



Innovation Strategic Priority Project Report

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Acronyms

AEMPS - Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicines Agency)

AI – Artificial Intelligence

AIFA – Italian Medicines Agency

ANVISA –National Health Surveillance Agency, Brazil

COFEPRIS –Federal Commission for the Protection against Sanitary Risks, Mexico

DKMA – Danish Medicines Agency

EMA - European Medicines Agency

EU – European Union

FDA – Food and Drug Administration

HC – Health Canada

HPRA – Health Products Regulatory Authority

HS – Horizon Scanning

HSA - Health Sciences Authority, Singapore

ICMRA – International Coalition of Medicines Regulatory Authorities

ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Medsafe –Medsafe, Ministry of Health, New Zealand

MFDS - Ministry of Food and Drug Safety

MHLW/PMDA –Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency, Japan

MHRA – Medicines and Healthcare Products Regulatory Agency, United Kingdom

MPA – Medical Products Agency, Sweden

NRPL – Novel Regulatory Pathway to Licensing

PEI – Paul Ehrlich Institute, Germany

SAHPRA – South African Health Regulatory Authority

Swissmedic – Swissmedic, Switzerland

TGA - Therapeutic Goods Administration, Australia

UK – United Kingdom

USFDA – United States Food and Drug Administration

WS1 – Work stream 1 of the ICMRA Innovation Project – Horizon Scanning Methodologies

WS2 – Work stream 2 of the ICMRA Innovation Project – Horizon Scanning Outcomes and Expertise Development

WS3 – Work stream 3 of the ICMRA Innovation Project – Novel Approaches to Licensing

1. Introduction

In the ever-changing regulatory landscape, new products, technologies, and production models are constantly challenging existing regulatory frameworks. In response to this, regulators are reviewing their regulatory policies to find ways to enhance and adapt the use of existing approaches to meet emerging and future requirements, as well as exploring new regulatory tools to ensure safe and timely access to innovative health products. Increasingly it is the case that the regulatory system needs to become more flexible and adaptable to fulfil its role in facilitating access to innovation for improved health outcomes. The pace of innovation in medical devices has surpassed medicines due adaptable approaches to the regulation of innovative products. While the existing novel licencing pathways for medicines have seen positive results in providing timely patient access, current and upcoming innovations will continue to challenge regulators. It is necessary for regulators to explore new approaches in order to provide adaptive as well as comprehensive regulatory oversight to facilitate the timely approval of new medicines and technologies, while at the same time protecting public health.

ICMRA, as an organisation comprised of the heads of the world's medicine regulators, is ideally positioned to take the lead in enabling interagency cooperation and collective engagement with stakeholder groups. Fostering collaboration between regulators, industry, and academia will ensure optimal positioning to meet the challenges described above. Earliest identification of future regulatory challenges posed by innovation and collective working at a global level to address these, will not only ensure timely and safe access but will also serve to ensure harmonisation in approach.

2. ICMRA Innovation Strategic Priority

Innovation as a new strategic priority, emerged from the ICMRA 10th Annual Summit in Switzerland in November 2016 as part of the review of the Strategic Framework and Activities. In order to identify topics where there was the greatest interest and need among regulators, a survey was conducted among members in early 2017. The results of the survey provided the basis of an in depth discussion at the ICMRA Plenary meeting on the margins of the DIA meeting in Chicago in June 2017. A new Strategic Priority on Innovation (SPI) was formally approved by ICMRA at the 11th Annual Summit held in Kyoto, Japan in October 2017.

What is "innovation", in the context of the SPI?

The focus of the SPI is on R&D of novel and/or disruptive medical products, techniques, and technologies. Examples of these include: newly devised concepts that may lead to the development of new categories of therapeutics (e.g. novel cell and gene therapies), and use of new approaches and methods in drug development and regulation (e.g. use of artificial intelligence and real world data in premarketing evidence generation and the authorisation of medicines, risk-based approach in inspections, etc.)

Many of the challenges posed by the emergence of such innovations will be common throughout the global regulatory community, particularly the rapidly deepening complexity of these products. As increasingly transformative innovations continue to come under regulatory scrutiny, regulators need to be open to innovation and also be able to adapt as needed. Preparedness will enable regulators to fulfill their responsibilities, while mitigating any inhibitory effect regulatory procedures may unintentionally have on future research and development (R&D) or impediments to swift patient access.

There is an opportunity for ICMRA to provide strategic leadership and direction under the new SPI to avoid duplication of work by multiple regulators and to enhance harmonisation of regulatory procedures pertaining to medical innovation.

3. Project scope

Throughout the discussions on innovation among ICMRA members, there was a clear consensus on the need for an innovation project which incorporated horizon scanning and novel approaches to licensing as key focus areas. There were two areas identified under the umbrella of horizon scanning: analysis of global best practices in horizon scanning methodologies and leveraging from the outcomes of horizon scanning (innovation of products and technologies and required expertise). Novel approaches to licensing would explore current processes for authorising innovative products and the associated regulatory challenges e.g. early access based on early data, stakeholder engagement etc.

The themes for three work streams were agreed upon as follows:

Work stream 1 (WS1) analysis of global best practice in horizon scanning.

Work stream 2 (WS2) leveraging outcomes of horizon scanning.

Work stream 3 (WS3) novel approaches to licensing.

3.1. Horizon scanning methodologies

ICMRA members conduct horizon scanning activities at varying levels of novelty, complexity and maturity. Appropriate infrastructure must be in place for horizon scanning to ensure that regulators have the capability to evaluate innovative products. Horizon scanning should ideally be conducted using consistent and harmonised methodologies. It was therefore proposed that an overview of methodologies currently being used among members would be mapped out to detect best practises. The need for engagement and outreach are central to success. This includes partnerships with industry, academics, R&D start-ups, SMEs, funders and other stakeholders. Even though some interactions occur at local level, leveraging from ICMRA, as a collective, to act as an engagement point with industry and potentially other stakeholders was seen as an additional valuable outcome from the work stream.

3.2. Leveraging on the outcomes of horizon scanning

Under horizon scanning it was also deemed critical to look at how regulators are leveraging the outcomes of horizon scanning. This includes the identification of products and technologies early in the pipeline and particularly those which do not easily align with the existing regulatory framework. Sharing the outcomes of horizon scanning would help to ensure a clear understanding of potential barriers and future regulatory requirements. In line with this, the Work Stream would look to implement a framework to facilitate sharing outputs of horizon scanning and develop a system in which global regulatory gaps/solutions would be identified/discussed.

The challenges presented by convergence were recognised as being unique and should be a key focus given that innovation in this area is progressing quickly and the scope of technologies involved will be broad. There is a need to determine where flexible and regulatory science based approaches will be required into the future and ICMRA is an ideal platform to lead these discussions on a global

level, opening debate and influencing policy makers so that the required approaches may be addressed in a timely manner.

3.2.1. Expertise

All regulators have approaches to adapting to innovation from the perspective of diversifying expertise and skills. However, there is a need to identify where there is a scarcity of expertise and skills and work collectively to find solutions in addressing the gaps. Establishing a framework for information sharing in relation to emerging novel areas of expertise or successful approaches to upskilling in niche specialities would add value to the network. Such an information resource could be used as a mechanism to support capacity building and potential opportunities for collaboration among ICMRA members.

3.3. *Novel approaches to Licensing*

Discussions on novel licensing schemes in which ICMRA members participate recognised the need to focus on the outcomes of such schemes as a key priority. Therefore, as an initial step it was considered that an analysis of the current scope of novel licensing schemes and early access schemes that exist on a global basis would be beneficial. Other areas for consideration within the analysis of outcomes included the successes that have been achieved globally utilising such schemes. This should include the specific impact on healthcare outcomes for patients that have been delivered. An analysis of this nature would act to support the progression of further approaches.

It was acknowledged that there are many barriers that may have prevented the establishment of novel approaches or access programmes and/or impeded their success and outcomes. An overview of barriers would assist ICMRA's consideration and leadership on how these might be overcome through more flexible regulatory approaches and policy requirements.

The reflection on the success and failure is essential to the continued and future success of such initiatives, thereby facilitating more timely patient access to innovative medicines and therapies. There is significant variation in respect of what early access schemes cover and it is important to ensure that ICMRA is working from a harmonised understanding of this. Outreach with stakeholders was identified as an important component in enabling success of novel approaches to licensing and ICMRA should explore routes to enhance their engagement with stakeholders involved this area of regulatory innovation.

3.4. Interlinking the three work streams

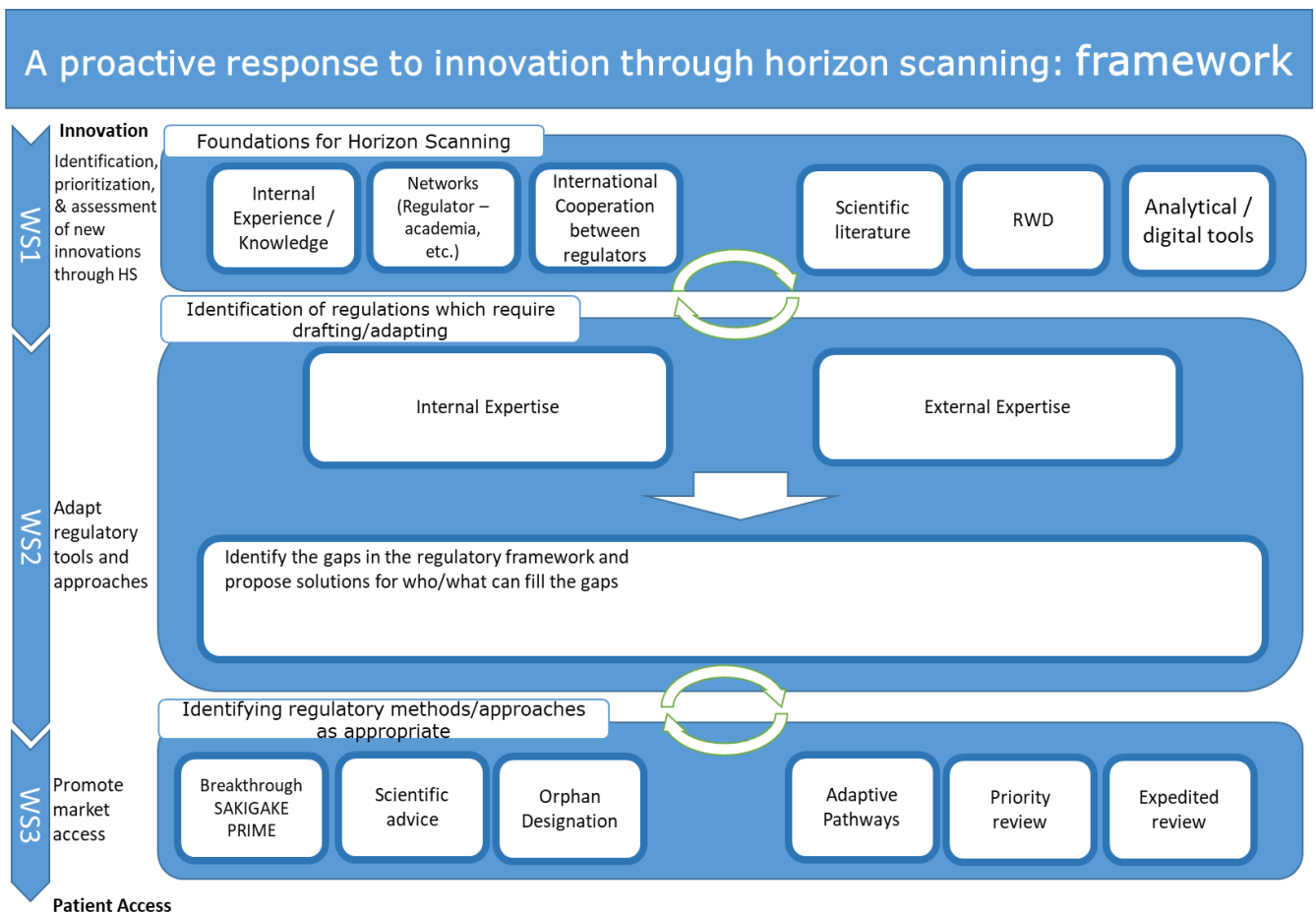


Figure 1: Relationship between patient access to innovative products / technologies and the ICMRA Innovation Project work streams

As shown in Figure 1 above, the left hand side indicates the steps from initial innovation to the final end user of innovation, the patient. Information on new concepts/products/technologies are collected via HS activities and this information can help inform where there are gaps in the regulation or where adaptations are required. Subsequently solutions can be proposed for who/what could be utilised to fill the gap. This process corresponds to the work of the three work streams. WS1 identified the foundations for HS, which feeds into WS2, aiming to leverage the outcomes of HS, specifically through identification of regulatory barriers hindering regulation. This process of addressing the gaps in the regulatory framework in turn feeds into the work of WS3, reviewing current novel regulatory approaches, their challenges/barriers and successes for early access.

Since the initiation of the project it was clear that there would be strong sequential interdependencies between WS1 and WS2, and WS2 and WS3. The link between WS1 and WS3 was less apparent given the two distinctive time frames within their analysis i.e. initial HS to late stage regulatory approval.

4. Overview of the three work streams

4.1. Work stream 1 - Horizon Scanning Methodologies and Best Practice

WS1 led by MHLW/PMDA conducted a survey of ICMRA members on HS methodologies to capture current methods being undertaken (details of the questionnaire and the responses are included in Annex 2 WS1 Interim Report). HS case studies from EMA, HPRA, US FDA, and HC were reviewed with their methodologies and outcomes documented in the report.

The case studies revealed how HS for most regulators is still in its infancy. Most of the HS programs studied were less than three years old and in the planning, pilot, or phased implementation stages. As regulators are still in the early stages of developing their HS capacity, there are potential opportunities for increased cooperation and learning between agencies to ensure the establishment of comprehensive HS methods.

The survey identified available resources for HS as a key challenge. The majority of regulators participating in the survey and undertaking HS activities had very few staff dedicated to HS, with many having no staff dedicated entirely to HS activities. The responses also highlighted the need to secure support from senior management for HS activities and recommended actions arising from HS so that agencies can prepare themselves for the future growth of innovative products.

Stakeholder engagement was also reported as a challenge for HS. If structured appropriately, stakeholders were able to provide valuable information from the forefront of innovation and to assist regulators in identifying the most appropriate areas of focus. However, it was found that the key to useful stakeholder engagement is information sharing on truly emerging technologies, rather than evolving technologies.

Based on the analysis from the survey and case studies, WS1 compiled a HS methodology framework and an overview of best practice in HS.

4.2. Work stream 2 - Leveraging the outcomes of Horizon Scanning

WS2 aimed to identify regulatory science considerations linked to emerging and regulatory challenging products and technologies detected via HS. Several examples of products and technologies from existing HS that test the limits of the current regulatory system and require regulatory science approaches were put forward by WS participants. Three case studies were chosen for further exploration and presented by HPRA, EMA and HSA-MHLW/PMDA: additive manufacturing, genome editing and artificial intelligence (AI). The science behind these technologies and their impact on the regulatory system were presented to WS2 members.

A number of regulatory challenges were identified in analysing the three case studies including the need for new regulatory tools and expertise in non-regulatory specific areas e.g. AI and Information and Communication Technology (ICT). The products and technologies explored in the case studies show that many regulatory science tools are missing at present (e.g. off-target effects detection methods) and must be developed in order for regulators to be able to assess the products across their life-cycle. In addition, new technologies (such as additive manufacturing) require adaptation of the existing regulatory frameworks, as they facilitate the production of more complex products at the point of care rather than in dedicated manufacturing sites. Appropriate regulatory approaches and standards will need to be put in place to effectively regulate such products while recognising potential benefits for patients and healthcare professionals.

The case studies also showed how different expertise from academia, technology or industry (e.g. AI, ICT) will be required. Agencies will need training to upskill staff but will also have to access experts outside the regulatory sector (e.g. software engineers) who will also require regulatory training to undertake regulatory tasks.

In order for regulators to adapt to the changing environment, the WS proposed the development of a capacity framework for expertise as a common resource for the network. This would involve mapping of the required skills and expertise for various types of products or technologies which would assist regulators in identifying their capacity needs.

4.3. Work stream 3 – Novel Approaches to Licensing

The objectives of WS3 included mapping out novel approaches to licensing, identifying barriers, and determining new approaches to the licensing of medicines and medical products. WS3 examined the various international regulatory approaches to licensing that aim to address the demand for timely access to innovative products.

The group led by HC designed a questionnaire about novel regulatory pathways which was distributed among ICMRA member countries from which a horizontal analysis of the responses was conducted.

The current novel regulatory pathways to licencing (NRPL) captured by the survey are categorised as either “expedited” or “facilitated” and are implemented through legislation, regulation, and policy. Expedited pathways aim to improve efficiencies in the product authorisation process to achieve timely patient access to medicines. Facilitated pathways aim to support patient access to innovative products through efficiency in the system that is often gained through collaboration among the health authorities, such as Health Technology Assessment Agencies (HTAs), and early engagement with the stakeholders.

The survey and case studies highlighted some key challenges which included the generation of quality evidence for innovative products utilising adaptive pathways, stakeholder engagement, international collaboration and regulatory/policy flexibilities for non-traditional pathways.

The WS3 interim report highlights areas where ICMRA could facilitate/influence strategically in addressing some of the challenges identified and an ICMRA proposal to interested parties for further regulatory science research in the areas of common interest, e.g., common characteristics of novel regulatory pathways and quality by design for evidence generation.

4.4. Collaboration between the three work streams

Since the project initiation, the three work stream leads have coordinated teleconferences with their members as well as teleconferences among the work stream leads in order to discuss the synergies and possible areas of convergence between the three groups. Ongoing project updates have been provided to the ICMRA executive committee and recently to the wider ICMRA membership at the ICMRA Summit in Washington, September 2018.

Information has been exchanged between the three WS leads on a regular basis. Constructive discussions between WS leads and overlapping WS membership allowed the project’s participants to explore future synergies.

The collaboration between the three work streams was further progressed at a joint face to face meeting of the innovation project held in November 2018 at DIA Japan. All project leads and

representatives from all three work streams participated in the meeting, which discussed how to put together the outputs of the meeting, the activities of the innovation network, and the remaining work of the Innovation project.

The key areas of collaboration are highlighted below.

- The WS1 HS questionnaire included questions relating both to the methodology for HS and how individual competent authorities leveraged the outcomes of HS. The latter responses provided helpful input into the WS2's work.
- The case studies analysed in WS2 outlined the HS methodologies implemented in researching these innovative technologies e.g. AI, Genome editing, additive manufacturing. These methodologies were summarised and provided additional data to contribute to the work of WS1.
- WS2 and WS3 also had ongoing interactions to identify existing regulatory pathways for innovative products. They also discussed the challenges arising in the regulation of disruptive innovations which do not fit established regulatory approach.

5. Overall Project Recommendations

The overall recommendations from the three work streams are outlined below.

Establishment of an Innovation Network

- The establishment of an Innovation Network within ICMRA which will be based on a proposal agreed by ICMRA members.
- The development of a capacity framework for expertise required for regulation in the future which would be undertaken by the Innovation network, once established.

Drafting of an ICMRA Statement on Innovation

- A statement on behalf of ICMRA regarding innovation which may be used to communicate the challenges faced by regulators in a fast paced innovation environment and to highlight the priorities and adaptations required at policy level for regulators to deliver on timely access to innovative products.

Conducting an in-depth case study

- WS3 proposed an in depth analysis a WS2 case study, additive manufacturing, which would be undertaking utilising a schematic framework shown in Figure 1. The study will be started initially under WS3 will be carried forward to be part of the work programme of the ICMRA Innovation Network.
- The analysis will include how additive manufacturing has progressed through the various phases of bringing a new innovation to the market and to highlight the challenges posed by the disruptive technology at the various stages and potential solutions. This will make use of the work carried out by WS3 on novel pathways.
- A significant outcome of the review will be identification of how solutions to regulatory barriers might be progressed and in particular the parties that ICMRA might liaise with to open debate and influence in order to give effect to these.

Summary of Common Characteristics of Optimized Novel Regulatory Pathways to Licensing

- The articulation of the common characteristics of optimized novel regulatory pathways to licensing, which could be used as a tool to assist the analyses and considerations of new/existing regulatory methods.

6. Next steps

A framework for an Innovation Network will be developed that would take the SPI beyond the initial project based phase to a longer term sustainable priority within ICMRA. Such a platform will require leadership within ICMRA to proceed with activities based on the project recommendations and to ensure stakeholder engagement as the network is established.

Annex 1 – Innovation project membership

Work stream	Project lead/Participation interest
1. Horizon scanning: methodologies and best practice	Lead: MHLW/PMDA Participants: AIFA (Italy), DKMA (Denmark), EMA (EU), FDA (US), Health Canada (Canada), HPRA (Ireland), MFDS (Korea), MHRA (UK), MPA (Sweden), and Swissmedic (Switzerland)
2. Horizon scanning outcomes: products; technologies; regulatory science approaches and expertise.	Leads: EMA, HPRA Participants: AEMPS (Spain), AIFA (Italy), DKMA (Denmark), Health Canada (Canada), HSA (Singapore), MFDS (Korea), MHLW/PMDA (Japan), MHRA (UK), MPA (Sweden), PEI (Germany) and Swissmedic (Switzerland)
3. Novel approaches to licensing, identification of barriers and methods to address these.	Lead: Health Canada TGA (Australia), ANVISA (Brazil), EMA (EU), AIFA (Italy), MHLW/PMDA (Japan), COFEPRIS (Mexico), MedSafe (New Zealand), SAHPRA (South Africa), Swissmedic (Switzerland), MHRA (UK).

Table 1: Membership of ICMRA Innovation work streams