ICMRA Rare Disease Workshop Report

Introduction

On 17th September 2024, the International Coalition of Medicines Regulatory Authorities (ICMRA) and Swissmedic co-hosted a workshop in Lugano, Switzerland, for participating regulatory authorities to discuss technological and regulatory challenges encountered with rare diseases and suggest potential solutions (see Annex 1 for the workshop program). The workshop discussions were informed by a symposium held the day before (16th September 2024), during which selected stakeholder organizations shared their perspectives on evolving technological and regulatory initiatives for rare diseases drug development (see Annex 2 for the symposium program).

The objectives of the symposium and workshop were to:

- Discuss with stakeholders, including industry, academia and patient advocates, challenges and opportunities, such as the utilization of digital health technologies (DHTs) in the clinical development of drugs for rare diseases
- Share regulatory authorities' current efforts to advance development of drugs for rare diseases
- Summarize the current challenges and opportunities with the aim of identifying opportunities and actions through which ICMRA could provide tangible and concrete support on a global scale.

Key messages from the multi-stakeholder symposium on 16 September 2024

At the beginning of the ICMRA workshop, a high-level summary of learnings from the multi-stakeholder symposium was presented, as follows:

As flagged by patient representatives, the world is facing a **global health crisis as** there is an estimate of about 60 million children with rare diseases and an increasing number of rare disease (between 6 000 and 9 000 depending on granularity and developing science). Applying the current model of drug development for every disease at a time means that the problem will persist for many years ahead and most of the very rare diseases will never see a treatment.

There is a need for **understanding of the terminology used in the rare disease and orphan drug regulation space.** It was concluded that even if it is not the mandate or scope of the group to provide (new) definitions, a list of terminology and their meaning under various jurisdictions could be created and made available to a wide international audience.

Rare diseases need to be better defined. Even if there are existing definitions of a rare disease, some differences between jurisdictions do exist. This has two consequences:

- Some products might be recognized as orphan drugs in some regions and not in others.
- The understanding of the rare diseases might differ among stakeholders and regions.

Different terms are mentioned in the public domain, such as 'orphan drug', 'orphan-like drug', 'ultra orphan drug', so there is a need for clarification and understanding of the concept of the orphan drug designation in different dimensions: definition, criteria and regulatory incentives. This would ideally be based on an international review among regulators. Although the focus was not on considering an 'ultra-rare orphan drug

designation', a discussion and mutual understanding of what constitutes an ultra-rare disease would be of value.

Clinical evidence generation for rare diseases is challenging but solutions are evolving. There are many innovative methods and trial designs as well as alternative data sources being used to overcome the challenges of clinical evidence generation within rare diseases. Examples include platform trials, pragmatic trials, adaptive study designs, use of DHTs, synthetic control arms, real-world evidence (RWE) etc. Having well-defined biomarkers and natural history data remain key. It is also essential that stakeholders continue to learn from past experiences (failures as well as successes). Pediatric rare disease trials are particularly challenging to design and execute; this is an area that needs further de-risking.

Adaptive approaches are becoming the norm. Developers in the rare disease space are increasingly using novel approaches such as platform trials, adaptive designs, pragmatic trials. In the platform approach one compound is developed with the view to develop several others very similar to the first compound. This approach aims to leverage data from the first compound. It was recognized that clear regulatory guidance on the place and acceptability of such approaches is needed.

The exponential growth of digital tools opens new opportunities, but not everything that can be measured should be measured. Digital health technologies can be useful in all stages of drug development, and this provided many opportunities for accelerating the development of rare disease treatments. One proposal was related to use of DT for common endpoints that can be applied across multiple rare diseases. It is essential for all stakeholders to discuss early and agree what should be measured using the available measurement tools.

Bridging the gap between regulators and early academic research. Academic research is key to the development of rare disease treatments however it is not well connected to regulatory discussions. There needs to be more opportunities for regulators to engage and support researchers working in the pre-competitive space, including exploring the use of public-private partnerships.

Involve patients early on. It is critical that developers identify and consult with patients early to understand what outcome measures are most relevant to their disease, what is feasible in terms of clinical research and participation in clinical trials. Patient organizations can help to drive research but need to be supported and empowered by the regulatory community and other stakeholders.

The importance of data sharing was flagged as another important element for accelerating research and development in the rare and ultra rare disease space. Examples were provided such as a 'pragmatic evidence lab' as a model of leveraging patient registries and despite disease heterogeneity applying AI learning systems for patient identification and recruitment.

The concept of **'disease agnostic approach'** in developing outcome measures with the use of digital tools was discussed as well. The burden of qualification of outcome measures was recognized and related to the concept of developing, validating and qualifying some core measures relevant across diseases was proposed (e.g. sleep, fatigue, dementia, tremor, ataxia, etc). This can be done in a pre-competitive setting and with support by regulators.

The industry speakers expressed their need for **'health authority concordance'** as another important way of accelerating drug development for the very small patient groups (n of 1, n of few).

Summary of Workshop Discussions on 16 September 2024

Updates from Regulatory Authorities

Participants representing different regulatory authorities provided updates on current efforts such as projects, initiatives and regulatory guidance by their agencies to advance development of drugs for rare diseases. Key points from these presentations are summarized below.

Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER) update – Dr Kerry Jo Lee

FDA CDER established the Accelerating Rare Disease Cures (ARC) Program to synergize rare disease initiatives across CDER to better interface and communicate on rare disease drug development both internally (with other FDA Centers and Offices) and externally (with the rare disease community). ARC does this through it's mission to drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases, harnessing information that can be fed back into scientific and regulatory innovation and stakeholder outreach and education. Included in ARC is the translational science team, which has been launched to advise on use of translational science to support novel surrogates and confirmatory evidence approaches, in addition to another multidisciplinary team focusing on assessment and application of innovative trial design and methodologies to rare disease drug development programs. While not directly under ARC, the Rare Disease Endpoint Advancement (RDEA) Pilot Program, a joint CDER and CBER program, enables sponsors to collaborate with FDA to create a novel efficacy endpoint for development programs that are intended to establish substantial evidence of effectiveness for rare disease treatments.

Under the ARC program, CDER developed the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER-3D) initiative to identify educational opportunities that will help stakeholders understand how to construct a regulatory fit-for-purpose trial. Various activities have been implemented, such as enhancing the ARC website to make guidance and other resources easier to find, and conducting community workshops on a range of topics e.g. natural history studies, novel endpoints, 'N-of-1' etc. For more on the ARC Program, and it's initiatives, ARC has released an annual report for 2024.

FDA also has a Rare Diseases Cluster between FDA, European Medicines Agency (EMA) and Health Canada conducts joint meetings to facilitate information exchange under disclosure agreements about protocols, product licensing, and informational topics about rare disease drug development products and programs between these agencies.

FDA Center for Biologics Evaluation and Research (CBER) update – Dr Celia Witten

CBER regulates several different types of biological products for rare diseases, including gene therapies, which were the focus of this presentation. CBER's current efforts to address challenges in gene therapy development focus on:

- advancing manufacturing of gene therapy;
- implementing the platform technology provision in recent legislation;
- more clearly defining the use of accelerated approval for gene therapy;
- exploring concurrent submission and product review with other regulators, including with EMA through the Collaboration on Gene Therapies (CoGenT) Global Pilot; and
- providing eligible sponsors that are developing gene therapies for rare pediatric diseases with more opportunities to interact with FDA via a communication pilot called Support For Clinical Trials Advancing Rare Disease Therapeutics (START).

CBER continues to develop new guidance and update existing guidance relevant to cell and gene therapies for rare diseases. For example, CBER is developing new guidance on the evaluation of efficacy in small patient populations and plans to update the available guidance, titled 'Expedited programs for the development of regenerative medicine therapies for serious conditions'. In October 2023 CBER issued guidance describing a voluntary standards recognition program for regenerative medicine therapies at CBER. Relatedly, the Center supports the Standards Coordinating Body for Gene, Cell and Regenerative Medicines and Cell-Based Drug

Discovery (SCB). Among other activities, CBER is engaged in partnership with the NIH, industry, and nonprofit organizations in the Bespoke Gene Therapy Consortium, a public-private partnership that aims to streamline the development and delivery of adenovirus associated vector (AAV)-based 'bespoke' gene therapies for rare and very rare diseases. In addition, CBER provides stakeholder engagement events such as the RegenMedEd webinar and seminar series aimed at patients and caregivers, and gene therapy-focused virtual town halls aimed at industry.

EMA update – Dr Violeta Stoyanova-Beninska

EMA has several touchpoints with the developers of rare disease drugs throughout the entire life cycle of a medicine. The Orphan designation (OD) is a very important mechanism for incentivizing drug development in rare diseases, as an OD comes with eligibility (and fee reductions) for several other procedures including protocol assistance.

Other supportive programs at EMA include the Innovation Task Force, a multidisciplinary platform for preparatory dialogue on innovative methods, technologies and medicines; the Quality Innovation Group, which is set up to support the translation of innovative approaches to the design, manufacture and quality control of medicines, to bring new therapies and help improve the supply of existing medicines to patients (with a particular focus on ATMPs); a Qualification of novel methodologies which is a voluntary, scientific pathway that advises on innovative methods and drug development tools as well as endorsing their use in specific scenarios; and the Priority Medicines (PRIME) scheme, which offers enhanced support for the development of promising medicines that target an unmet medical need. EMA also has specific offices that support small and medium-sized businesses (SMEs) and academic developers.

The Committee for Orphan Medicinal Products (COMP) is running a pilot in collaboration with the European rare disease patient group, EURORDIS, to assess whether an AI-based patient engagement tool can be used for regulatory purposes. The tool, called *Collaborare*, uses generative AI and patient organization validation to efficiently identify patient needs and relevant endpoints for clinical trials in rare diseases. COMP is also running a project on ultra-rare disease submissions to assess the characteristics of applications seeking initial orphan designations and determine whether success rates differ by the type of applicants, products, evidence provided etc.

Scientific publications can be a useful communication tool for European regulators to share learnings and experiences more efficiently and complementing regulatory guidance. Several examples were provided including a EMA recently published summary of RWE pilots with its different committees, including COMP, which highlighted the importance of having the right data sources to answer the intended research questions.

Swissmedic update – Dr Eveline Trachsel

Swissmedic supports the development of novel therapeutic products through its Innovation Office, which, since its establishment in 2022, has offered early advice to academics and SMEs developing ATMPs. International partnerships are also key; Swissmedic participates in the Access Consortium, Project Orbis and EMA Open. Despite Swissmedic's relatively strict criterion for the rarity of a disease to apply to the disease in its entirety, not to an isolated disease stage or sub-group, a significant proportion of approvals are for orphan drugs (around 60% in 2023, as shown in CIRS R&D Briefing 93).

Instead of having a dedicated team working on rare diseases, Swissmedic has multi-disciplinary working groups focused on different topics relevant to rare diseases. For example, the RWE Working Group has developed a guidance document positioning Swissmedic's thinking on the use of RWE. While submissions exclusively based on RWE are unlikely be sufficient to support a new marketing authorization, RWE alone could potentially be used to extend the therapeutic use of a medicinal product.

Swissmedic has a sandbox initiative that allows for the experimentation of new regulatory approaches in a safe environment. For example, an ongoing project is trialing the use of AI models to generate the non-clinical sections of public assessment reports (SwissPAR), ensuring that proprietary data are de-identified. Volunteer assessors are starting to familiarize themselves with the technology and have reported finding it useful so far.

Medicines and Healthcare Products Regulatory Agency (MHRA) update – Viji Ajith

The MHRA is involved in numerous national and international initiatives to address rare disease drug development challenges. One such initiative is the UK Highly Personalised Medicines Expert Working Group, which is creating a regulatory pathway for personalised cancer vaccines, setting stage for rare diseases. The UK Clinical Trial Reform introduces a flexible risk-proportionate framework, with patient public engagement adjusted to small populations, supporting multi-country trials and solutions for slow recruitment to name the few. Additionally, the Rare Therapies Launch Pad, a consortium-led initiative is focused on developing innovative therapies, with the MHRA's role is to create a proportionate regulatory pathway to ensure rapid access to life -saving treatments while independently assessing safety, quality and efficacy.

The MHRA also supports digital innovations, including in silico trials using physiologically based pharmacokinetic (PBPK) modelling and draft guidance on using Real-World Evidence (RWE) as an external control arm. Tools like Data Analytics Recruitment Tool (DART) and Speedy Patient Recruitment IN to Trials (SPRINT) speed up patient recruitment, while the AI Airlock Pilot Programme explores AI-powered devices to solve data challenges. Further, the Yellow Card Biobank utilises genetic data to enhance drug safety and personalised medicine, alongside the Large Language Model (LLM) Pilot, which uses advanced data analysis to aid rare disease research.

In repurposing medicines, MHRA has seen successes with Propranolol and Fenfluramine, accelerating access to life-saving treatments. CPRD, a key UK real-world research service provided by the MHRA, supports rare disease research, validating patient cohorts like those in Haemophagocytic Lympho Histiocytosis (HLH). While MHRA doesn't conduct the research, CPRD data helps external researchers advance knowledge, improve outcomes, and create clinical trial opportunities.

MHRA is also part of the Access Consortium, which launched the New Active Substance Work Sharing Initiative (NASWSI) to streamline reviews for critical therapies and established the Access Clinical Trials Working Group (CTWG) to facilitate regulatory information exchange on novel trials and safety.

Medicines Evaluation Board (MEB) update – Dr Marjon Pasmooij

The MEB Regulatory Science Program focuses on regulatory system improvement and innovation, using scientific publications as a channel for sharing the learnings of its research. In the area of rare diseases, MEB participates in two key projects: the International Rare Diseases Research Consortium (IRDIRC) N-of-1 Treatment Task Force and the European Medicines Regulatory Database.

The IRDIRC N-of-1 Task Force was established in 2023 to connect different N-of-1 (or single patient) treatment efforts to reduce duplication and achieve global consensus on the development and implementation of N-of-1 treatment. The Task Force has developed a roadmap for N-of-1 treatment (currently in press at *Nature Review Drug Discovery*) and is currently finalizing recommendations to tackle the major challenges hampering development and timely patient access to N-of-1 therapies.

The aim of the European Medicines Regulatory Database (EMRD) is to make data evaluating medicine regulation in Europe more accessible. An AI-based approach was used to extract and curate data from over 16,000 regulatory documents from the EMA website and European Commission Register, including European Public Assessment Reports (ePARs), Summaries of Product Characteristics (SmPC), orphan drug decisions and Pediatric Investigation Plans (PIPs). The EMRD allows users to select different variables, for example, related to

orphan drug designation, and create their own graphs that can be downloaded and used for further research. The last set of variables are currently being validated and a publication finalized. EMRD is expected to be made available in 2025. Future work for the project includes automatically mapping wording of the indications to SNOMED and ICD-11 disease terminology systems.

Saudi Food and Drug Authority (SFDA) update – Ahmed Alkhaldi

To help give more attention to rare diseases in Saudi Arabia, the SFDA launched its Orphan Disease Initiative in 2022. A focus group was conducted to better understand different stakeholder perspectives on the gaps for orphan R&D and how these can be addressed. In 2023, SFDA published its first guidance for orphan designation, focusing on disease prevalence (fewer than 5 in 10,000 individuals affected in Saudi Arabia) and lack of financial plausibility for orphan drug development. Incentives for SFDA's orphan drug designation include scientific advice, priority review and market exclusivity (although this is challenging in practice due to conflicting open market regulations in Saudi Arabia).

Between September 2023 and August 2024, SFDA received nine applications for orphan drug designation, mostly relating to cancer and neurological conditions; four applications were accepted, two were rejected and three are still under review. The first orphan designation application took 150 days to review, but more recently reviews have become much quicker, taking a few weeks on average.

Pharmaceuticals and Medical Devices Agency (PMDA) update – Dr Yoko Aoi

While drug lag is not a new issue for Japan, in recent years there appears to be an evolving issue of 'drug loss', where submissions never make it to Japan. This may be because a growing proportion of drug development (particularly orphan drugs) is attributed to emerging biotechnology companies, who have no or limited experience of submitting in Japan compared to large multi-nationals.

To help address orphan drug loss in Japan, the orphan drug designation criteria were revised in January 2024 to encourage more and earlier designations. Key changes include expanding the range of orphan subsets considered acceptable (there must be clear medical or pharmaceutical reasons), and further clarification to the definition of medical needs and the possibility of development criteria.

The Japanese government has a strategic goal to enhance Japan's drug discovery capabilities and support early availability of innovative drugs. To help promote decentralized clinical trials across Japan, PMDA has issued guidance on eConsent, direct drug delivery and remote data acquisition. In addition, discussions are underway on how to optimize Japan's compassionate use program, which currently does not cover individual patient (N-of-1) treatment.

Summary of discussion

Following the updates from the regulatory authorities, the workshop participants were split into groups and discussed two main topics:

1) Methodological/technological challenges and potential solutions for rare disease trials
2) Regulatory challenges and potential solutions with n-of-1 or small subsets within rare populations.

Participants were also asked to consider possible action points or recommendations for the global regulatory community that may help to address some of the challenges.

1) Methodological/technological challenges and solutions for rare disease trials

Participants acknowledged and discussed the challenges raised by stakeholders the previous day and two key methodological/technological challenges for which ICMRA could potentially facilitate a solution, were identified:

- Lack of common understanding about different terminologies;
- Lack of awareness about different endpoints used in clinical development of therapies for rare diseases between regions.

Potential solutions proposed for these two key challenges were:

- The development of a global glossary of terms with regulatory references, and
- Multi-Agency participation in workshops and sharing on key topics of interest such as endpoints and innovative trial designs.

Other challenges raised by stakeholders during the symposium were:

- Differences in regulatory requirements between regions;
- Need for qualification of novel methodologies;
- Need for global patient registries.

Although it was recognized that providing solutions to these additional challenges would require efforts beyond ICMRA, it was considered that identification and discussion of these issues at regulators workshops could be a useful starting point.

2) Regulatory challenges and solutions with n-of-1 or small subsets within rare populations

Key regulatory challenges identified by participants for which ICMRA might have a role toward a potential solution were:

- Confusing use of different terminologies in describing very small or N-of-1 populations (including subsets of rare populations) and
- Need for more global discussion on statistical methods and outcome validation of N-of-1 trials.

Also in this case, the development of a glossary was seen as an area where ICMRA could add value, as well as the organization of regulators' workshops on relevant topics of interest, in particular, enabling global discussion on statistical approaches for extremely challenging clinical trials such as N-of-1 trials. Similarly to 1) above, feasible further actions in which ICMRA could be involved and add value were identified as:

- Development of a glossary of terms used in small population drug development across regions and
- Organization of workshops on relevant topics of interest including statistical challenges and approaches.

Also in this area other challenges raised by stakeholders during the symposium were acknowledged, such as big difficulties related to reimbursement by payers, non-authorized or off-label treatment, and gene therapy ethical considerations. It was considered however that these are beyond ICMRA's mandate to address.

Recommended areas where ICMRA involvement could add value

- **Create and publish a glossary of common terms** used in drug development for rare diseases within the global regulatory community with regulatory references such as a link to relevant guidance provided for each term
- Conduct **workshops** on topics of interest for regulators and stakeholders such as drug developers and patient advocates to **enhance global collaboration**. More specifically such workshops could focus on:
    - Regulator's view and acceptability of alternative approaches in trial designs, lessons learned from oncology and successful use cases of historical controls, platform trials/technology/manufacturing, synthetic control arm, digital tool qualification, natural history, N-of-1 trials/treatments etc.
    - Explore the feasibility of developing a **toolbox or "one-stop shop"** in which developers of rare disease treatments can find information on commonly accepted endpoints and other areas of alignment across regulators.
    - Explore the feasibility of establishing **global patient registries** for specific rare diseases in collaboration with patient communities.

Annex 1 – Symposium program

Symposium agenda & concept (V.10) – Day 1 (September 16, 2024)	
12:00 - 13:00 (CET) **Check-in & Welcome Beverages**	
13:00 – 13:15 (CET) **Welcome**	· Emer Cooke (EMA) & Raimund Bruhin (Swissmedic) · Claus Bolte (Swissmedic) & Kerry Jo Lee (FDA)
13:15 – 14:30 (CET) **Keynote 1 Clinical Focus (High-level Overviews)** · More opportunities than challenges today! · Clinical & translational research · Pharma R&D (clinical development) · Pragmatic evidence generation in routine care	· Maria Ester Bernardo, Pediatrician · Tiina K. Urv, NIH (US) · Thomas F. Miller, Industry (US), InsideScientific · Lars Hemkens (CH), DKF USB, Pragmatic Evidence Lab
14:30 – 15:10 (CET) **Panel 1 Evidence Generation** · Academic clinicians and investigators · (Ultra-)Orphan Drug Designation?	· Keynote 1 speakers plus · Daniel Michaeli (D) Nat. Center for Tumor Diseases
15:10 – 15:40 (CET) **Brain & Bio Break**	
15:40 – 16:55 (CET) **Keynote 2 Digital Health Technologies (DHT)** · Showcasing exciting tech developments · How rare diseases became common · (What) can we learn from Oncology? · Linking regulators and tech	· Jennifer Goldsack (US), Digital Medicine Society · Dan O'Connor (UK), ABPI · Blythe Adamson (US) · Klaus Romero (US), Critical Path
16:55 – 17:35 (CET) **Panel 2 Integrating DHT** · How can DHT help (recruitment, data)? · Regulatory Science evolving · Low- and middle-income countries	· Keynote 2 speakers plus · Elisabeth Kunkoski, FDA · Steffen Thirstrup, CMO EMA
17:35 – 17:50 (CET) **Brain & Bio Break**	
17:50 – 18:35 (CET) **Lakeside chat with caregivers** · How to better appreciate and integrate their journeys and experience?	· Bob Stevens (UK), MPS Society · Christoph Poincilit (CH), NPD Suisse · Klaus Rose (CH), Pediatrics, Sturge–Weber syndrome · Julia Vitarello (US), Mila's Miracle Foundation
18:35 – 18:45 (CET) **Wrap-up**	· Claus Bolte (Swissmedic) & Kerry Jo Lee (FDA)
Adjourn @18:45 (CET) (ICMRA Steering Committee & Faculty Dinner @20:00 (CET))	

Annex 2 – Workshop program

Workshop agenda (V.2) – Day 2 (September 17, 2024)	
08:00 – 08:30 (CET) **Welcome Coffee**	
08:30 – 08:45 (CET) **Intro** What did we hear on day 1 / Introduction Day 2	· Violeta Stoyanova-Beninska – Wrap up (10 minutes) · Kerry Jo Lee: Overview of Day 2 (5 minutes)
08:45 – 10:15 (CET) **Insights** · Brief overviews of ongoing projects, initiatives, guidances focused on innovations relevant to Day 1 topics · What tools do we have in the toolbox?	· Kerry Jo Lee, Celia Witten, FDA (CDER and CBER) – 20 minutes · Violeta Stoyanova-Beninska, EMA – 10 minutes · Eveline Trachsel, Swissmedic –10 minutes · Viji Ajith, MHRA – 10 minutes · Marjon Pasmooij, MEB – 10 minutes · Ahmed AlKhaldi, SFDA – 10 minutes · Yoko Aoi, PMDA –10 minutes
10:15 – 10:35 (CET) **Coffee Break**	
10:35 – 11:20 (CET) **Breakout Session 1** (discussion in 2 groups, according to separate list) Methodological/Technological Challenges and Solutions	Given innovations presented and input from yesterday, what are the key challenges in these trials, how can digital technologies and other advancements help, what else could still be done to move forward as a global regulatory community?
11:25 – 12:10 (CET) **Breakout Session 2** (discussion in 2 groups, according to separate list) Regulatory Challenges and Solutions	What are current regulatory challenges with n of 1 or small subsets within rare populations? How can emerging innovations help to address these challenges?
12:15 – 13:15 (CET) **Group Report Out and Discussion**	· Reporting out from breakout groups and group discussion · Distill learnings and next steps
13:15 – 13:30 (CET) **Next Steps & Wrap-up**	Determine next steps (publication, assignments to move forward, etc.) · Claus Bolte (Swissmedic) & Kerry Jo Lee (FDA)
13:30 – 14:30 (CET) **Standing Lunch**	