New ways of working for medicines development:

How is the regulatory and HTA landscape evolving?

25-26th April 2023

Workshop Report

CIRS Centre for Innovation in Regulatory Science

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS' 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 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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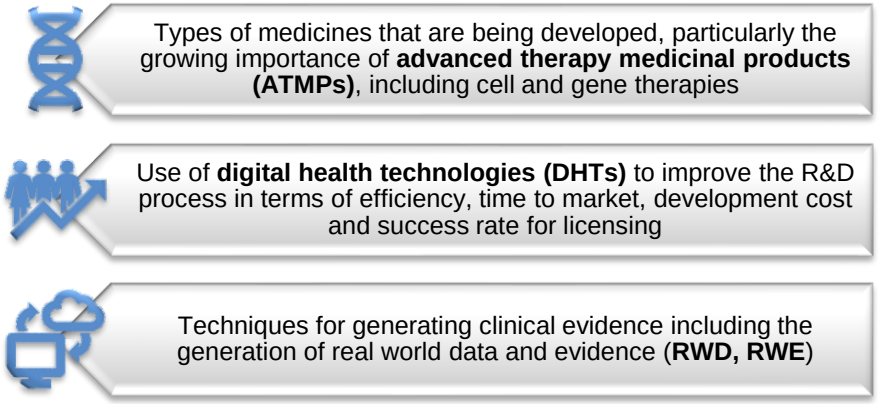
BACKGROUND

CIRS brought agencies and companies together in a workshop to discuss new ways of working and how the regulatory and HTA landscape in mature and maturing countries should evolve over the next 10 years as new technologies and evidence generation methodologies develop, as well the competencies and expertise required within companies and agencies.

This workshop builds on the CIRS 2021-2023 research theme to evaluate new ways of working and how the regulatory and health technology assessment (HTA) landscape will change. The medicine development landscape is evolving at an unprecedented pace in terms of:



As agencies around the world are developing guidelines and policies to support these new ways of working, it is important that pharmaceutical companies and agencies not only stay up to date and ensure that the areas evolve as the regulatory science develops, but also horizon scan on the future direction of medicines development. It is important that agencies and companies put in place the capacity and competencies to ensure that their requirements, guidelines and processes are effective and efficient as well as fit for purpose.

In 2022, CIRS undertook a regulatory landscaping exercise focusing on Brazil, Argentina, Mexico, Colombia, China, Taiwan, South Korea, Saudi Arabia, Russia, South Africa, Canada and Australia. The study aims were to:

- Evaluate changes to the regulatory environment across ATMPs, DHTs and RWD/RWE for the selected countries, which are either evolving their regulatory systems as well as more established, similarly resourced agencies that will be used as a “reference”.
- Understand trends across recent guidelines/policies, current challenges as well as possible solutions and enablers (such as worksharing and collaboration efforts) that are influencing the regulatory landscape for ATMPs, DHTs and RWD/RWE.

One of the main feedback items from the industry survey was the need for cross jurisdictional and multi-stakeholder discussions to understand perspectives, to ensure creation of fit-for-purpose frameworks and alignment with international best practice. A reciprocal survey was undertaken with regulatory agencies and the results presented at this workshop alongside the results from the industry survey.

MEETING OBJECTIVES

- Discuss the changing regulatory and HTA landscape for new products and how evidence is generated and utilised including both challenges and opportunities.
- Identify through specific areas such as ATMP review and use of RWE and DHT, how agencies are adapting their requirements to enable the development and review to ensure an efficient, effective and sustainable system.
- Make recommendations on how companies and agencies need to evolve to enable global development and registration of medicines, as well as what should be considered regarding convergence, alignment and harmonisation.

MEETING VENUE

The workshop took place at the Voco, Orchard, Singapore.

DEFINITIONS

Digital health technology (DHT): A system that uses computing platforms, connectivity, software, and/or sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device.

WORKSHOP PROGRAMME

Affiliations are stated as they were at the time of the meeting.

Day 1: 25th April 2023

SESSION 1: NEW WAYS OF WORKING AND NOVEL EVIDENCE GENERATION – WHAT ARE THE REGULATORY AND HTA OPPORTUNTIES AND CHALLENGES?	
10:00	**CIRS introduction and welcome**
10:05	**Chair's welcome and introduction** **Prof Hans-Georg Eichler**, Consulting Physician of the Association of Austrian Social Insurance Institutions
10:15 ***10:35*** ***10:55***	**Horizon scanning for new ways of regulatory and HTA working: the next ten years and beyond - As new technologies and new evidence generation techniques evolve what will be the key trends competencies/mindsets that will be needed within companies and agencies?** **Regulatory agency perspective – Adjunct Prof John Skerritt,** Adjunct Professor, University of Sydney, Australia and Chair, Scientific Advisory Council, CIRS **HTA agency perspective – Dr Francois Maignen**, Principle Scientific Advisor, Scientific Advice Team, NICE **Company perspective – Dr Patrick Brady,** Vice President, Regulatory Affairs Bayer, Germany
11:15	**Discussion**
11:30	**What are the opportunities and challenges for middle- and low-income countries as regulatory science and landscapes changes to encompass new ways of working?** **Dr Samvel Azatyan**, Team Lead, Regulatory Convergence and Networks, WHO
11:50	**Mature regulatory agency perspective – How does an agency evolve to ensure new ways of working are implemented in a way that provides regulatory direction and enables good regulatory decision making?** **Dr Steffen Thirstrup,** Chief Medical Officer, EMA
12:10	**Discussion**
12:20	**Results of a company and regulatory agency survey on New Ways of Working** **Dr Magda Bujar,** Senior Manager, Regulatory Programme and Strategic Partnerships, CIRS
12:40	**Discussion**
12:45	**Lunch**

SESSION 2: HOW ARE AGENCIES ADAPTING AND EVOLVING THEIR FRAMEWORKS TO ENABLE NEW WAYS OF WORKING?	
13:45	**Chair's Introduction** **Fabio Bisordi,** Global Head International Regulatory Policy, F.Hoffmann-La Roche, Switzerland
	Focus on new technologies/products such as ATMPs - Case studies/perspectives
13:50	**Medicines development of ATMP's and what needs to be in place to provide regulatory oversight?** **Adj Assoc Prof. Danny Soon,** Chief Executive Officer, Consortium for Clinical Research and Innovation Singapore
14:05	**What are the regulatory challenges for a company developing a new technology and its submission to mature and maturing countries?** **Finny Liu,** APAC Regional Regulatory Policy Lead, Roche, Singapore
14:20	**Discussion**
	How are regulatory agencies developing their regulatory framework and capacity to provide direction for clinical development and undertake reviews - What are the key considerations?
14:30	**South Korean Ministry of Food and Drug Safety (MFDS) perspective – Dr Jin Wook Kang,** Senior Scientific Officer, MFDS, South Korea
14:45	**Brazilian Health Regulatory Agency (ANVISA) perspective** – **Fabrício Oliveira**, Head of Biological Products and Advanced Therapy Medicinal Products Office, ANVISA, Brazil
15:00	**Assessment of new technologies/products such as ATMP – How are HTAs in Asia preparing for these advanced therapies and what are the key considerations?** **Dr Izzuna Mudla binti Mohamed Ghazali,** Deputy Director, Ministry of Health, Malaysia
15:15	**Discussion**
15:20	**Break**
15:45	**Chair's Introduction** **Dr Steffen Thirstrup**, Chief Medical Officer, EMA
	How are regulatory and HTA agencies approaching the evaluation and use of RWE/D within their regulatory framework – Is there clear direction for applicants and reviewers?
15:50	**Swissmedic perspective – Dr Claus Bolte,** Head of Sector Marketing Authorisation, Swissmedic
16:05	**Taiwan Food and Drug Administration (TFDA) perspective - Mei-Chen Huang**, Section Chief, TFDA
16:20	**RWE use by HTA agencies in Asia – Dr Michael Coory**, Public Health Physician, Technology Assessment and Access Division. Australian Government Department of Health
16:35	**What are the key challenges for using RWD/E in company submissions and how would sponsors like to see the regulatory landscape evolve?** **Dr Sannie Chong,** Senior Director, AP Lead, Global Regulatory Policy, MSD, Singapore
16:50	**Discussion**

17:05	**Focus on DHT in Clinical Development: What types of DHT are being used for medicines development and what needs to be in place to provide regulatory oversight?** **Prof Dean Ho,** Provost's Chair Professor, University of Singapore
17:25	**What challenges do DHT pose for HTA agencies as they asses the evidence for new medicines?** **Dr Pritaporn Kingkaew**, Head of Research Unit, Health Intervention and Technology Assessment Program (HITAP), Thailand
17:45	**Discussion**
18:00	**Closing remarks and instructions for day 2**
19:00	**Reception and dinner**

Day 2: 26th April 2023

SESSION 3: SYNDICATE SESSIONS	
08:45	**Introduction to Syndicate sessions**
09:00	**A: Focus on ATMP - How does the global medicines development landscape need to evolve to ensure availability and access in maturing countries?** **Chair: Dr Claus Bolte,** Head of Sector Marketing Authorisation, Swissmedic **Rapporteur: Brian Chen**, Market Access Director Asia, AbbVie, Singapore **B: Focus on Real World Data and evidence for use in global submissions - What are the considerations/ best approach and how should the global medicines development landscape evolve?** **Chair: Prof Hans-Georg Eichler,** Consulting Physician of the Association of Austrian Social Insurance Institutions **Rapporteur: Stephanie Chen,** Associate Director, AP Regulatory Policy, MSD, Singapore **C: Digital Health Technology - What are the considerations/best approach and how should the global medicines development landscape evolve a fit for purpose regulatory framework, and how might various stakeholders within and beyond the regulatory agency align?** **Chair: Dr Brian O'Rourke,** Chair, CIRS HTA Steering Committee **Rapporteur: Helene Sou,** Director, Global Regulatory Policy and Innovation, Growth and Emerging Markets, Takeda, Singapore
10:30	**Short break – 10 mins**
12:30	**Lunch**

SESSION 4: SYNDICATE SESSIONS FEEDBACK	
13:30	**Chair's introduction** **Adjunct Prof John Skerritt,** Deputy Secretary for Health Products Regulation, Department of Health, Canberra, Australia
13:40	**Feedback of Syndicate discussions and participants' viewpoints – Policy/Action considerations**
14:40	**Break**
SESSION 5: ALIGNMENT WITH INTERNATIONAL PRACTICE HOW AGENCIES CAN DEVELOP THEIR INTERNAL COMPETENCIES - PANEL DISCUSSION	
14:55	**What needs to be in place to enable global development using new ways of working as well as what should be considered regarding convergence, alignment and harmonisation?** **Regulatory agency perspective – Lorraine Danks,** Project Manager, South African Health Products Regulatory Authority (SAHPRA)
15:05	**HTA agency perspective – Andrew Mitchell,** Member, CIRS HTA Steering Committee
15:15	**Academic perspective – Dr James Leong,** Assistant Professor, Head, Health Products & Regulatory Science Centre of Regulatory Excellence (CoRE), Singapore
15:35	**Discussion**
15:50	**Closing remarks**
16:00	**Close of Meeting**

SESSION 1: NEW WAYS OF WORKING AND NOVEL EVIDENCE GENERATION – WHAT ARE THE REGULATORY AND HTA OPPORTUNTIES AND CHALLENGES?

Horizon scanning for new ways of regulatory and HTA working: the next ten years and beyond - As new technologies and new evidence generation techniques evolve what will be the key trends competencies/mindsets that will be needed within companies and agencies?

Regulatory agency perspective - Prof John Skerrit, Adjunct Professor, University of Sydney, Australia and Chair, Scientific Advisory Council, CIRS

Introduction

Society is in a challenging position in terms of health and well-being, as the COVID pandemic has in part contributed to the neglect of many chronic diseases and delays in the diagnosis of cancers in many people. We are seeing decreasing life expectancy in some of the richest countries in the world, notwithstanding the role t technology has played a significant role in improving life expectancy and quality of life over the last 50 to 100 years. Having good medicines are not enough to enable better health outcomes; they must be combined with policy change, involvement of clinicians and investment across health systems.

Late-stage clinical trial failures are an increasing concern and overall, the cost of bringing medicines to market is increasing. While there was a short-term increase in profitability during the pandemic, commercial rates of return from investments are low, meaning that industry may be more reluctant to invest, or will invest more conservatively in “me-too” products rather than in products that could genuinely represent breakthrough therapies. Regulators need to be responsive to what is submitted to them, but they also need to be aware of what is on the horizon, including what is coming through in a range of technological developments. Personnel within industry, regulators and HTA organisations need to maintain strong horizon scanning skills to identify suitable prospects and potential challenges, both in terms of commercialisation, regulatory and reimbursement.

Focus on ATMP and gene therapies

ATMPs and gene therapies are areas that have significantly grown, but not as quickly as predicted. A significant challenge to getting more of these products out to market has been the need to establish consistent manufacturing and scale-up despite robust clinical data. Technical challenges can involve trial design for small studies including whether to use externally controlled arms; inability to blind for ethical reasons; and issues of durability of the clinical effect for “single-shot” cell and tissue therapies. For gene replacements, how much expression and how many copies of a gene do you need to get a significant clinical effect? Also, what is the predictive value of animal trials given that toxicology effects have been missed in some studies? Market challenges pose potential issues as it is hard to price and cost these therapies, and the high costs of many gene therapies has made some governments reluctant to fund them. Additionally, market size predictions can be uncertain because technical, commercial and HTA challenges are unknown.

The Therapeutic Goods Administration (Australia) commissioned a survey asking stakeholders ranging from small and medium enterprises, academic researchers, industry and HTA bodies, what support they needed around cell and tissue product regulation. Key messages included:

- A need for more regulatory support because the developers (particularly for small businesses) and the inventors did not really understand their regulatory pathways. They needed scientific advice and clearer regulatory guidance.
- There is confusion between roles of government bodies such as gene technology regulators, HTA groups and medicines regulators.
- Several developers noted issues getting clinical trials approved and were asked by regulators to include internal control arms etc, which they did not consider to be ethical or appropriate.

- Small clinical trial sizes were criticised, even for rare diseases. It was considered important that if a similar cell therapy had been approved by another regulator, then there needed to be some facilitated pathways available. Indeed, there was a particular request for a priority review pathway. In response, Australia has introduced a priority review pathway for these products.

Focus on Digital Health Technologies

When used in the medicines area, DHTs can be broadly divided into those that can monitor patient outcomes in clinical trials or during therapy and those that are a drug-like intervention (and in some countries require a prescription). Overall, DHTs have numerous potential advantages as therapeutics they are drug-free. They can allow personalisation or tailoring of a treatment more readily than tailoring a dose and can provide real world feedback. However, regulatory schemes for DHTs are not uniform, nor are they well developed in many countries, and it is very hard in many countries to get a reimbursement. While we are celebrating the growth of digital technology there has been some consolidation and contraction of companies this year as they have found it hard to receive income for their products.

A more structured scheme for integrating digital biomarkers into clinical trials during the drug development process requires consideration. Companies agree that some form of validation of these biomarkers is needed; however, some conduct in-house internal validation, based on which the regulator will likely ask a lot more questions. To this point, some companies are taking the approach of registering validation software as a medical device product rather than using in house validation only, so that neither a medicine regulator nor the HTA will ask questions about its validity.

There are three broad approaches to digital tool use in drug development in clinical trials:

- Digital markers and digital technology can be used to do the same as a traditional disease endpoint.
    - Digital technology can be used remotely and can provide more data points, which for hypertension or glaucoma intraocular pressure for example, can be advantageous over single measurements.
- Can provide broad outcome measurements such as those associated with quality of life and sleep.
- Can lead to the development of novel endpoints.

Artificial intelligence (AI) may have a wide range of applications but there are limited skills for their evaluation among medicines regulators. There is also the issue of bias as the data set used for learning may not be representative of a real-world set of patients.

Focus on regulators and Real World Evidence (RWE)

Use of RWE in understanding treatment acceptability/compliance has greater feasibility than ever. It is mostly used for post-marketing safety currently but there is increasing interest in its use for label (indication) extensions for medicines. A particular challenge to the wider use of RWE include access to, recording and validation of high-quality data.

The Therapeutic Goods Administration recently conducted a consultation on how RWE could be better used. Key points included:

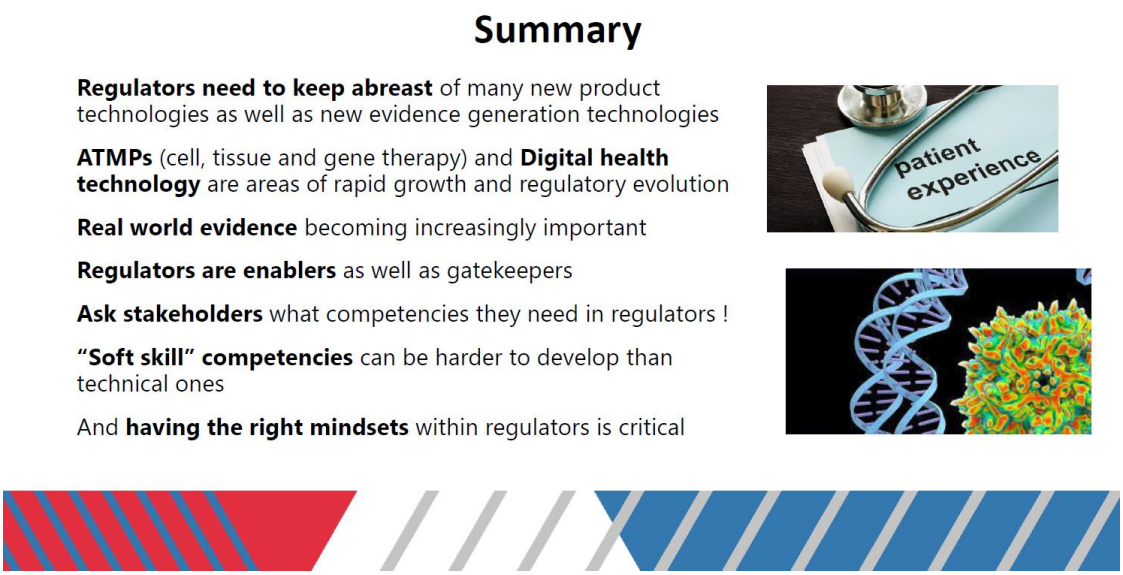
- Adequate definition – document when and why it is being used in the regulatory submission
- Ensure that sources of RWE are credible
- Look at the quality of that data and provide regulatory guidance on the use of RWE
- Learn from studies globally, especially those in the Europe and in the US.

Competencies and mindsets

Regulators need to keep abreast of new technologies around products as well as new evidence-generation technology. DHTs require development of specific skills among regulators to allow timely response to market authorisation applications involving emerging technology. Most regulators have developed regulatory science strategies, focussing on capacity building, international collaboration,

responsiveness to emerging technologies and engagement with researchers and other groups on those technologies. Common themes include support for innovative trial design, use of RWE and alignment of regulatory and HTA requirements.

So-called 'soft skills' competencies include an inquiring mind, an openness to new forms of evidence generation and good collaboration skills (working with other groups and payers and HTA). Regulators need to be open to their role as a facilitator, not just a gate keeper. In addition, dealing with uncertainty is key as decisions need to be made and not deciding can be worse than making a negative decision. Overall, communication is important, whether with the industry, with health professionals, or with HTA.



HTA agency perspective - Dr Francois Maignen, Principle Scientific Advisor, Scientific Advice Team, NICE

Communication and technologies

We are living in healthcare systems which are under financial constraint and pressure. These constraints hugely impact the way we are working to try to improve the cost-effectiveness of interventions and public health inequalities (e.g., geographical and ethnic inequalities). Numerous factors, including aging populations and a richer population with an increasing prevalence of chronic diseases (diabetes, cardiovascular disease, dementia), are contributing to struggling healthcare systems globally. We are also living in a changing scientific landscape in many ways, including new approaches to development of interventions with the advent of complex innovative clinical trial designs (as evidenced during the COVID pandemic). Information delivery has also changed: the increased speed of availability of new clinical research results (pre-peer review) as well as faster development and earlier access to new medical interventions have dramatically changed the landscape of the way we work. Social media has completely changed our way of working on the communication and delivery of information but may also be linked to dubious research practices, conspiracy theories and scientific scepticism. In turn, misinformation is something that we are now actively asked to fight. Integrated technologies with medicinal products, medical technologies and AI combined, will provide wider opportunities to screen, diagnose and treat patients in a much more effective way. Artificial Intelligence (AI) particularly is gaining momentum in diagnosis, screening and treatment.

The National Institute for Health and Care Excellence (NICE) provides scientific advice support at all the different stages of clinical development and published a consensus on the design and conduct of complex innovative clinical trials in 2022. The International Council for Harmonisation of Technical Requirements

for Pharmaceuticals for Human Use (ICH) will soon be publishing a guidance on adaptive clinical studies. ICH have also published the M15 guideline regarding modelling from drug development. For HTA agencies this means that authorisations will not be granted on clinical evidence only but may derive from pharmacokinetic or pharmacodynamic models that try to extrapolate the clinical effectiveness from one indication to another. These models will be used to try to estimate the cost-effectiveness of new interventions. We are moving from a paradigm of development that is based on clinical evidence only, to clinical developments that will also be based on simulation studies.

Decentralised clinical trials will have a major role to play in trying to address health inequalities, including identification of populations who are often missed in clinical trials, such as ethnic minority groups, socioeconomically disadvantaged groups, people with disabilities, populations with subpopulations with longer barriers, etc. Such trials will provide an opportunity to collect information and allow patients to be followed in their own homes (for example decentralised clinical trials for Parkinson's Disease in the UK). NICE has developed a new project focussed on integration of surrogate outcomes in cost-effectiveness models, meaning that in some instances, products may be authorised based on very preliminary surrogate endpoints. They are working with other organisations to try to develop common recommendations on the use of surrogate outcomes in cost-effectiveness models.

In terms of regulatory and HTA interactions, enhanced engagement and flexibility for clinical trial planning and design is required and will inform the clinical and cost-effectiveness of new interventions in a meaningful way. A more integrated approval and reimbursement system across the line with accelerated-access initiatives, which will try to promote, identify and speed up transformative interventions within the system is also required. Benefits of early HTA engagement have been demonstrated: the median time from authorisation to NICE recognition is approximately three months shorter for products that received HTA advice versus those that did not seek early engagement.

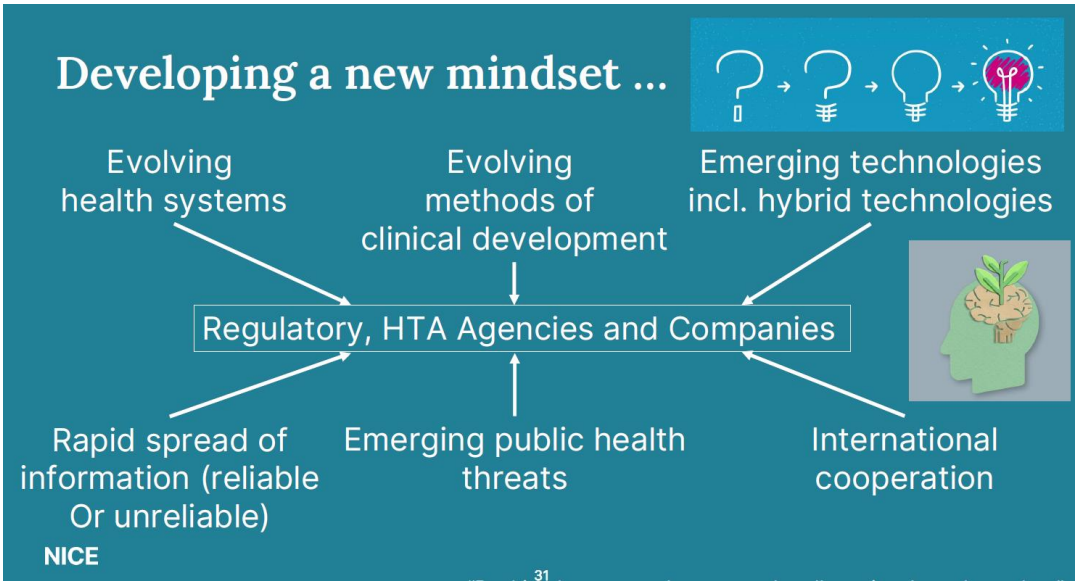
New ways of working and approaches to horizon scanning

Horizon scanning can be divided into two types: primary (classic) horizon scanning derives from searches, including from other government departments and advisory bodies, while applied (targeted) horizon scanning scans in specific circumstances to try to promote and facilitate the development of new candidates. Examples of the latter include RAPID C-19, an initiative to identify and prioritise potential new transformative technologies used for the treatment of COVID and point-of-care-manufacturing. The benefits to applied horizon scanning include rapid identification of new, effective and potentially transformative therapies, the capability to foresee changes in legislation and evolution of methods of evaluation (including support and prioritisation) and development of new expertise when needed.

Guidance should be published that is useful, usable, and timely. NICE is implementing a proportional approach to assessing medicines and developing living guidelines so that the validated clinical information is made available as soon as possible to prevent the spread of misinformation via social networks. Finally, there are benefits to extending horizon scanning to worldwide collaborations and the NICE international strategy is aimed at improving the scale of outcomes across the world.

Mindset

A sense of ubiquity is required, as is having improved regulatory-HTA collaborations worldwide. Rapid adaptation of emerging technologies to public health threats, strong and flexible methods of evaluation that are rapid and efficient, as well as reliable information and communications, will be paramount to the system.



Company perspective - Dr Patrick Brady, Vice President, Regulatory Affairs, Bayer, Germany

The past as a prologue to future prospectives

Examples of progression in the regulatory space over the previous 10 years include:

- Programmes that brought forward the idea of breakthrough therapy designation.
- Developments in the use of big data in healthcare and regulatory decision making.
- Implementation of the Sentinel Initiative for medical product safety.
- Delivery of RWE via the Data Analysis and Real-World Interrogation Network (DARWIN EU).
- Efforts around globalisation and ICH reforms, including formation of the International Coalition of Medicines Regulatory Authorities (ICMRA).
- Advancements in patient engagement and drug development.

Current perspectives

Post-COVID, there appear to be emerging trends around localisation versus globalisation, including more nationalistic thinking about 'protecting our own backyard' rather than thinking about the global environment that we work in. However, at the regulatory level there is progress towards regulatory convergence with several examples, including Project Orbis, the ZaZiBoNa initiative and the emergence of the African Medicines Agency. There is also great activity by the Health Emergency Preparedness and Response in Europe and Biomedical Advanced Research and Development Authority in the US that are trying to position many countries and governments for future public health preparation. The Prescription Drug User Fee Act (PDUFA) VII program is undergoing major investments in advancement of the IT environment to foster the development of cloud-based submissions and to allow a more fluid and dynamic exchange of information between and among regulators and between and among regulators and sponsors. PDUFA is also investing in full-time employees within the Center for Biologics Evaluation and Research organisation in readiness for the coming wave of cell and gene therapy applications. A continued acceptance of RWD and RWE is anticipated.

Future perspectives

Given the globalised civilisation, the ability to move across geographies so easily, population density and climate change, readiness for future public health crises are important. This includes the impact of

microbial resistance which may be more difficult to treat (than by vaccination, for example). It will be important to monitor trends around globalisation versus nationalism so that in the interests of public health, the regulatory community continues to operate beneath the political level. To this point, might there be the potential for a global regulatory agency that helps coordinate the regulatory work of various agencies around the world and that makes best use of individual capabilities and capacities while still preserving the local decision-making within the purview of the local regulatory agency? Might we also see the emergence of a global (or regional) HTA coalition, where HTA decisions are consolidated while still preserving the decision-making at the local or the regional level?

The future requires 'professional chimerism', i.e., greater cognitive flexibility, digital literacy and computational thinking, the application of judgment and decision-making and more emotional and social intelligence. This reflects a move from regulatory professionals and enablers of innovation focusing on a specific set of technical skills to a more adaptable way of working across different domains. Regarding use of AI and machine learning for the purposes of drug development, how far might we be away from this and what does it look like in terms of restructuring work?

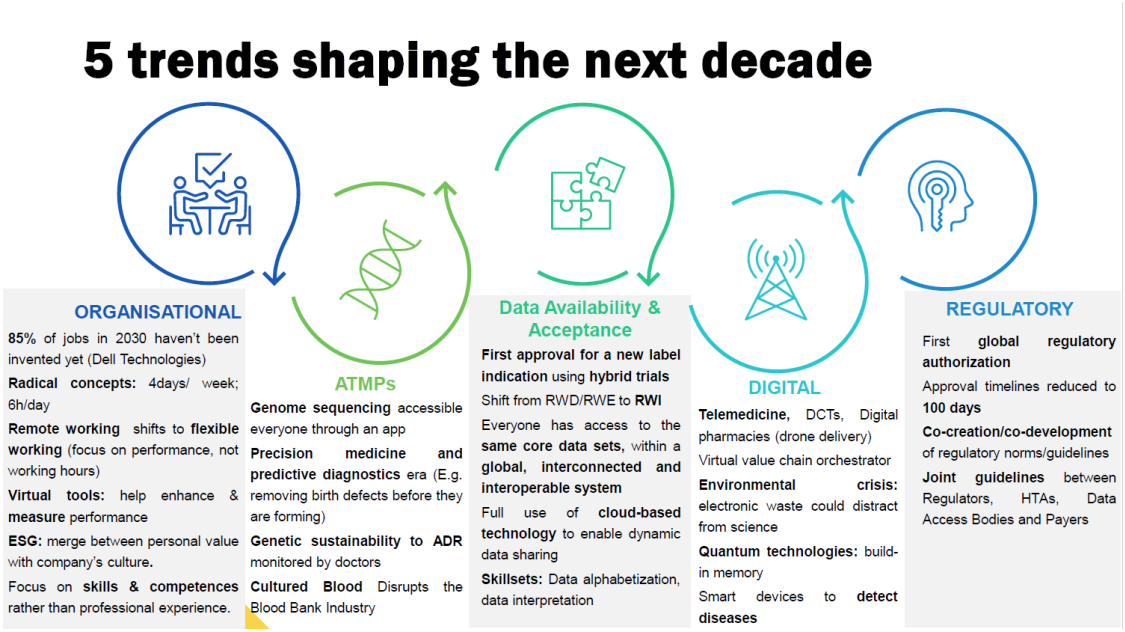
Key areas were identified as possibly shaping the next decade. The first was talent perspective, i.e., a paradigm shift for regulatory professionals to be 'innovation hunters', willing to go where the science leads, be pipeline agnostic, and then be fluid and agile to the organisation.

Development of new modalities was discussed (i.e., the use of cell and gene technologies) and the paradigm shift of illness management to cure. Here there may be questions around sustainability, market assets and legal and ethical frameworks. The messenger RNA technology story is a reminder of the capabilities of what regulatory agencies can and will do in the face of crisis and also how a platform can be built, validated, and then utilised in different therapeutic directions in a very rapid manner.

Data availability and reliability is a shift from just talking about RWD or RWE to talking data availability and the acceptance by all stakeholders. This may include use of hybrid trials in approvals of new indications, i.e., an approach that leverages both an interventional classic randomised controlled trial with some kind of RWE as a basis for a regulatory approval. There may be opportunities to leverage digital tools and technologies in drug development to make the process more efficient, to reduce burden on patients and to help improve patient diversification in clinical trials. The environmental and sustainability impacts of increased digital tools are considerations.

Regarding developments in the regulatory environment, is there the potential for global regulatory approval? For accelerated pathways, might we see the first 100 days approval? The potential for rapid advances of new therapies in chronic diseases (heart disease, stroke, diabetes etc.) that also represent major public health emergencies is an important future consideration. Might we be able to develop well-characterised platform technologies, advance them into human testing and then be able to pivot into different disease areas more rapidly, just as we did in the development and regulatory approval of the COVID vaccine?

Finally, patients are increasingly collecting self-generated data. How these data are collected and used by regulators and sponsors is a point of consideration, including how patient engagement strategies in early research and development may be developed so that information collected can be legitimised. Inviting patients into the co-creation of policies may be beneficial.



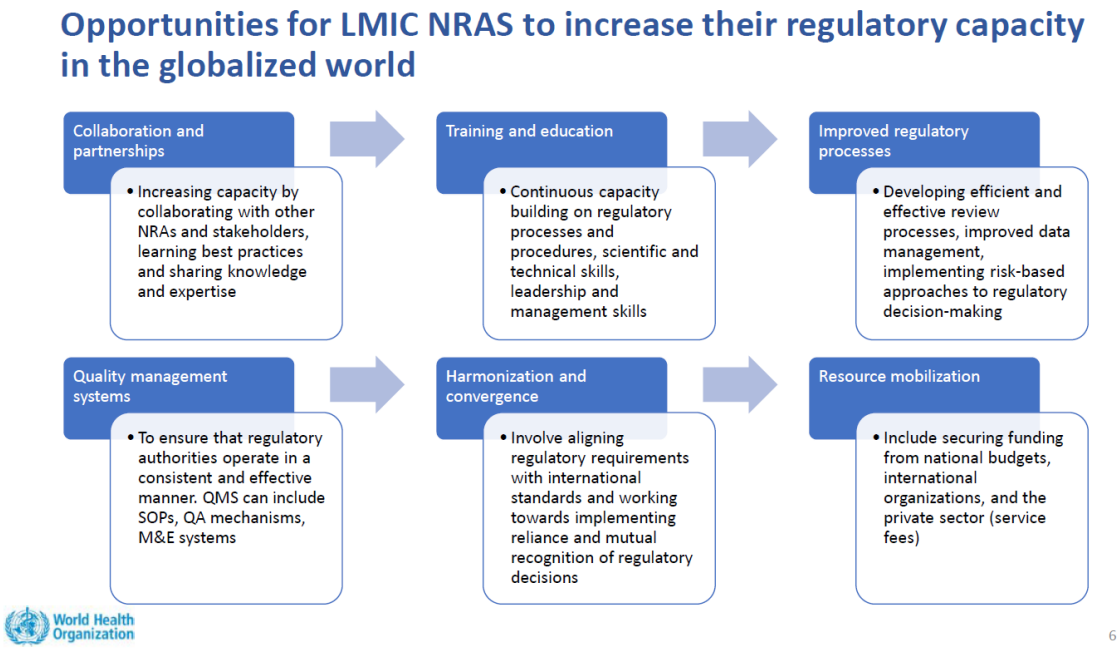
What are the opportunities and challenges for middle- and low-income countries as regulatory science and landscapes changes to encompass new ways of working? - Dr Samvel Azatyan, Team Lead, Regulatory Convergence and Networks, WHO

Overview

Strong regulatory capacity is considered as an essential component of a well-functioning healthcare system. However, there is a global lack of regulatory systems that can perform key regulatory functions (corresponding to World Health Organization [WHO] Global Benchmarking Tool maturity levels three or four). Challenges facing such regulatory authorities include resources and funding, such that it becomes unrealistic to manage all key regulatory functions under one roof in one national setting (as is true for most national regulatory authorities), limited access to new technologies and limited collaboration and networking among regulatory authorities. In addition, new products can be complex and require advanced health systems. Are all regulators able to assess and inspect all products coming to their markets? If yes, is the benefit-risk assessment considering the health systems in which the product is to be launched? What competencies are needed for regulators to be able to perform their key regulatory functions?

What are the opportunities for low- and middle-income countries to increase their regulatory capacity?

There are greater opportunities for collaboration and partnership with other regulators in the same region or globally, helping to teach best practices and allowing for sharing of knowledge, experience and expertise. There are also now many more training and capacity-building opportunities available, but it is important that regulatory authorities have well-designed in-house training capacity-building opportunities within their own scope. There are opportunities for improved regulatory processes to develop efficient and effective review processes, improving management of data using modern technologies and implementing risk-based approaches for regulatory decision-making. There are also opportunities in quality management systems for operational consistency and effectiveness (including standard operating procedures, quality assurance mechanisms, monitoring and evaluation systems and harmonisation and convergence) and resource mobilisation, including securing funding from national budgets and from international organisations and the private sector.



In its role as a health agency of the United Nations organisation, WHO aims to: promote good governance and transparency in the medical products sector through good regulatory practices process; promote and facilitate the processes for building strong national regulatory systems as part of overall health system strengthening in line with the global benchmarking process; see regulatory authorities as an important contributor for achieving universal health coverage and being able to address public health priorities; and support regulatory workforce development through a global regulatory curriculum and competency framework. Ultimately, WHO promotes regulatory cooperation, convergence, and harmonisation based on the concept of reliance on the work of other trusted regulatory authorities, to help to inform a good quality national regulatory decision.

A patient-centric approach (proactive involvement/engagement with patients and their respective organisations and associations) should be central to the regulation of medical products: the needs and expectations of the patients should be properly considered in all decision-making processes by national regulatory authorities. This approach also prioritises patient safety, access to effective treatments, and improved health outcomes. Ultimately it will lead to more effective and meaningful regulation which will benefit both patients and the healthcare system. Patients need also to have confidence in regulation because this is the only prerequisite for them to have confidence in the ability of the healthcare system to provide all necessary services.

Adapting to new ways of working can help national regulatory authorities to align and keep pace with new sophisticated technologies and tools. Worksharing through collaboration and cooperation among different regulatory authorities can ensure efficient and effective regulation of medical products. Implementing these types of worksharing practices requires strong leadership, clear communication and a shared commitment to implementation of reliance and cooperation; there must be a willingness to support these types of activities.

Information which could potentially facilitate in-country approval of medical products can be obtained via the WHO prequalification program and from stringent regulatory authorities who also provide good quality and trusted information. But how do we get products which are pre-qualified by WHO and/or approved by stringent regulatory authorities to the patients faster and more efficiently? How do we ensure continued supply of these quality-assured products after they have been registered in the countries? Options to facilitate regulatory decisions (all of which focus on reliance) include the standard process, so-called independent reviews, based on independent decisions following reviews by the regulatory authorities and their own inspections (a long process with unpredictable outcomes), or worksharing, including joint

activities and applying various abridged pathways using reliance. The latter leverages regulatory work done by others and as such, the regulatory decision is faster, of better quality and is more predictable.

WHO good reliance practices were published in March 2021 and are available on the WHO website in English, French and Spanish. E-learning modules are also available and recommended. Reliance is defined as the act whereby the regulatory authority in one jurisdiction considers and gives significant weight to the assessments performed by another regulatory authority or trusted institution or to any other authoritative information, and this is enriching its own decision. For many years, reliance has been implanted in facilitated regulatory pathways, which are supported by WHO. Reliance is critical from the point of view of importance of international cooperation – to ensure the safety, quality, and efficacy or performance of locally used medical products. The WHO document also provides opportunities on how to make best use of available resources and expertise and help avoid unnecessary duplications.

Finally, a harmonised regulatory framework that would promote global health is necessary. Public health should be the primary objective of national regulatory authorities. More standardised and harmonised regulations, which could help to facilitate the easy exchange of information and expertise between regulatory authorities in different countries and regions, are required.

Mature regulatory agency perspective – How does an agency evolve to ensure new ways of working are implemented in a way that provides regulatory direction and enables good regulatory decision making? - Dr Steffen Thirstrup, Chief Medical Officer, EMA

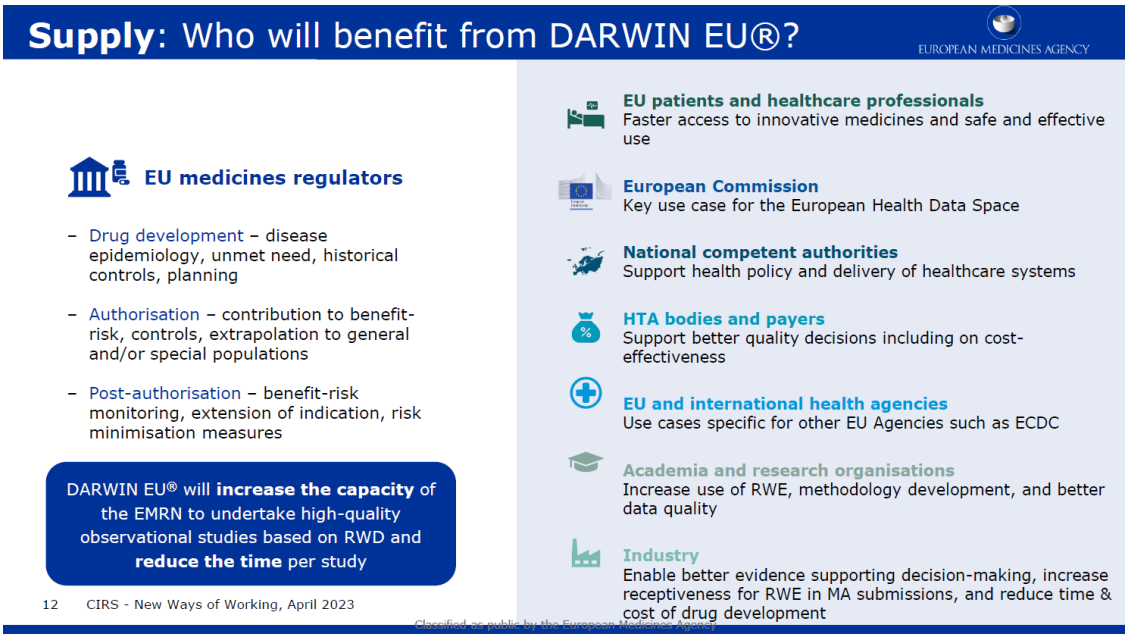
Europe uses the PESTLE analysis annually which takes Political, Economic, Societal, Technological, Legal and Environmental issues into consideration with a forward-looking approach. The EMA considers itself a European network of regulators that is highly dependent on collaboration, mutual recognition and worksharing but also works internationally. Avoiding duplication of work is key. The agency has a plethora of 'priorities' to manage and has created an innovation network, a radar system that is conducting the horizon scanning. Within this, the Innovation Task Force is a discussion forum that offers advice to developers. This can also help EMA to identify early technologies and establish working parties (and sometimes committees), which go on to create guidelines and guidance documents prior to public consultation, an important aspect of guidance development. If the political system wishes, some working parties/guidelines may become legally codified. EMA needs to gather intelligence, and then build capacity within the agency and in the network to deliver. Regulators need to be playing a role in driving this innovation.

Example – Implementation of RWD in the European regulatory system

To extend RWD beyond classical pharmacoepidemiology, to diversify use and establish value, access to big data is required. Standards need to be set, methods validated and staff trained. The process requires quality and discoverability at an international level, and finally, changes need to be implemented. EMA is managing this process by creating a big data steering group. A goal for RWD is to support the decision making of EMA's scientific committee system, including understanding the clinical context and identifying the most appropriate comparator that may also be of interest to HTA. Different member states may be treating patients differently, not necessarily according to the official international guidance, but also driven by local access etc., therefore, understanding the full picture is important.

In addition to EMA (as the national competent authority), medicines developers and academic associations can work collaboratively to provide data. The flagship of RWE in Europe is the Data Analysis and Real World Interrogation Network (DARWIN EU). Europe has numerous national databases linked to national healthcare systems, academic institutions or disease registers; however, data should remain local to avoid exchange of confidential and personal information. With DARWIN, data stays local, but is centrally requested and output is provided from the various databases. This approach does require development of a common standard regarding data exchange.

DARWIN is starting to progress and to develop data. It is anticipated that by 2025, the DARWIN system will provide 150 RWE studies annually (some as re-occurring analyses for regulatory updates and others dependent on need). The system will ideally become 'pan-European' with every European able to have an app on his/her phone with access to personal medical records (translated into different languages). Secondary to this, the data may be able to be used to look at drug utilisation, hospitalisations and mortality etc. Discussions around an opt-in or opt-out system and the impact of this on data generation and equitability are ongoing. Smaller studies using the DARWIN are also ongoing to see what data could be obtained by having a European Health Data Space.



RWE is also on the agenda at the International Coalition of Medicines Regulatory Authorities (ICMRA) where progress is being made. Other considerations around RWD include the importance of agreement on terminology i.e., what we understand by RWE or RWD, looking at ways for agencies to work together to use data, and how best to demonstrate transparency in the decision-making process and in data utilisation.

Results of a company and regulatory agency survey on New Ways of Working - Dr Magda Bujar, Senior Manager, Regulatory Programme and Strategic Partnerships, CIRS

New ways of working have been an area of focus for CIRS as part of its 2020-2023 agenda. High level findings from an agency survey conducted by CIRS on this topic were shared. Emerging areas included in this study were: new product types (ATMPs), use of digital health technologies (DHTs) and real world data/evidence (RWD/E) generation. Objectives of the survey were to understand how agencies are currently evolving these new ways of working, including what systems and practices they have in place and what they view as challenges and opportunities going forward.

Through this study, CIRS also wanted to understand the regulators' point of view on how new ways of working are evolving to understand the landscape and to undertake a gap analysis compared to the industry survey undertaken by CIRS in 2022. A key goal was to identify gaps between science and policy for new ways of working, where COVID has catalysed this process to an extent, for example decentralised trials that have been accelerated as a result of the pandemic. Other key questions included 'how can new systems be introduced to ensure convergence globally?' 'Is there an opportunity for

alignment?' 'How do we ensure a change in mindset to enable these new ways of working to be implemented?'

Agency survey results

Twenty agencies responded: Argentina, Australia, Brazil, Canada, Chile, China, El Salvador, Europe (EMA), GCC, Ghana, Japan, Malaysia, Mexico, Nigeria, Peru, Saudi Arabia, South Africa, South Korea, Switzerland, Taiwan ROC. In terms of background information on the participating agencies, the WHO maturity level (ML; relating to medicines) varied from ML2 to ML4; the total staff at the agency for medicinal products for human use ranged from 39-2000, whereas the total number of reviewers for marketing authorisations of medicinal products for human use varied from 22-3000.

1) Guidelines, frameworks and strategies

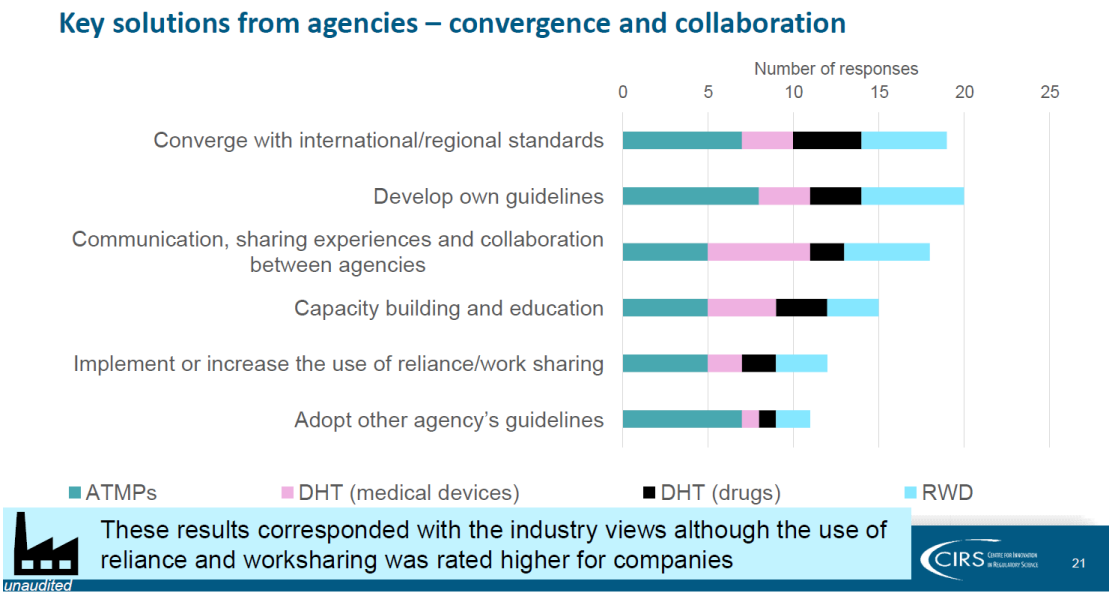
ATMPs, DHTs and RWD were within the remit of responsibility for the majority of the agencies surveyed. When asked about availability of guidelines or frameworks for ATMPs, DHTs and RWD, ATMP guidelines (or frameworks for medicines that encompass ATMPs) were most developed. Very few agencies noted a formalised framework for DHTs. RWD had the largest proportion of responders noting a lack of developed guidelines. All in all, there was divergence in the way that agencies are operating and the frameworks or practices they have in place for new ways of working. These results were comparable with CIRS's industry survey.

When asked about their experience in all these different ways of working, ATMPs was the area within which most agencies have regularly reviewed information or data submissions compared to DHT and RWD/E. When asked what strategies the agency is currently utilising to have a structured approach in place for new ways of working, responses were mixed. Some agencies are adopting other agency guidelines for ATMP, DHT and RWD/E, mostly EMA and FDA guidelines; however, a number of countries are still developing their own guidelines for new ways of working. How it can be assured that divergent guidelines don't impact global development is a consideration.

2) Challenges, solutions and prioritisation

Overall, the greatest challenge for ATMP/RWD and DHT to agencies was lack of guidelines, pathways and frameworks. Other challenges highlighted included having the technical knowledge to review the information, capacity, knowledge of the science and lack of opportunity to modify the landscape. Notably, lack of guidelines, capacity and technical knowledge were also highlighted as the main challenges in the industry survey. For RWD, availability of governance systems and divergence in definitions were highlighted as challenges.

The top categories for solutions suggested by agencies for new ways of working were converging with international standards and developing guidelines (regulators may be adapting some of the main guidelines, but developing other parts of the guidelines that are relevant for their own population), communication and collaboration, capacity building and education. When asked about strategies the agencies are putting in place to ensure preparedness for the future, the primary responses were to establish frameworks and guidelines, ensure staff training and monitor regulatory guidelines (e.g. other agencies, ICH). This was reflected in the industry study, where the top strategies utilised by internal company regulatory groups to adapt/prepare for the future focused on horizon scanning, monitoring guidelines and developing policies across the three areas. When asked about prioritising future preparedness for the three areas, agencies noted that ATMPs was the highest priority, followed by DHTs and RWD. Overall, survey results highlighted that new ways of working are seen as high priority to regulators.



3) Recommendations for the future

Having the ability to modify agency frameworks to implement these new ways of working, ensuring convergence and enabling greater discussion between companies and agencies, were generally recommended by agencies as critical changes that need to occur in the future to ensure an efficient and effective regulatory landscape across each of the three areas.

For ATMPs, modification of the legal framework to include ATMPs, process simplification and ensuring stakeholder engagement were considered important. When considering DHTs for drugs, greater collaboration and integration of the platforms (that may be across different countries) was recommended. When considering DHTs for medical devices, capacity building for staff around different new technologies, either educational or via specific forums, was noted. Regarding RWD, training and capacity building and having more guidelines (which is already a topic for ICH harmonisation), were recommended.

The findings from the study were used to inform the syndicate Workshop discussions.

SESSION 2: HOW ARE AGENCIES ADAPTING AND EVOLVING THEIR FRAMEWORKS TO ENABLE NEW WAYS OF WORKING?

Focus on new technologies/products such as ATMPs - Case studies/perspectives

Medicines development of ATMPs and what needs to be in place to provide regulatory oversight? - Adj Assoc Prof. Danny Soon, Chief Executive Officer, Consortium for Clinical Research and Innovation Singapore

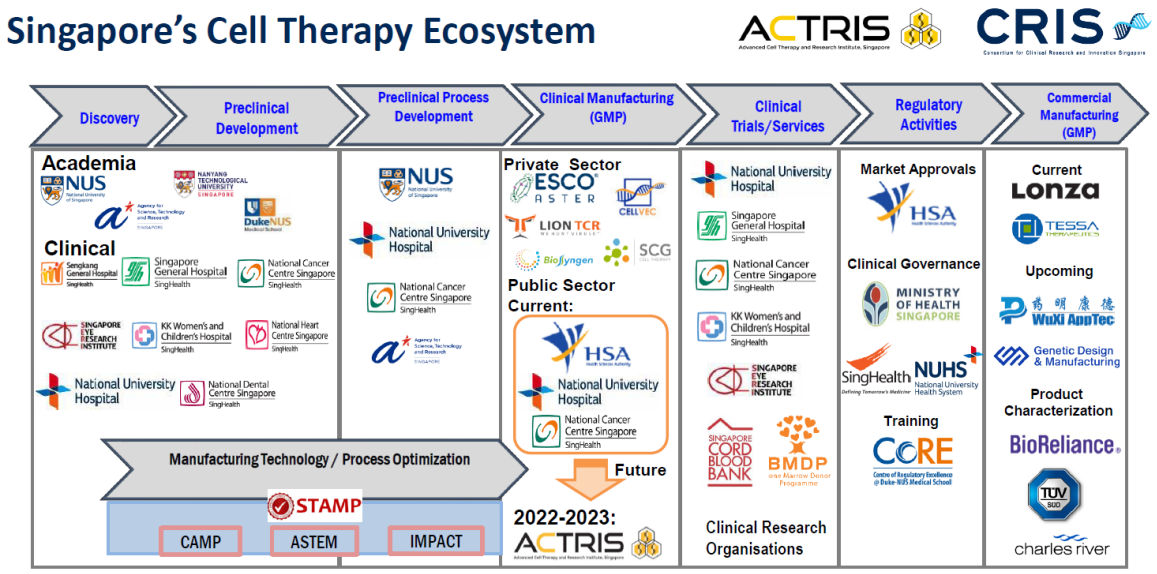
According to the EMA and other definitions, ATMPs are medicines for human use that are based on genes, tissues, and cells and can be classified in three main types: gene therapy medicines, somatic cell, and tissue-engineered medicines (allogenic or autologous). They offer ground-breaking opportunities for the treatment of diseases and injuries, but they are complex entities for which the science, biology and application are still evolving (albeit rapidly). From the perspective of the developer, manufacturing, clinical development, equity and access represent specific challenges. In terms of manufacturing, it is critical to ensure consistency of the production and transport administration (starting materials, the matrix construction process, temperature control, length of incubation, potency assays and biosafety, shelf life and the logistics of transportation both to the manufacturing site, and then back to the patient etc). All will influence the quality of the product, its efficacy and safety. Indeed, ATMPs are a unique paradigm in which the clinician treating the patient and monitoring for side effects may also be directly involved in the manufacturing of the product.

Obtaining clinical data can be challenging. Sometimes, because of the nature of the ATMP, and the fact that they are often used in compassionate use cases means that randomised controlled double-blind trials may not be feasible or ethically justifiable. As such, side effects may need to be evaluated over longer periods. Other challenges include uncertain correlation between gene expression and pharmacodynamic/functional parameters, and the effects of pre-existing immunity. Socioeconomic factors are also a consideration given that manufacturing sites may need to be trained, qualified and have the right equipment etc. Developers need to assess their return on investment in terms of developing these therapies. Interaction with HTA is critical early in the development process to ensure that endpoints are relevant and to consider what is fundable for patient use in a widespread way.

Regulatory oversight for ATMPs can be considered in four categories: policy, talent, data and stakeholder support. ATMP policy is typical for many regulatory agency bodies around the world, with overlapping regulations that regulate the clinical trials, the types of products, manufacturing etc, that over time will become out of date or need to be superseded by others (that then encompass the activities that need to be pursued for development). Regarding talent, a complex multidisciplinary skill set is required. As noted above, it may be the clinical team who are manufacturing the therapy. Science training and analytical scientists are critical. HTA is also required, to understand how the technology fits in, and how it can be paid for. Formal training may be required as staff exchange across agencies and/or workshare.

ATMPs generate large amounts of data, and the link from biology to source material, manufacturing process, reagents, administration, efficacy and adverse effects, is long and convoluted. In addition, it is challenging to manage information flow across different stakeholders (scientists, companies, clinicians, patients, payers and regulators). Multi-stakeholder support is critical to help bring an asset to market.

The current cell therapy ecosystem in Singapore has evolved over recent years. Investments in academic research over the past decade means that there is significant activity ongoing. Manufacturing also sees much activity – several companies, have or intend to set up their own GMP facilities. The Advanced Cell Therapy and Research Institute (ACTRIS) is the national cell therapy manufacturing unit that will serve the whole community of Singapore from a clinical service delivery standpoint, as well as supporting research programs and biotech companies. CoRE is the Centre of Regulatory Excellence in Singapore and provides training.



STAMP: Singapore Cell Therapy Advanced Manufacturing Programme; **ASTEM:** Allogenic Stem Cell Mfg Programme;
IMPACT: Integrated Mfg Programme for Autologous Cell Therapy; **CAMP:** Critical Analytics for Manufacturing Personalized-Medicine Programme

What are the regulatory challenges for a company developing a new technology and its submission to mature and maturing countries? - Finny Liu, APAC Regional Regulatory Policy Lead, Roche, Singapore

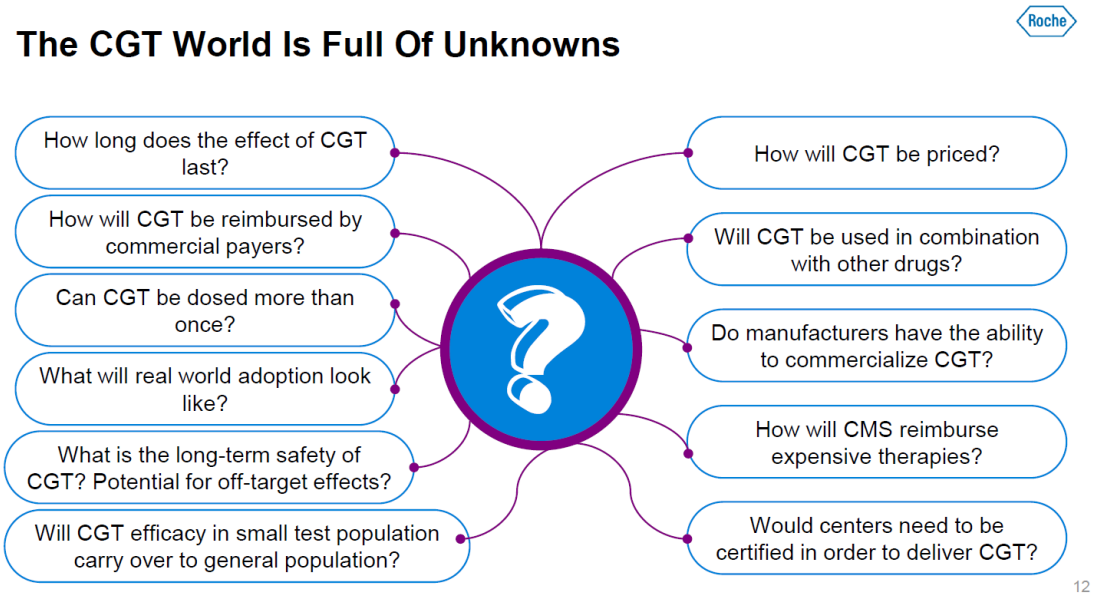
Cell and gene therapy product manufacturing is a new paradigm for which there are two approaches: 'make to order' (for a particular patient), or where a very small lot of product is produced that can be used to treat very few patients. There is a need to regulate ATMPs differently because the manufacturing situation is so different to that of traditional biological products. In many countries, ATMPs are regulated under biological product regulation but ATMPs are different, and this impacts their ability to comply to existing regulatory requirements. Some countries require in-country testing, this is not a feasible approach especially for 'make-to-order' products, as the batch size is very small so that test samples compete with patient treatment. In some countries, a portion is required to be retained by the health authority. Transportation, storage condition and distribution of ATMPs are also different to traditional biological products.

For cell and gene therapy, several countries have already developed guidelines but there are still numerous regulatory challenges including lack of a harmonised global regulatory document, global alignment, i.e., lack of experience in the health authority and the company with new technology that is evolving very quickly and various regulatory requirements, including not knowing how much information will be needed for the approval.

Most new traditional drugs are developed by big pharma and the approval or requirement process is very well established. For the cell and gene therapy area, there are varying regulatory pathways and requirements across markets and many developers are new start-ups who may not be familiar with how to present their product in the international market. Despite challenges, there is good progress in harmonising the regulatory requirement: WHO has published WHO considerations on Regulatory Convergence of Cell and Gene Therapy Products and WHO approach towards the development of a global regulatory framework for cell and gene therapy products. The International Pharmaceutical Regulatory Program (IPRP) have established working groups on gene therapy and cell therapy (guidelines in key markets). ICH has a gene therapy discussion group (established in 2002) and have provided several ICH Consideration documents for gene therapy. They have recently also published the ICH guideline S12 (nonclinical biodistribution considerations for gene therapy products).

There are other inherent challenges to ATMPs because there are so many unknowns, such as can a patient get another dose? How long will the effect last? How should ATMPs be reimbursed? What should

be the long-term safety and efficacy follow-up strategy? All are important to consider for ATMP production. Sample sizes in the clinical trials for ATMPs are very small raising the question of how to establish efficacy and safety. To this end, long-term follow up is critical. In addition, comparative arms are challenging, and natural history can be sparce.



Currently there is no global alignment for evidence-based regulatory decision-making, but numerous regulatory groups are working on harmonisation. Genetically modified organism (GMO) consideration is also important in terms of future environmental impacts. It is hoped that there will be flexibility to use universal labelling for non-individualised cell and gene therapy products as this could be a 'quick win' for the industry to consider in order to launch a cell and gene product in a given market.

There needs to be convergence on definitions and the classification in order to adopt the reliance pathway. Collaboration is critically important in development of regulatory frameworks (as evidenced by the EU and US where there are a large group of industry associations). How this can be repeated in international markets is a consideration. Flexibility is required to avoid inhibiting improvements to manufacturing process in the ATMPs; use of a risk-based approach is encouraged because while some products are high-risk, there are some cell and gene therapy products that are not particularly complicated.

How are regulatory agencies developing their regulatory framework and capacity to provide direction for clinical development and undertake reviews - What are the key considerations?

South Korean Ministry of Food and Drug Safety (MFDS) perspective - Dr Jin Wook Kang, Senior Scientific Officer, MFDS, South Korea

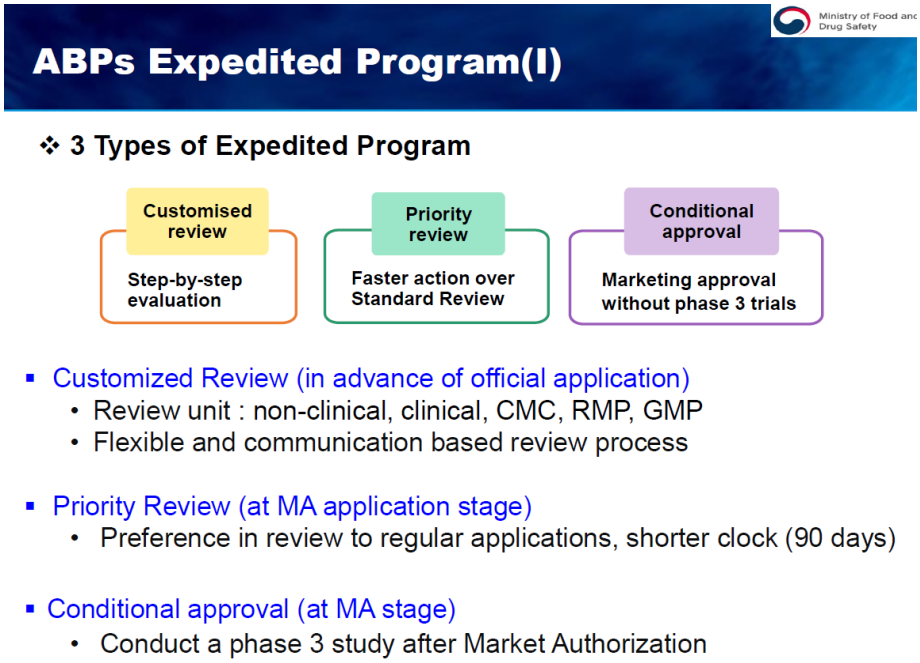
New Korean law on advanced regenerative medicines and advanced biopharmaceuticals

The Korean Act on the Advanced Regenerative Medicine (ARM) and Advanced Bio-Pharmaceutical (ABP) was legislated in August 2020 and aims to address safety management of ARM and ABP through to the manufacturing process, supply and medical field use. ABPs are mostly made to order, produced in small quantities, target incurable disease and require special safety considerations. ARM is regulated by the Ministry of Health and Welfare; ABP is regulated by the Ministry of Food and Drug Safety (MFDS). MFDS and the Regulation Science Center operate long-term follow-up of ABPs. ARM clinical research is

classified into low-, medium- and high-risk clinical research. For high-risk clinical research the developer is required to submit quality and non-clinical documents for additional review.

Types of ATMPs in Korea include cell therapy products, gene therapy products, tissue engineering products, advanced biological combination products with the medical devices and other drugs containing cell tissue and genetic materials. The approved scope of gene therapy products includes three categories: products intended for treatment of life-threatening disease resulting in serious disorder, the gene therapy product is superior to other available therapies and those deemed necessary by the MFDS. In the new Act, there is a safety control on cell processing and supply.

Korea uses three types of expedited programs: customised review, where the developer submits all data separately and MFDS reviews the data according to the review plan; priority review, where products are reviewed ahead of other submissions; and conditional approval where products may be expedited in the case of life-threatening disease and prevention against infectious disease. The developer can apply for permission on the condition of managing the safety of the product after it is released to the market. Conditional approval requests should demonstrate efficacy on a surrogate endpoint with the predictable clinical benefit, as well as demonstrating a positive risk benefit. In addition, for an investigation new drug (IND) or marketing approval, it is mandatory to plan a long-term follow-up study which should be submitted to MFDS. Notably, ABPs including cell therapy, gene therapy and general genetic cell products require a long-term follow-up study of up to 30 years.



Current approval status of cell and gene therapy products in Korea

There are currently 15 cell therapy products in Korea (mostly somatic cell products; others are stem cell and immune cell products). There are four market-authorised gene therapy products; two are chimeric antigen receptor T-cell (CAR-T) products. Since 2001, ~ 360 cell therapy product INDs have been approved (the majority are stem cells).

Support programme for developing companies and researchers

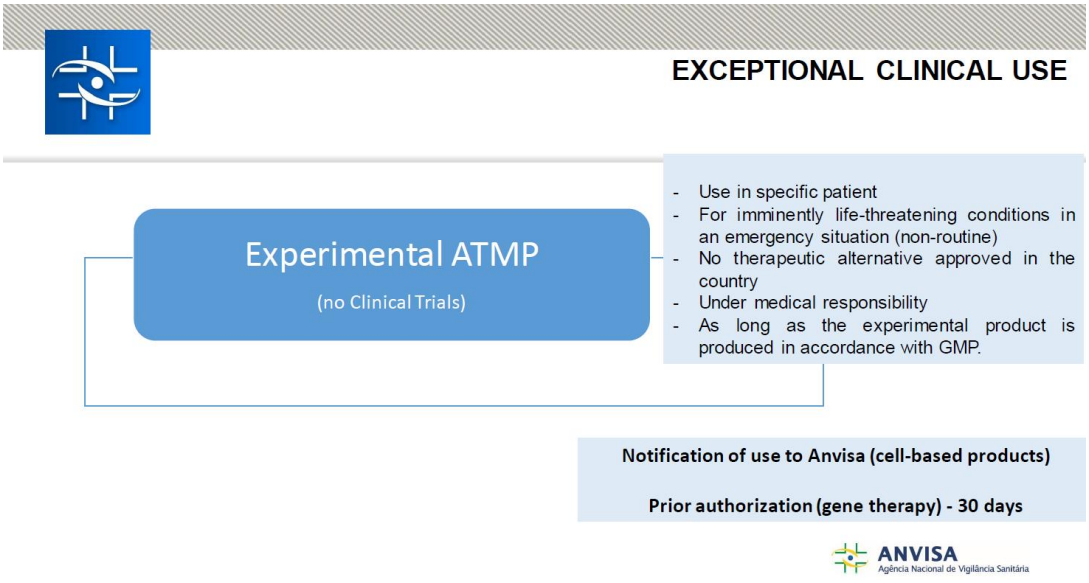
MFDS runs training workshops for developers. In the development stage, sponsors can liaise with the MFDS reviewer every month. In later stages of development, sponsors can seek consultation on request.

Brazilian Health Regulatory Agency (ANVISA) perspective - Fabrício Oliveira, Head of Biological Products and Advanced Therapy Medicinal Products Office, ANVISA, Brazil

ANVISA is the Brazilian National Health Surveillance Authority and is responsible for the market authorisation for all kinds of products, including medicines, medical devices, blood, tissue, cells, organs, and advanced therapy products. The organisation has recently divided its management of general medicines into two categories: small molecules and biological drugs (including human origin products). It was acknowledged by ANVISA that advanced therapies require publication of specific guidelines with specific technical standards. For this, therapies are categorised as advanced cell therapies, tissue engineering products and gene therapy products in line with other international agencies.

ANVISA has specific regulations for advanced therapeutics (marketing approval authorisation, clinical trials, good sales practice, ATMP [published in 2021]) and is proposing a new regulation that is harmonised with the PIC/S annex 2A regulation, in an effort to align with international regulations for ATMPs. Per law, ANVISA has 365 days to conclude the evaluation of a new submission, unless designated as a priority, where the review period is 120 days. Approval may be granted with conditions so that a product continues to be monitored in the market. The average approval time for an ATMP by ANVISA is similar to the FDA timeline (265 days) and shorter than the EMA (325 days). There is no reliance program for ATMPs currently since more experience with authorisation of ATMPs is felt to be required (although the public reports available from other authorities are consulted as part of the evaluation process). ANVISA guidelines will incorporate a mandatory pharmacovigilance period of at least 15 years.

ANVISA has a special kind of authorisation. An 'exceptional clinical use' policy is written into the guidelines permitting ATMP use under very strict conditions for specific patients, to be used for imminent life treating conditions in emergency situations when no therapeutic alternative is available. This is under the responsibility of medical staff, but ANIVSA collects data to assess use.

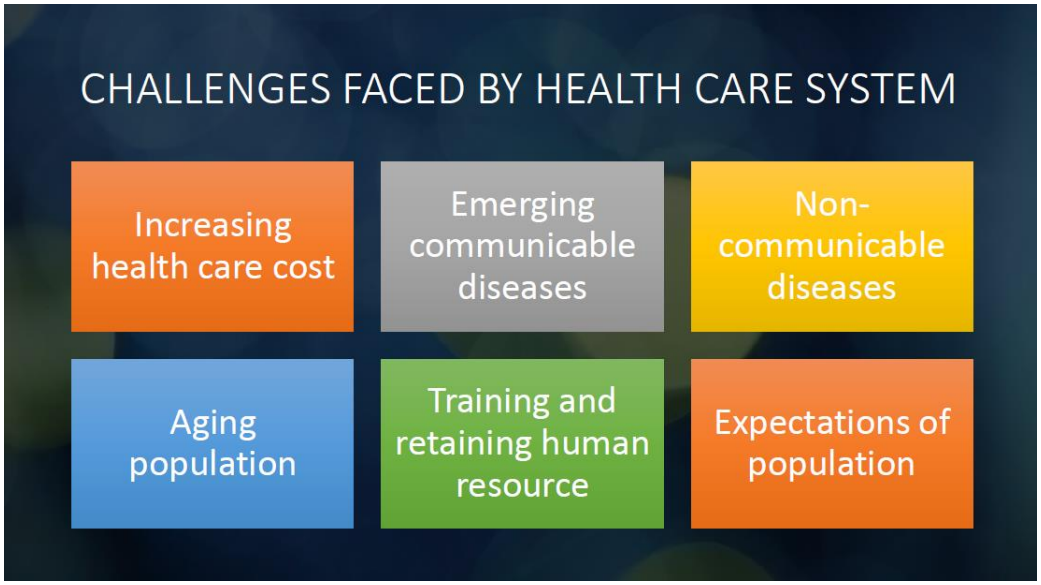


Academia/specialists support the assessment and evaluation of submissions via a committee for advanced therapies, including confirming the product meets scientific criteria for definition as an ATMP. This committee also helps to create new regulations and to better understand the process. All members sign confidentiality and conflict of interest terms. A good balance between the regulatory requirements for ATMPs and the access to patients is required. It is important to evolve regulations and guidance to reduce costs and to have a good benefit-risk relationship as ATMPs are expensive. For example, Brazil is discussing point-of-care facilities to help reduce costs of transportation and storage of products, and to provide benefits to patients. Since many aspects of ATMP production and treatment cannot be monitored by ANVISA, it is important to monitor aspects that can, i.e., by controlling inspections etc.

Assessment of new technologies/products such as ATMP – How are HTAs in Asia preparing for these advanced therapies and what are the key considerations? - Dr Izzuna Mudla binti Mohamed Ghazali, Deputy Director, Ministry of Health, Malaysia

Health system in Asia

It is important to note that the health system in Asia is diverse and encompasses developed countries to low-income countries. The health financing arrangement is heterogeneous between countries. Some are government-funded through a tax-based system while some countries have social health insurance. The share of healthcare spending finance through the government and compulsory health insurance schemes is higher in high-income versus low-income countries. Out-of-pocket payment is high in low-income countries versus higher-income countries. The quality of healthcare is also better in the higher-income countries. Access to healthcare also differs. Some countries are still struggling to get the basic care while others that are more developed are looking towards advanced care. Challenges faced by the healthcare system in Asia include increasing healthcare costs, double burden of diseases, where communicable diseases are still an issue and increasing burden of non-communicable diseases. In addition, challenges include an aging population, issues relating to training and retention of healthcare workers and expectations of the population.



HTA in Asia

HTA was established in Asia in 1995 in Malaysia and Singapore. While some countries have formal HTA in this region there are informal HTA activities in some countries. The mandate and merits of HTA in these agencies may be different; some HTA agencies cover drugs or pharmaceuticals only, while others cover all the health technologies. The capacity of these agencies varies greatly.

Challenges to HTA agencies

Rapid evolvement and complexity of the health technologies that require evaluation (including personalised medicine such as ATMPs and DHTs) are challenges to HTA. During the COVID-19 pandemic, some HTA agencies were also involved in public health interventions which presented unique challenges including the complexity of clinical trials and assessments required for urgent decisions. Other challenges faced by HTA agencies include consideration of environmental or planetary health as well as incorporation of stakeholders into the assessments (including industry, patients and patient groups) and human resource and capacity (personnel within HTA agencies to conduct the assessment and the capacity of the countries or the environment to support itself in order to have a more effective or efficient

HTA). In addition, variations of technologies (for DHTs) present challenges because traditional HTA may not assess other domains like accessibility, data security and protection and the interoperability of the technology itself. No countries in this region have a framework to assess digital technologies but a few countries are studying or looking to adopt the framework developed by NICE and other more established agencies. Reimbursement of the technologies is a challenge as most are being used by patients at home and there is an overall need to improve digital health literacy.

How HTA agencies are getting prepared and key considerations

Not only is the assessment itself important, but also the readiness of the health system, policies and guidelines and the ability of a country to implement a technology. Capacity building within the HTA agency itself is key. Networking and collaboration are very important. Involvement with networks such as the International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment International (HTAi), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International HealthTechScan (i-HTS), and HTAsiaLink are very important to build the capacity of the HTA agencies in this region.

Use of the lifecycle approach in assessment of health technologies is a key consideration. A few countries have established horizon scanning activities as part of their HTA activities to identify new or emerging technologies that are expensive (i.e., ATMPs and digital technologies), so that early preparations can be made by the country. Some countries also initiate the economic evaluation of technologies at an early stage, with later reassessments. Managed entry agreements have also been introduced in some of the countries, either by the HTA agencies, or by the regulatory agency.

Guidelines on use of RWE have been prepared to guide the HTA agencies in this region but it is important that the assessment is accepted by the end user, i.e., clinicians agree that the RWE is valid. It is agreed that RWE can be used for assessment of technologies for rare disease and for situations where there is an urgency to do so for decision-making.

Involvement of multi-stakeholders in assessment of these technologies is very important (clinicians, epidemiologists, patients, scientists, researchers and industry) to identify acceptable outcomes and comparative effectiveness or cost effectiveness for a given technology. Finally, innovative funding mechanisms that ensure appropriate implementation are important (this is being discussed at a country-level).

How are regulatory and HTA agencies approaching the evaluation and use of RWE/D within their regulatory framework – Is there clear direction for applicants and reviewers?

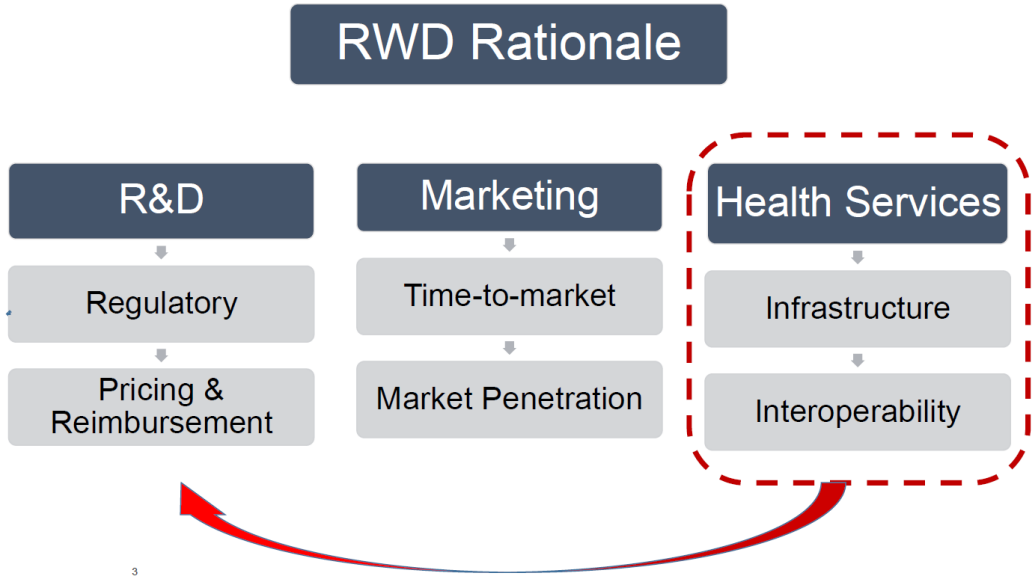
Swissmedic perspective - Dr Claus Bolte, Chief Medical Officer, Swissmedic

Perspectives on the current landscape

A possible clear direction depends on the regulatory and legal framework of the jurisdiction to which you want to submit your application. Currently, these frameworks are heterogeneous at best. In general, the evaluation and use of such data is well-established in the post-marketing space, mainly for pharmaco-vigilance purposes. Real-world data (RWD) collection and analyses are also being used in the clinical development or pre-marketing space - in terms of epidemiology, burden of disease, incidence, prevalence and in pharmaco-economic models. However, new indications and line extensions only rarely depend on real-world evidence (RWE) alone (i.e., registry data, claims data bases, or electronic health records). The Covid-19 pandemic also highlighted the use of observational trial data (i.e., Israel, UK) for evaluating the safety and efficacy of booster vaccines. More recently, patient-centred drug development includes wearables and mobile apps generating huge amounts of (unvalidated) data by patients themselves.

Why do we want, or why do some stakeholders want to collect RWD, which may eventually become RWE?

The promise of RWE as a valuable subset of RWD is two-fold: 1) data generated or collected in a real-world setting can be fed back into clinical development to support line extensions, variations or label updates etc. without necessarily designing difficult-to-recruit-for clinical trials, so the burden on patients is reduced but they can be involved by collecting outcome or safety data themselves; this is particularly true for rare conditions or small sub-populations; 2) efficiencies can be gained based on the latter, potentially expediting development, review as well as reimbursement, provided there is indeed agreement on suitability and technical requirements between applicant, regulator or HTA agency.



Lack of harmonisation aside technical challenges remain in terms of data standards and format as well as data quality, all of which have to be pre-defined. The correlation with well-established clinical endpoints is part of ongoing qualification procedures on a product-specific level.

The Swissmedic position

Given these dynamic developments and growing expectations regarding the use of RWE, Swissmedic has prepared a position paper to offer some initial guidance to applicants. Among other things, the position paper sets out the types of applications where Swissmedic is open to consider RWE:

https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl/positionspapier-verwendung-real-wordl-evidence.pdf.download.pdf/Positionspapier%20RWE_EN.pdf

It was published in July 2022 and includes practical requirements, such as a description and justification for the rationale of using RWD/E instead of clinical trial data, data sources and quality, a statistical analysis plan, including data handling procedures.

Eventually, cloud-based solutions can serve as repositories hosting pertinent data, including RWD/E from various sources (industry, academia and patients for selected purposes: development, regulatory, HTA etc).

Taiwan Food and Drug Administration (TFDA) perspective - Mei-Chen Huang, Section Chief, TFDA

According to FDA guidance, RWD is the data relating to a patient's health status, which is routinely collected from a variety of sources. Computers, mobile phones, and wearable devices have rapidly increased the availability and variety of health data which in turn has the potential to become RWE that can facilitate medicinal product development. While application of RWD/RWE throughout the drug lifecycle has gained attraction around the globe, its applicability to regulatory decision making still poses challenges and needs more discussion between different regulators and industries.

A clear regulatory framework is important to drive the future direction. TFDA have developed a series of guidance documents related to RWD and RWE since 2020, including basic considerations for the use of RWE to support medicinal product development, use of electronic health records in clinical research, pragmatic trials, data relevance and reliability, and notification of submitting documents utilising RWE for a new drug application. Most guidance documents were formulated with reference to FDA guidance, published literatures as well as collaboration with industry. Indeed, the regulatory framework began with a working group to which international pharmaceutical companies were invited to share their experiences.

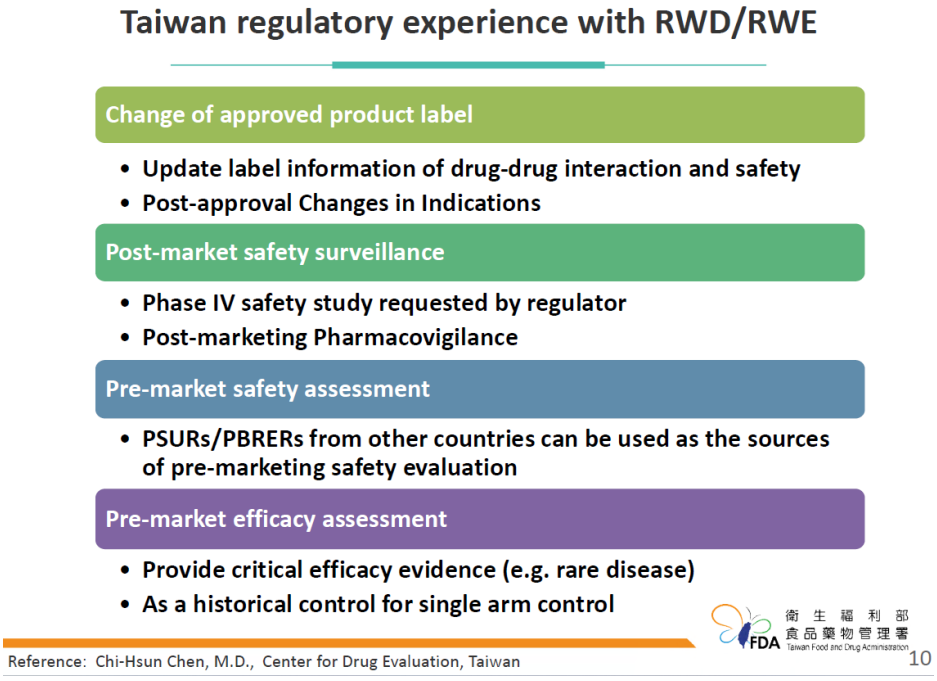
Basic considerations for use of RWE to support regulatory decision making

For sponsors and regulators, several questions should be carefully evaluated and considered in advance including: 'what is the scientific question to be solved and its regulatory purpose?' and 'is RWE suitable to answer the question?' In addition, identification of the potential sources of RWD and how to choose adequate sources to answer the question are important, as well as a predefined study protocol and study conduct/compliance.

The quality of RWD/RWE highly depends on three major factors: 1) fit-for-use of the RWD (i.e., relevance and the reliability of the data including consideration of whether the data source can represent the target population, sample size, follow-up period, quality control, data assurance etc.); 2) adequacy of the study design; and 3) compliance of the study.

Experience from TFDA

TFDA has considerable experience in using RWE for post-approval or pre-approval safety assessments. RWE has also been used to support evaluation of drug efficacy and the pre-market approval for some rare diseases.



Challenges and opportunities

Robustness of evidence compared with randomised clinical trials is a challenge and it is therefore recommended to consult with regulators early. While good sources of RWD exist, there remain challenges regarding data quality, standardisation and accessibility. The rapid development of digital technology and big data can offer added value for utilisation of RWD.

Summary

Leveraging RWE to support medicinal product development and regulatory decision making are emerging around the world and RWE plays a valuable role. The quality of RWD/RWE is key for its utilisation in regulatory decision making. Early engagement with regulators is highly recommended. Collaborations among different stakeholders to improve data quality, availability, access, standardisation and to develop better research methods are needed to expand the potential of RWD/RWE.

RWE use by HTA agencies in Asia - Dr Michael Coory, Public Health Physician, Technology Assessment and Access Division, Australian Government Department of Health

Is RWD/E being submitted and utilised for decision making? Are frameworks in place or is more needed? What are the key challenges for the agency? When thinking about RWD, it is useful to distinguish between using RWD to make causal claims versus using RWD for description. This distinction is important because using RWD for causal claims is more methodologically difficult.

Using RWD for causal claims

A relatively uncommon use of RWD is where the pivotal study for marketing approval is a randomised controlled trial on an intermediate endpoint followed by a non-randomised RWD data study in the subsidy space to provide comparative data on a later endpoint. Most commonly, these studies would use electronic health records from Europe or the US (rather than Australian data). The validity of these non-randomised RWD studies would be tested using a standard set of criteria such as those used by Cochrane which uses Robins I-tool to assess the risk of bias in non-randomised studies of interventions.

More commonly, we see RWD used where the pivotal data for marketing approval is a single-arm study on an early endpoint. This is expedited/accelerated/provisional approval depending on the region and is used for lethal diseases where there is unmet clinical need and no effective treatments. In this situation, the RWD provides not only a comparison on the later endpoint, but it also the external control arm.

The two key criteria that are specific to non-randomised comparisons using RWD are baseline imbalance bias or confounded by indication and time zero bias. In the subsidy space, we need to use the single-arm trial and the external control arm to obtain an estimate of a patient-relevant endpoint, such as overall survival. Typically, anchored matching adjusted indirect comparisons are used to statistically adjust for baseline imbalance bias; however, it is difficult to statistically adjust for all baseline imbalances between a single-arm trial and external controls, particularly because the early phase single-arm trials tend to be conducted at academic treatment centres where patients have better outcomes than those in other settings.

Indeed, according to the FDA, ‘time to’ endpoints, such as progression-free survival and overall survival in oncology studies cannot be accurately interpreted from single-arm trials as the comparison with an external control introduces a bias. Also, overall response rate, i.e., tumour shrinkage, has not been established as a surrogate for overall survival. Overall, there is possible disconnect between the regulatory reasoning and the subsidy reasoning (‘Is the benefit-risk balance favourable?’ Versus ‘What is the size of the treatment effect on a patient-relevant endpoint?’)

More methodological work is required in the subsidy space on how to deal with expedited marketing approvals. The FDA has published draft guidance for accelerated approvals in oncology for the purposes of seeking comments. It is also putting forward a one-trial approach, where accelerated approvals would

be based on randomised data on early endpoints, such as response rates, and then there would be further follow-up of this randomised trial to provide confirmatory data. The one-trial approach may need consideration in the subsidy space too.

Using RWD for description

In Australia, the most common use of real-world data is for financial forecasts. A less common descriptive use of RWD is to assess the applicability of the population of patients in the randomised controlled trial for marketing approval versus the population of patients who will receive the medicine, should it be subsidised. This can be important as patients in randomised trials are often highly selected. This is a promising use of RWD, which would support subsidy decision making and may be area for international collaboration.

What are the key challenges for using RWD/E in company submissions and how would sponsors like to see the regulatory landscape evolve? - Dr Sannie Chong, Senior Director, Asia-Pacific Lead, Global Regulatory Policy, MSD, Singapore

Asia-Pacific landscape

Company filings for RWD/RWE are either via ad-hoc communication or data put directly into the dossier and then submitted. Asia-Pacific (AP) countries are mostly in the maturing stage. The top three recommendations from industry, based on the 2022 CIRS focus study survey of companies, are to converge with international best practices, make guidelines available/develop guidelines and to implement or increase use of information sharing, reliance and worksharing.

Recommendations

Case studies on MSD GARDASIL®9 HNC show that RWE has been used in AP to support conditional regulatory approval in Taiwan as well as inform National Immunization Program (NIP) decision making in Taiwan and Philippines:

- Estimating the burden of illness related to genital warts in the Philippines: a nationally representative cross-sectional study (2019) [1]
- The Clinical and Economic Impact of a Nonavalent Versus Bivalent Human Papillomavirus National Vaccination Program in Taiwan (2022) [2]

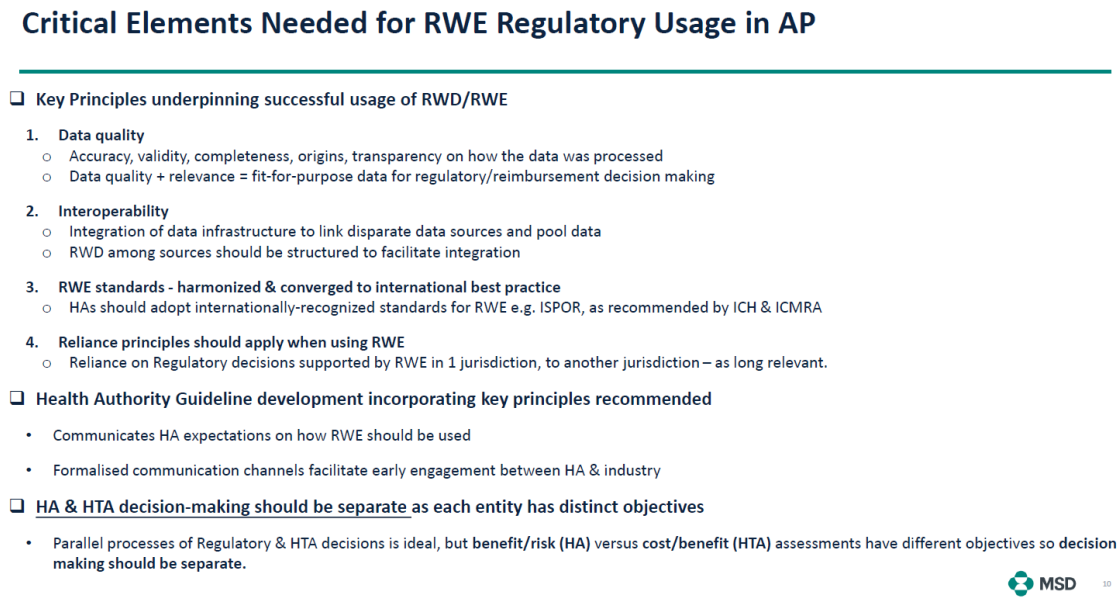
RWE studies on Head and Neck Cancers (HNC) incidence has helped to inform HPV NIP decision making to include males in both Korea and Taiwan:

- Incidence, cost and gender differences of oropharyngeal and noncervical anogenital cancers in South Korea (2020) [3]
- Economic Burden of Cervical and Head and Neck Cancer in Taiwan from a Societal Perspective (2023) [4]

Key principles underpinning successful usage of RWD/RWE are:

- Data quality – data should be accurate, valid, complete, transparent in how it was processed, fit-for-purpose for decision making and demonstrate reimbursement considerations.
- Interoperability and integration of data infrastructure
- Harmonisation and convergence towards international best practices and reliance practices.

When regulators start thinking about developing these guidelines, early engagement with industry and other stakeholders is welcomed. While health authorities and HTA have different objectives and look at different outcomes, processes that increase synergy (parallel vs sequential processes and reduced duplication of work), are ideal.



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Focus on DHT in clinical development: What types of DHT are being used for medicines development and what needs to be in place to provide regulatory oversight? - Prof Dean Ho, Provost's Chair Professor, University of Singapore

Translation and impact can mean different things and require definition. The US National Academy of Medicine uses a 'T0-T4 Research Classification' approach to define stages of innovation from T0 through T4. T0 is cells, tissues and animals. T1 human, T2 to patients, T3 to practice, T4 communities. Academia (conducting basic research) typically resides at T0. At the National University of Singapore (NUS) the goal is to be T2. This will require validation and advancement of technologies that can potentially transform practice. They are using their technologies to develop new combination regimens, all the way to how to dose patients. At present, there are many trials in academia in which novel therapeutics and diagnostics are being developed. Ensuring that trials are registered and outcomes are properly reported

in accordance with CONSORT etc. is not familiar to all of academia. To uniquely optimise patient treatment, the Institute for Digital Medicine (WisDM) at the National University of Singapore (NUS) has two arms, an ideation arm which includes expertise in AI and clinical medicine; and an implementation sciences and evaluation arm which also includes expertise in reimbursement.

Real-world use cases of technology were presented. It was noted that the AI presented does not use big data. Only a patient's own data is used to manage their care. It was explained that when a patient walks in the door, we have no data on them at all because we know that we are all different from each other. But when you have enough data to use and if the model is sophisticated enough, you can potentially overcome that noise of people being different from each other.

Importantly, the team at WisDM noted that there is a need to personalise treatment based on data that is dynamic over time, and that optimised treatment should be modulated to evolve alongside the disease itself. For example, a clinical use case was shown whereby a reduced dose was suggested to increase the efficacy of treatment for a stage IV solid cancer patient. Traditionally, dose modification is conducted based on treatment toxicity. However, in this case, dose modification was suggested based on efficacy – a major paradigm shift that resulted in a durable response for the patient.

The approach creates a 'digital avatar' for the patient. By understanding each patient across a different range of doses (dynamic dosing), it is possible to understand how to better dose each patient in time. When each single data point is added in for the dose response, the profile can morph, doses can be adjusted and the likelihood of finding a dose that responds to care increases. This contrasts with traditional trial designs, where patients are randomised to a dose and if they don't respond, they are removed from the trial and we would never know if they could have responded to a different dose.

Using rapid optimisation platforms in other fields (such as infectious diseases and antimicrobial resistance) was discussed where there may be a need to be able to prioritise or de-prioritise therapeutics faster, especially combination regimens rather than a hit-and-miss trial. This approach is looking for something very different than traditional dose-response-driven combinatorial design. Specifically, using an AI optimisation platform that iterates experimentally, not purely computationally, an iterative set of combinations can be run on a live virus/pathogen (a small set of experiments that can be completed in about 3 to 4 days; approximately 100 experiments that represent approximately half a million possible combinations). This is known as a hybrid of experimentation. Within that span of time, a ranked list of best to worst combinations is provided.

How trials were recruited was addressed. With every interventional trial conducted, WisDM at NUS attaches an implementation sciences team to understand who the user is (not always the patient) and the community they are aiming to help.

AI and regulatory considerations

Big data may be needed when using AI for diagnostics or for precision medicine, but in the realm of dynamically personalised interventions, sometimes small data can be sufficient. Can we rethink how we look at study designs? It was noted that trial design innovation is needed.

Dose optimisation can be dynamic. Dose changes can be constant over time, and if it can be done with small amounts of data while also considering the economics then accessibility can come into play. By using a person's own data for their care, bias can be mitigated. In summary, intervention is a space where AI can make a substantial impact but will require different thinking from a regulatory perspective, a technological perspective and beyond.

Digital therapeutics

Software as an intervention was presented, i.e., by dynamically modulating the intensity of each module, the system can pull out individualised profiles on how to optimise cognitive trajectory in the users.

Summary Slide

- It is important to consider **how much data** is needed versus **how data is acquired**.
- **Clinical Trial Design Innovation** will be critical towards safely accelerating innovative interventions with patients.
- **Interventional AI** should be increasingly discussed in the AI/Data regulatory space.
- Digital Health Technologies/AI are playing an important role in healthcare/medicine development.
- Multiple use cases indicate promising path forward for DHT.

What challenges do DHT pose for HTA agencies as they assess the evidence for new medicines?
Dr Pritaporn Kingkaew, Head of Research Unit, Health Intervention and Technology Assessment Program (HITAP), Thailand

Digital literacy in Thailand is not well developed and the healthcare system is fragmented. Three public health insurance schemes (mostly funded through taxation) exist but they do not communicate and are not standardised. Thailand has an HTA process for pharmaceutical products and a separate HTA process for vaccines. Currently, the process of getting an intervention into the benefits package is fragmented and takes considerable time. The concern is that the same would happen with DHTs.

Human resources are limited and so a topic prioritisation process (multi-criteria decision analysis) is utilised. The Health Intervention and Technology Assessment Program (HITAP) will assess the intervention (including cost effectiveness criteria, safety, efficacy, affordability and acceptance by the clinicians or users) and then submit it to committees who will make a decision. Once the decision is made, those interventions will be included into the benefit package. The HTA process is standardised but works in silo. Rapid HTA is ~6 months currently and full HTA is ~one year. This will be too long a period for DHTs that will rapidly evolve.

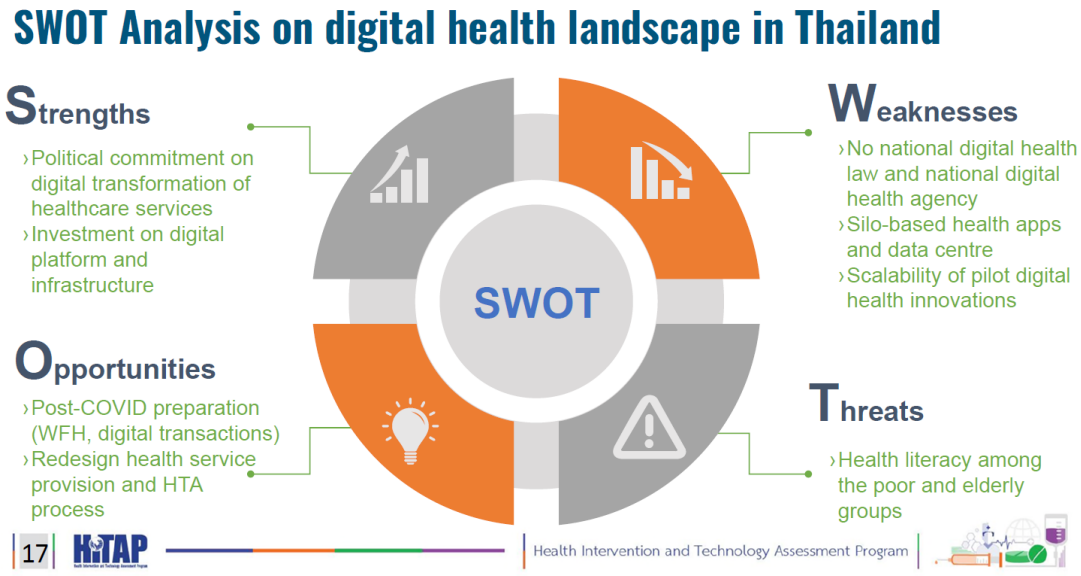
The vision for DHTs in Thailand

The vision is that in 5–10 years, care will be more ambulatory (virtual hospital) utilising point-of-care tests. While a policy is place (national strategies, legislation about patient protection, data protection and cybersecurity etc.) there is no National Digital Health Act yet. This will be important because health systems are not linked currently. Data is not shared between healthcare settings due to data protection concerns.

RWD/RWE from a claims database is only available from one public health insurance scheme currently (accounting for 7% of the population). This is problematic for the HTA who want to use the RWD but are challenged by its limited capacity. If RWD were to connect to cost data and health outcomes, the decision-making process would be much quicker.

Implementation of DHTs in Thailand are hampered by poor internet and low digital literacy in the elder generation (although digital health during COVID has enhanced knowledge of digital platforms). To have a successful digital health solution, core functions are required for how to collect the data and how the

data talk to each other, including health and digital literacy, feasibility and data security and proven benefits and clinical validation.



Challenges and future applications of DHTs

Thailand needs to reinvent or revise their HTA process to work at the early stage (like NICE), to be able to work with the developer, decide on how an intervention would be more cost effective, or how to set the price to fast track into the reimbursement list.

This is quite challenging in Thailand, because there is a lack of research funding to support the public sector to do early HTA. Since HTA submissions are not accepted from the private sector, all the HTA research must be conducted by the public sector. Regarding capacity of research there are issues with staff retention and turn-over rates. Process challenges include setting up price per item – should this be pay for services/utilisation (preferred by health insurance schemes) or outcomes? How should this be decided?

A benefit of digital health solutions is their potential to not only affect the individuals, but other sectors such as environment or education. User involvement is required to make the DHTs more effective. It was noted that typical analyses that use cost per QALY gain as a criterion to determine cost effectiveness or not, may not fit some of the solutions that do not just look at the quality of life of the patients.

SESSION 3: SYNDICATE SESSIONS

Three Syndicate sessions were conducted in parallel (see below). Feedback from each session was provided in SESSION 4.

Syndicate session A: Focus on ATMP - How does the global medicines development landscape need to evolve to ensure availability and access in maturing countries?

Syndicate session B: Focus on RWD/E for use in global submissions - What are the considerations/best approach and how should the global medicines development landscape evolve?

Syndicate session C: Focus on DHT - What are the considerations/best approach and how should the global medicines development landscape evolve a fit-for-purpose regulatory framework, and how might various stakeholders within and beyond the regulatory agency align?

SESSION 4: SYNDICATE SESSIONS FEEDBACK

Feedback of Syndicate discussions and participants' viewpoints – policy/action considerations

Syndicate discussion A: Focus on ATMP - How does the global medicines development landscape need to evolve to ensure availability and access in maturing countries?

Objectives*:*

- Discuss the key global regulatory and HTA challenges for the development review and reimbursement of ATMPs.
- Identify potential solutions and how the solutions can be practically addressed in short and long term.
- Make two or three recommendations as to the way forward for this topic.

Chair: Dr Claus Bolte, Head of Sector Marketing Authorisation, Swissmedic

Rapporteur: Brian Chen, Market Access Director Asia, AbbVie, Singapore

Discussion

Key global regulatory and HTA challenges for the development review and reimbursement of ATMPs were grouped into three categories:

- Clinical development
    - Lack of established clinical development methods and guidelines.
        - This observation was consistent with the findings of the CIRS survey.
        - Typically, US FDA, EMA, or WHO guidelines are referred to.
        - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), International Pharmaceutical Regulators Programme (IPRP) etc guidelines typically take 4–6 years to develop and align. Is it feasible to do something faster?
        - It is unclear how to draw meaningful conclusions from preliminary data to design clinical trials.
    - Limited resources to execute robust clinical trials.
        - Recruitment and long-term follow up are difficult due to limited patient populations, especially since ATMPs are typically later lines of therapy.
        - Limited technical knowledge/talent and infrastructure to administer clinical trials.
    - Evolving regulatory approval process
        - With small patient samples, long-term data are difficult to gather.
        - Phase 3 requirements need refinement which can be challenging as some approvals need to happen quickly.
        - Every review can be unique, leading to longer approval times.
- Manufacturing
    - Limited manufacturing hubs and local manufacturing.
        - Sometimes there is a need to ship patient samples to Europe and process there; the whole process can take several weeks.
    - GMP requirements at sites (local hospital vs large-scale manufacturing facility).
    - Chain of custody and Quality Control – keeping track of the drug product across the manufacturing process.
        - What do those requirements look like across the entire chain of product movement?
        - How do you ensure patient material comes back to the same patient?
    - Lack of technical knowledge across manufacturing stakeholders (hospital, industry)

- Socioeconomic/patient access
    - Funding to elevate healthcare, research and administration infrastructure.
        - Clinician expertise needed to administer advanced therapies and conduct long term follow up
        - If medical tourism was an option, how would patient follow-up work?
    - Identifying appropriate patient populations for these therapies.
        - How large are appropriate patient populations in each country or jurisdiction?
        - Pricing and reimbursement: how do you price these therapies?
        - Different therapeutic areas have different competitors, spaces, different value that each medicine brings.
    - Mitigating pricing and clinical uncertainty.

Potential solutions for these challenges were summarised and prioritised as follows:

Solution	**Rank**	**Addressed in short term (<12 months)**	**Addressed in long term (>12 months)**
Establish Regional Working Group to facilitate learning/exchange of experiences/best practices/scientific advice Stakeholders: patients, clinicians, regulatory, payer/HTA, policymakers	1	Y	
Build infrastructure: train personnel who can manufacture ATMPs, build optimal manufacturing hubs, clinical trial readiness	2		Y
Establish commercialisation roadmap and criteria: investment needs, patient population, affordability, clinical, manufacturing, and commercial infrastructure	3		X
Establish pricing & reimbursement framework: • Cost-effectiveness models – develop or adapt existing? • Establish appropriate endpoints in clinical trials for reimbursement • Reduce uncertainty with clinical trials (longevity and durability of efficacy and safety) • Reimbursement model: risk-sharing, reimbursement criteria	4		

Syndicate session B: Focus on RWD/E for use in global submissions – what are the considerations/best approach and how should the global medicines development landscape evolve?

Objectives:

- Discuss the key global regulatory and HTA challenges for the creation and utilisation of RWD/E in global submissions/assessments.
- Identify potential solutions and how the solutions can be practically addressed in short and long term.
- Make two or three recommendations as to the way forward for this topic.

Chair: Prof Hans-Georg Eichler, Consulting Physician of the Association of Austrian Social Insurance Institutions

Rapporteur: Stephanie Chen, Associate Director, AP Regulatory Policy, MSD, Singapore

Discussion

The main issues that the different stakeholders face in the usage of RWD/E in global submission/assessment were summarised as follows:

- Lack of transparency among healthcare stakeholders:
    - Confidentiality issues
    - Restricted access to data in national databases
    - Lack of data privacy frameworks
    - Rationale of data assessment is not revealed by decision makers, so it is not easy for industry to derive any lessons learned.
- Lack of understanding of the “fitness-of-purpose” of RWE in answering the scientific question (relevance and data quality):
    - Uncertainty is present among some stakeholders; context is key and that determines how RWE can be suitably used to complement the whole evidentiary picture.
- Lack of common recognition of international RWD/E standards:
    - Divergence in the use of RWE across markets.
    - Local studies are being conducted instead of doing reliance where it makes sense; duplication of work should be avoided.
- Low quality data sources.
- Complexity of cutting-edge technologies that are coming through the pipeline.
- Lack of understanding of different healthcare stakeholders’ objectives - this causes an eventual delay in access.
- Lack of technical capacity.

The syndicate group were asked to identify potential solutions and how the solutions can be practically addressed in short and long term. The following solutions were not ranked because the group felt this was dependent on the opportunity that exists.

Solution	Addressed in short term (<12 months)	Addressed in long term (>12 months)
Healthcare stakeholders coming together to **create a list of RWE examples/ case sharing that suitably answer the scientific question** to increase understanding	Examples from US & EU already present	
Bridge the connection between HTA-HA decision makers - **understanding how RWE is evaluated by HA & HTA bodies** can serve to speed up access to patients, where **RWE can act as a bridge between HA & HTA agencies** who jointly look at the same RWE – though for different purposes		
Increased circles of transparency that promotes understanding and collaboration among stakeholders for long term benefit	Differentiating what can be shared or not and targeting common ground	Address the issue of extrapolating data to different jurisdictions, trade secrets
Reliance when using RWE, if it is relevant, increasing the understanding of what can be extrapolated across markets (less ethnic dependant)		
Leverage existing collaboration/partnerships among various healthcare stakeholders to drive the implementation of lessons learnt, use cases, capacity building etc.	CIRS/CoRE as a platform	

To ensure that regulators and other stakeholders can obtain and evolve the necessary subject matter expertise, the syndicate group felt that several systems and tools are needed:

Stakeholder	What is needed
Regulators, HTA, academia, HA	**Joint dialogue of regulators-HTA (scientific advice meetings)** to get attendees up to speed, serves as education
Companies, HTA, HA	**Fee based system for advice** – companies charged per advised dispensed from HTA/HA interactions
Companies, HTA, HA	**Fee based system for training**
	Reliance, twinning of agencies – leveraging existing regulatory collaboration and extending partnerships to HTA space

Syndicate session C: **Digital health technology (DHT) - What are the considerations/best approach and how should the global medicines development landscape evolve a fit for purpose regulatory framework, and how might various stakeholders within and beyond the regulatory agency align?**

Objectives

- Discuss the key global regulatory and HTA challenges for the utilisation of DHT in global development and submissions/assessments.
- Identify potential solutions and how the solutions can be practically addressed in short and long term.
- Make two or three recommendations as to the way forward for this topic.

Chair: Dr Brian O'Rourke, Chair, CIRS HTA Steering Committee

Rapporteur: Helene Sou, Director, Global Regulatory Policy and Innovation, Growth and Emerging Markets, Takeda, Singapore

Discussion

Key regulatory and HTA challenges for the use of DHT as part of global development and submissions/assessments were summarised as follows:

- Broad scope of DHTs is a challenge for companies, regulators and payers.
    - Different types (tools, applications etc) as well as uses (clinical research, direct from patients)
    - Disruptive technologies – they are complex and evolve quickly.
    - Various stakeholders involved e.g. medical device industry, software developers, pharmaceutical companies
    - data collection from DHTs)
    - Issues around interoperability and how to exchange data.
    - Data quality and how to ensure data is reliable.
    - How to assess the value of DHTs from the HTA perspective (they may not provide a single outcome at a specific time).
    - Who pays for the tools – would the healthcare system support these DHTs? Would the payers be the patients at some level?
- Lack of global coordination among various stakeholders - from companies to developers, everyone has their areas of expertise.
- Lack of aligned standards/ guiding principles that makes it difficult for companies, regulators and HTA to assess DHTs.
    - For regulatory affairs: some countries use medical device frameworks, risk-based classification from International Medical Device Regulators Forum (IMDRF) for Software as a Medical Device.
        - Are these fit for purpose? This needs to be discussed among various types of stakeholders and not individually.
    - For HTA: need to build the assessment framework, value proposition from the company, and pricing and reimbursement models.
        - Given different country-specific considerations depending on the local environment and means, a common HTA framework is likely not possible.

It was noted that low- and middle-income countries (LMICs) have additional challenges related to infrastructure, connectivity, capacity building and lack of medical device frameworks.

Potential solutions for these challenges were developed into recommendations for future research/work (see below). It was suggested that research should be a first step, followed by a multi-stakeholder workshop, and that CIRS was well-placed to facilitate these. The outcome of scoping papers/workshops should be disseminated, through different publications and networks within industry and the regulatory and HTA communities.

Recommendations	Stakeholder	Timeline
1. Develop a **scoping paper** to better understand the areas that to be addressed in DHTs • Global research with an assessment of landscape by region, including LMICs • Identify existing guidelines/frameworks and key players • Identify gaps, duplications and major challenges	CIRS	3 – 6 months to develop
2. Discuss formation of a DHT **Topic Group** during the CIRS Scientific Advisory Council meeting	CIRS	June 2023
3. Submit **abstract for ISPOR Europe** conference in November 2023 to summarise the scoping paper • Attract attention from the various stakeholders and maybe a call for interest	CIRS	By 15th June 2023
4. Conduct a **CIRS Workshop** on DHTs • Invite key experts and interested parties e.g. Digital Therapeutics Alliance (DTA), ISPOR, HTA International (HTAi), WHO • Identify training needs – what are the skillsets and competencies in DHTs that are needed for the different stakeholders? Who could provide training and can existing trainings be leveraged?	CIRS	2024

SESSION 5: ALIGNMENT WITH INTERNATIONAL PRACTICE HOW CAN AGENCIES DEVELOP THEIR INTERNAL COMPETENCIES - PANEL DISCUSSION

Alignment with International Practice How Can Agencies Develop their Internal Competencies

Regulatory agency perspective - Lorraine Danks, Project Manager, South African Health Products Regulatory Authority (SAHPRA)

From a maturing regulator perspective, such as SAHPRA, very little is currently in place to deal with these new ways of working. The system is quite removed from reimbursement with government and RWD/RWE are not currently reviewed at all. Registration of medical devices has not yet started. A few formalised dialogues regarding ATMPs and DHTs with internal and external stakeholders are currently ongoing. However, SAHPRA has no suitably trained staff currently, no experience in these fields and no active regulation of these products. As for the majority of regulators on the African continent, SAHPRA is still in the horizon-scanning phase when it comes to these products, having neither received nor registered or authorised any cutting-edge products. As such, takeaways from CIRS workshops are invaluable.

ATMPs and DHTs require fit-for-purpose structure or regulation enabled through staff with multidisciplinary skills, including biochemical engineers and software analysts, etc, but also with the proper soft skills and inquiring minds. For SAHPRA, this is challenging because these skills are desperately lacking in the typical maturing agency. While there is a need to develop the necessary skills within the regulator, SAHPRA has several resource constraints that prevents attraction of the necessary talent to drive the agency in the above areas. In South Africa, remuneration cannot match that offered by private companies, and individuals with excellent credentials as well as with the required communication and collaborative skills, are generally snapped up by industry. They sometimes spend a year or two in the national regulatory agency getting experience and then move into industry. Retention is always a problem.

Currently, reliance is the only possible way forward and it is currently indicated as the basis for review of ATMPs and DHTs. While some regulators have chosen not to fully implement reliance on prior work of others, many agencies will have to rely on others' assessment until they can capacitate themselves sufficiently. This in itself could be a problem. As was found in SAHPRA, implementation of reliance practices sometimes takes a long time to be established in younger agencies, even with orthodox medicines, as the issue of trust continually plays a role.

Certain qualities such as flexibility, openness in thinking and transparency are not the usual hallmarks of a regulator and will require cultural transformation for some, in any case, to adapt to the new ways of working. However, the COVID-19 pandemic has forced many of the maturing regulators to deal with uncertainty, and regulators will hopefully be able to keep this momentum with increased adaptability and agility.

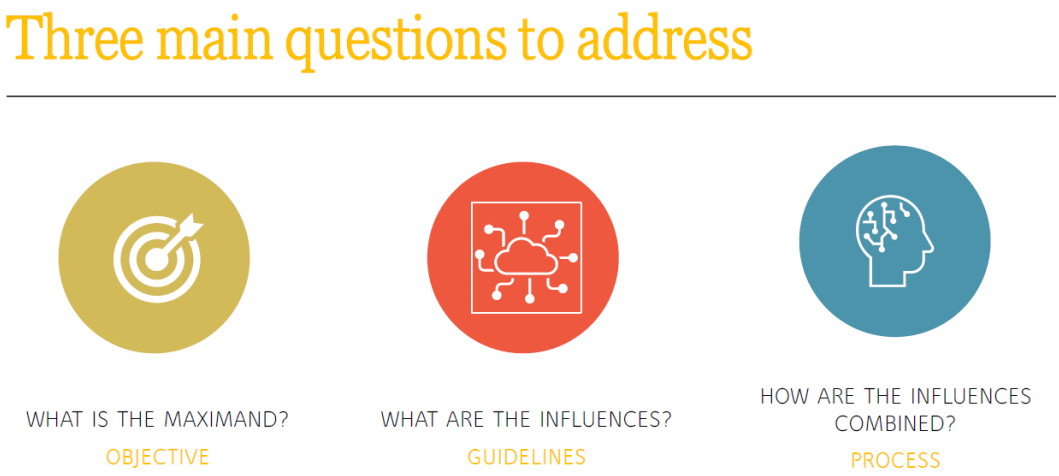
Action points for the maturing regulator include:

- Follow **international guidance** provided by the ICH and other bodies.
- Focus on **reliance**
    - Rely on mature agency reviews while also retaining your own decision-making outcomes.
- **Retention and training** (including of other in-house assessors) is important.
    - Onboarding of specialists in these fields is difficult.
    - Utilising expertise from the manufacturing sector is an option if finances permit.
- Set up **collaborative working mechanisms** with academia and industry and other stakeholders to learn together.
    - When it comes to new technologies, bigger agencies are working closely with the applicant and getting to understand the technology behind the product, from which the regulator learns also.
    - Engagement with industry and an understanding of the product, where it's coming from, where it's going etc are important. All the stakeholders learn together.
    - SAHPRA feels strongly about retaining open communication with industry and other stakeholders.

HTA agency perspective - Andrew Mitchell, Member, CIRS HTA Steering Committee

ATMPs, RWE, and DHTs are all promoted as being better but how do we know? In short, the new ways of working are better if they better meet the information needs of HTA-based decision makers. To establish this, we need to identify these unmet information needs.

Having done this, how can we then minimise any negative trade-offs in implementing and developing the new ways? This would be a call to action from an HTA perspective about how to enable global development using these new ways of working. And how might this affect convergence, alignment or harmonisation across HTA agencies?



First, the *objective* of what is trying to be achieved can vary across HTA agencies. HTAs may include one of more of the following objectives into their equations: incremental (net) health gain; incremental cost-effectiveness; social wealth; 'value flower'; and third-party payer value (some payer agencies don't have HTA in front of them). These different objectives and the way that they interact with each other are important. Where in the investment-disinvestment strategy is the HTA player? Most HTA agencies are in the investment space or the reinvestment space, but there are a few that are primarily in the disinvestment space. That context does change substantively the way an HTA will use onboarded information.

Second, the *influences* of the HTA can also vary across HTA agencies. Is the agency primarily addressing an economic question (if so, how is the overall incremental value best shared – supplier/patient/citizens), a clinical question (if so, what confidence is there in attributing the overall incremental value to the new intervention), or a mix of these questions (if so, how best to assign their relative influence)?

Third, how this information is assimilated by an HTA agency can make a difference on how the new ways of working might be taken on board but how are these influences combined? Single decision-maker? Committee of community representatives? Committee of relevant experts (preferred by most HTA agencies)? Or a formula of pre-assigned factors, weights and scores? The way that the information is eventually understood to support a decision is affected by how the HTA agency decides to do that key deliberative work.

Academic perspective - Dr James Leong, Assistant Professor, Head, Health Products & Regulatory Science Centre of Regulatory Excellence (CoRE), Singapore

Convergence is the basis of regulatory cooperation; however, understanding the utility and value that convergence and harmonisation would bring to an agency if achieved, is important. Even with convergence of technique requirements, local decisions are still needed (essential skills in the local regulatory duties are still required including benefit-risk profiling for the local population, pharmacovigilance and practical risk-management planning).

Enablers of how to pursue new approaches and new ways of working include strengthening of regulatory systems (competency to implementation, organisational changes, training and professional development), practice platforms (using real case, low-risk platforms, noting that this requires strong support from the industry and applicants) and measures/evidence of progress to demonstrate value and utility in impacting healthcare.

Challenges include not all stakeholders agreeing on the value and urgency of technical reliance, lack of justification for the risks that the new approaches bring, physician engagement with ATMPs, readiness of regulators for a new role and how aligned (phase of growth) regulators and agencies are given the potential collaboration.

APPENDIX: WORKSHOP ATTENDEES

*Presented via recording

Nélio Cézar de Aquino	General Manager of Medicines	ANVISA, Brazil
Abayomi Tosin Akinyemi	Assistant Director, ICT	National Agency for Food and Drug Administration and Control, Nigeria
Mario Alanis Garza	Senior Consultant	CIRS
Dr Samuel Asante-Boateng	Director, Drugs and Herbal Medicine Registration	Food and Drugs Authority, Ghana
Dr Samvel Azatyan*	Team Lead, Regulatory Convergence and Networks	WHO
Fabio Bisordi	Global Head International Regulatory Policy	F.Hoffmann-La Roche, Switzerland
Dr Claus Bolte	Head of Sector Marketing Authorisation	Swissmedic
Dr Piyanan Boonprasirt	Pharmacist, Professional Level	Thai Food and Drug Administration, Thailand
Dr Patrick Brady*	Vice President, Regulatory Affairs	Bayer, Germany
Dr Magda Bujar	Senior Manager, Regulatory Programme and Strategic Development	CIRS
Agnes Chan	Director, Therapeutic Products Branch	Health Sciences Authority, Singapore
Sandy Chan	Associate Director, Asia Pacific Regulatory Policy & Intelligence Lead	Janssen, Singapore
Brian Chen	Market Access Director, Asia Region	AbbVie, Singapore
Stephanie Chen	Associate. Director, AP Regulatory Policy	MSD, Singapore
Dr Sannie Chong	Senior Director, AP Lead, Global Regulatory Policy	MSD, Singapore
Dr Michael Coory*	Public Health Physician, Technology Assessment and Access Division	Department of Health, Australia
Lorraine Danks	Project Manager	South African Health Products Regulatory Authority
Dr Dirk Demuth	Head, Evidence Generation, VEO – GCI Region	GlaxoSmithKline, Singapore
Prof Hans-Georg Eichler	Consulting Physician	Association of Austrian Social Insurance Institutions
Noe García	National Director	National Directorate of Medicines, El Salvador
Dr Izzuna Mudla binti Mohamed Ghazali	Deputy Director, Medical Development Division and Head	Ministry of Health, Malaysia Malaysian Health Technology Assessment Section (MaHTAS)
Dr Ramiro Gilardino	Global HTA & Access Policy Lead	MSD, Switzerland
Vicky Han	Senior Director, Head of Regulatory Policy & Intelligence for Asia Pacific	Johnson & Johnson, Singapore
Gill Hepton	Administrator	CIRS
Eva Herlinawaty	HTA Team Officer	Ministry of Health, Indonesia
Prof Dean Ho	Provost's Chair Professor	National University of Singapore
Dr Li-Ying (Grace) Huang	Director, Division of Health Technology Assessment	Center for Drug Evaluation, Taiwan, ROC

Mei-Chen Huang	Section Chief	Food and Drug Administration, Taiwan, ROC
Serene Huang	Regulatory Sciences Manager	Pfizer, Singapore
Dr Jin Wook Kang	Senior Scientific Officer, Cell and Gene Therapy Products Division	Ministry of Food and Drug Safety, South Korea
Kuda Kapfumvuti	Senior Manager, Health Products Authorisation	South African Health Products Regulatory Authority
Adem Kermad	Senior Research Analyst	CIRS
Jackson Kiberenge	Drug Registration Officer I	Tanzania Medicines and Medical Devices Authority
Dr Pritaporn Kingkaew	Head of Research Unit	Health Intervention and Technology Assessment Program (HITAP), Thailand
Dr Alexandra Kitashova	VP Regional Regulatory Head, Greater China & Intercontinental	GlaxoSmithKline, Singapore
Sofia Kotelevtseva	Head of Regulatory Affairs, Asia and Eurasia	Sanofi, Singapore
Tania Krivasi	Market access lead Singapore and Asia Area	AstraZeneca, Singapore
Rosliza binti Lajis	Senior Principal Assistant Director	National Pharmaceutical Regulatory Agency (NPRA), Malaysia
Juan Lara	Senior Research Analyst	CIRS
Dr James Leong	Assistant Professor, Head, Health Products & Regulatory Science	Centre of Regulatory Excellence (CoRE), Singapore
Dr Sandra Lim	Vice President, Head of Regulatory Affairs Pharmaceuticals Asia-Pacific	Bayer, Singapore
Helen Ling	Associate Director, RAQAPV	Astellas, Singapore
Finny Liu	APAC Regional Regulatory Policy Lead	Roche, Singapore
Dr Francois Maignen	Principal Scientific Advisor	NICE, UK
Dr Neil McAuslane	Director	CIRS
Harriett Min	VP, Head of Regulatory Affairs, Asia Pacific	Janssen, Singapore
Andrew Mitchell	Member	CIRS HTA Steering Committee
Nancy Ngum	Programme Officer – Public Health	African Union Development Agency, (AUDA-NEPAD)
Dr Brian O'Rourke	Chair	CIRS HTA Steering Committee
Edosa Ogbeide	Director of Registration and Regulatory Affairs	National Agency for Food and Drug Administration and Control, Nigeria
Fabrício Carneiro de Oliveira	General Manager, Biological Products and Advanced Therapies Office	ANVISA, Brazil
Mi-Young Park	Director, Global Regulatory Affairs, Growth and Emerging Markets	Takeda, Singapore
Dr Rathi Saravanan	Lead Education Associate	Centre of Regulatory Excellence (CoRE), Singapore
Alexis Sciuk	Market Access Policy Strategist	Pfizer, USA
Dr Vinod Shetty	Head of Medical, APAC	Astellas, Singapore
Adj Prof John Skerritt	Adjunct Professor, and Chair, Scientific Advisory Council, CIRS	University of Sydney, Australia

Dr Belen Sola	Research Analyst	CIRS
A/Prof Danny Soon	Chief Executive Officer/A/Prof	Consortium for Clinical Research and Innovation Singapore
Helene Sou	Director, Global Regulatory Policy and Innovation, Growth and Emerging Markets	Takeda, Singapore
Dr Uttara Soumyanarayanan	Senior Education Associate	Centre of Regulatory Excellence (CoRE), Singapore
Dorte Strobel	Head of Regulatory Policy and Intelligence	LEO Pharma, Denmark
Asst Prof Wei Chuen Tan-Koi	Lead – Special Interest Areas	Centre of Regulatory Excellence (CoRE), Singapore
Lay Kheng Tan	Associate Manager, RAQA	Astellas, Singapore
Prof Steffen Thirstrup	Chief Medical Officer	European Medicines Agency
Hang Le Thi Thu	AAPAC Policy & Health System Shaping Lead	Roche, Singapore
Ariel Ting	Regulatory Policy & Intelligence Director, JAPAC	AbbVie, Taiwan, ROC
Phuong Tran	Official	Drug Administration of Vietnam, Ministry of Health
Alfonso Valencia	Ambassador	Embassy of El Salvador in Singapore
Prof Stuart Walker	Founder	CIRS
Dr Tina Wang	Senior Manager, HTA Programme and Strategic Partnerships	CIRS
Ada Wong	Public Affairs Lead Asia	Sanofi, Singapore
Sau-Wei Wong	Senior Director, Regional Regulatory Strategy	AstraZeneca, Singapore