO*	*INESSS, Canada*
Meindert Boysen	*Deputy Chief Executive and Director of the Centre for Health Technology Evaluation*	*NICE, UK*
Niklas Hedberg	*Chief Pharmacist*	*TLV, Sweden*
Jeanette Kusel	*Director, NICE Scientific Advice*	*NICE, UK*
Anne Lee	*Chief Pharmacist*	*Scottish Medicines Consortium*
Suzanne McGurn	*President and CEO*	*CADTH, Canada*
Dr Nicole Mittmann	*Chief Scientist and Vice-President of Evidence Standards*	*CADTH, Canada*
Scott Muir	*Chair, New Drugs Committee*	*Scottish Medicines Consortium*
Dr Brian O'Rourke	*Former CEO* *Chair of CIRS HTA Steering Committee*	*CADTH, Canada* *CIRS*

Pharmaceutical companies and consultancies		
Virginia Acha	*Associate Vice President, Global Regulatory Policy*	*MSD, UK*
Deborah Autor	*Vice President, Global Regulatory Excellence*	*AstraZeneca, USA*
Vanina Barroca Gil	*Regulatory Affairs Manager*	*AstraZeneca, Argentina*
Ginny Beakes-Read	*Executive Director, Global Regulatory and R&D Policy*	*Amgen, USA*
Annetta Beauregard	*Head of Global Regulatory Policy*	*Janssen, USA*
Helena Bebiano	*Regulatory Affairs/Quality/Market Access Manager*	*Ipsen, Portugal*
Fabio Bisordi	*Global Head International Regulatory Policy*	*Roche, Switzerland*
Dr Alison Bond	*Director, EMEA Policy Lead, Global Regulatory Policy & Intelligence*	*Janssen, UK*
Chris Celeste	*Director, Regulatory Policy & Intelligence*	*LEO Pharma, USA*
Dr Bettina Doepner	*Global Lead Regulatory Intelligence and Policy, Director*	*CSL Behring, Germany*
Eric Ducamp	*Senior Director, Head of Regulatory Analytics & Intelligence*	*Ipsen, France*
Andrew Emmett	*FDA Liaison & Head of US Regulatory Policy*	*Pfizer, USA*
Stephen Fawbert	*Director, Global Regulatory Policy EMEA*	*MSD, UK*
Dr Jillian Fuhs	*Advisor, Global Regulatory Affairs North America*	*Eli Lilly, USA*
Dr Louise Gill	*Vice President, Regulatory Policy*	*GlaxoSmithKline, UK*
Dr Clifford Goodman	*Senior Vice President*	*The Lewin Group, USA*
Maylis Guyot-Sionnest	*Global Regulatory Affairs Project Manager Europe*	*Ipsen, France*
Dr Adam Heathfield	*Pipeline and Early Access, Patient and Health Impact*	*Pfizer, UK*
Jonas Henningsen	*Director, Head of Regulatory Science*	*Lundbeck, Denmark*
Dr Claire Hill-Venning	*Senior Director, Regulatory Policy*	*Janssen, UK*
Dr Ceri Hirst	*Policy Lead, Integrated Evidence Generation*	*Bayer, Switzerland*
Dr Nadja Huttner	*Regulatory Affairs Manager - DACH*	*Ipsen, Germany*
Fred Ivanow	*Head of Global Regulatory Intelligence and Policy*	*Astellas, The Netherlands*

Dr David Jefferys	*Senior Vice President, Global Regulatory, Government Relations, Corporate Affairs and Patient Safety*	*Eisai, UK*
Angelika Joos	*Executive Director, Global Regulatory Policy*	*MSD, Belgium*
Anzhelika Kholod	*Regulatory Intelligence and Policy Associate*	*Astellas, The Netherlands*
Megan Klopchin	*Consultant - Policy Research, Global Patient Outcomes & Real World Evidence*	*Eli Lilly, USA*
Anders Lassen	*Senior Director, Patient Insights*	*Lundbeck, Denmark*
Emmanuelle Lecomte-Brisset	*Senior Vice President, Global Head Regulatory Affairs*	*CSL Behring, Switzerland*
Sabine Luik	*Chief Medical Officer and SVP, Global Medical, Regulatory and Quality*	*GlaxoSmithKline, USA*
Claire Martin	*Policy Lead, Integrated Evidence Generation*	*Bayer, Germany*
Dr Marian Mestdagh	*Head of Regulatory Safety Quality Benelux*	*Ipsen, Belgium*
Alexis Miller	*Executive Director, Global Regulatory Policy (US Lead)*	*Merck, USA*
Charlie Mortazavi	*Senior Manager, Global Regulatory Affairs*	*Sanofi, France*
Maria Cristina Mota Pina	*Director – Regulatory Policy and Intelligence Emerging Markets*	*AbbVie, USA*
Jesus Muniz	*Director, Global Regulatory Intelligence and Policy*	*Takeda, USA*
Rachel Newson	*Principal Research Scientist*	*Eli Lilly, The Netherlands*
Kirsten Palmer	*Head of Regulatory Affairs, Western Europe & Canada*	*Abbvie, UK*
Eva Prevc	*Director, Regulatory Affairs*	*Amgen, Austria*
Dr Matthew Raymond	*Director, Science and Regulatory Policy*	*Astellas, USA*
Katrin Rupalla	*Senior Vice President, Regulatory Affairs, Medical Documentation and R&D Quality*	*Lundbeck, Denmark*
Dr Bhushan Sarode	*Regulatory Policy Lead*	*Roche, Switzerland*
Dr Vanessa Schaub	*Senior Health Systems Strategy Leader HTA & Reimbursement*	*Roche, Switzerland*
Bruna Reis Furlan da Silva	*Regulatory Policy & Intelligence Manager - LATAM*	*AbbVie, Brazil*
Montse Soriano Gabarro	*Vice President, Head Partnerships and Integrated Evidence Generation*	*Bayer, Germany*
Jerry Stewart	*Vice President, Head of Global Regulatory Policy & Intelligence*	*Pfizer, USA*
Amelie Sylven	*Senior Regulatory Affairs Manager*	*Abbvie, Switzerland*
Aimad Torqui	*Executive Director, Global Regulatory Policy*	*MSD, The Netherlands*
Sarah Tuller	*Senior Director Regulatory Affairs*	*Astellas, USA*
Dr Joice Valentim	*Global HTA Strategy Lead*	*Roche, Switzerland*
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Dr Max Wegner	*Senior Vice Preisdent, Head Regulatory Affairs*	*Bayer, Germany*
Amira Deia Ali Younes	*Regulatory Policy and Intelligence manager, Middle East, Africa & India*	*AbbVie, United Arab Emirates*
Non-profit organisations and academic institutions		
Dr Samvel Azatyan	*Team Lead, Regulatory Convergence and Networks*	*World Health Organisation*
Dr Mary Baker	*Former President*	*European Brain Council*
Dr Mathieu Boudes	*Project Coordinator*	*IMI project PARADIGM*

Prof Marieke De Bruin	*Professor of Drug Regulatory Science*	*Utrecht University, The Netherlands*
Dr Petra Doerr	*Head of Unit Regulation and Safety*	*World Health Organisation*
Pat Furlong	*President and Chief Executive Officer*	*Parent Project Muscular Dystrophy*
Dr Helga Gardarsdottir	*Associate Professor of Drug Regulatory Sciences*	*Utrecht University, The Netherlands*
Dr Ian Hudson	*Senior Adviser, Integrated Development*	*Bill and Melinda Gates Foundation, USA*
Dr Nokuthula Kitikiti	*Senior Resident*	*Duke-NUS Centre of Regulatory Excellence, Singapore*
Prof Bert Leufkens	*Professor of Pharmaceutical Policy and Regulatory Science*	*Utrecht University, The Netherlands*
Prof John Lim	*Executive Director*	*Duke-NUS Centre of Regulatory Excellence, Singapore*
Dr Murray Lumpkin	*Deputy Director, Integrated Development and Lead for Global Regulatory Systems Initiatives*	*Bill and Melinda Gates Foundation, USA*
Prof Mamoru Narukawa	*Professor, Department of Clinical Medicine (Pharmaceutical Medicine)*	*Kitasato University, Japan*
Cherng Yeu Neo	*Associate Director, Strategic Engagement*	*Duke-NUS Centre of Regulatory Excellence, Singapore*
Prof Sam Salek	*Professor of Pharmacoepidemiology and Director of Public Health and Patient Safety Research Group*	*University of Hertfordshire, UK*
Dr Joseph Scheeren	*President and Chief Executive Officer*	*Critical Path Institute, USA*
Prof Adrian Towse	*Director Emeritus*	*Office of Health Economics, UK*

Centre for Innovation in Regulatory Science	
Dr Magda Bujar	*Manager, Strategic Development*
Dr Tsz Hong Law	*Research Analyst*
Dr Lawrence Liberti	*Head, Regulatory Collaborations*
Dr Neil McAuslane	*Director*
Dr Céline Rodier	*Senior Research Analyst*
Dr Jenny Sharpe	*Senior Scientific Writer*
Professor Stuart Walker	*Founder*
Tina Wang	*Manager, HTA Programme*

Special guests
Jean Breckenridge