Reliance - Towards a global regulatory standard

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Development of medicines is evolving

- **New wave of innovation** in health and biomedical science
- Significant developments promising to **transform healthcare and deliver better health outcomes for patients**:
  - targeted **cell and gene therapies**
  - adoption of **digital health technologies**
  - focus on harnessing the wealth of **health data and real world evidence**

**Regulatory environment must respond to these developments**
Highly Innovative pipeline -US

39 Total NAS launched in 2022
24 first in class
30 used expedited pathways

IQVIA Institute- global trends in R&D 2023
Highly innovative pipeline - EMA

Almost 50% of therapies in development are new products, among which lower incidence, previously omitted diseases are gaining interest (and investment), with 40% of the pipeline being orphan drugs. More than 90% of products in the pipeline are biologics and small molecules. However, the share of Next-Generation Biotherapeutics (NGB), such as cell, gene, and nucleotide therapies in clinical development continues to increase. In years 2014-2019 the number of NGB products has more than tripled, as they have high potential especially in previously intractable diseases.

A total of 55 New Active Substances EMA approvals in 2020
Some numbers from CIRS to start with…

Global Registration

Median time to roll out New Active Substances (NASs) approved 2016-2020 to Emerging Markets (EM) approved

CIRS RD Briefing 88
Bringing a new medicine through global approval is a complex and lengthy process

Illustration of the differences in the dossier for one same product, due to different country-specific requirements

CPP= Certificate of Pharmaceutical Product
HAQ: Health Authority Questions
Efficient regulatory system – a key for improved access to medicines

Ground-breaking advances in medicine are only meaningful when they reach patients.

How all stakeholders can work together towards this goal?
WHO regulatory system strengthening program

1. Build regulatory capacity in Member States consistent with good regulatory practices
2. Promote regulatory cooperation, convergence and transparency through networking, work-sharing and reliance

Why reliance?

- Good reliance practices, 2021
- Good regulatory practices, 2021

Slide adopted from M. Valentin, WHO presented at DIA CMC Conference, Sept., Sevilla 2022
Ultimate Goal: Global Convergence

- One product
- One regulatory standard
- One inspection
- One assessment
Global and regional initiatives driving regulatory convergence

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International Coalition of Medicines Regulatory Authorities (ICMRA)

MAIN OBJECTIVES
ICMRA promotes international cooperation among medicines regulatory authorities to strengthen global dialogue, facilitate wider exchange of reliable and comparable information, encourage greater leveraging of resources and work between authorities, and advocate for better informed risk-based allocation of authorities’ resources and deeper collaboration. The group also addresses current and emerging human medicine regulatory and safety challenges. These efforts aim to strengthen the quality, safety and efficacy of medicinal products globally.

WHO WE ARE
ICMRA is an informal group of leaders of medicines regulatory authorities that provides strategic directions for enhanced collaboration, improved communication and approaches to jointly address common challenges, such as the COVID-19 pandemic.

MISSION
ICMRA’s mission is to safeguard public health by facilitating strategic leadership and greater cooperation of international medicines authorities on shared regulatory issues and challenges.

MAIN WORKING AREAS
There are currently several ICMRA projects on Antimicrobial Resistance (AMR), communications, drug shortages, innovation, pharmacovigilance, regulatory convergence and alignment in the global COVID-19 regulatory response, and supply chain integrity.

❖ Currently chaired by Emer Cooke (EMA)
❖ 24 member agencies, 15 associate member agencies, and 1 observer (WHO)

Source: ICMRA Factsheet
Mission

❖ Achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

❖ Accomplished through development of Technical Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side

❖ Commitment of the ICH regulators to implement the final Guidelines is key to the success of the process
ICH Membership until 2010

Health authorities

• 1990-2010: US, EU and Japan

Source: www.ich.org, Company reported data
ICH Membership until 2018

*Health authorities*

- 1990-2010: US, EU and Japan
- 2010-2015: + Switzerland, Canada
- 2015-2018: + Brazil, South Korea, China, Singapore

Source: [www.ich.org](http://www.ich.org), Company reported data
Current ICH Membership

Health authorities

- 1990-2010: US, EU and Japan
- 2010-2015: + Switzerland, Canada
- 2015-2018: + Brazil, South Korea, China, Singapore
- 2018-2023: + Mexico, Egypt, MHRA, Saudi Arabia, Chinese Taipei, Turkey

Current observers: India, Cuba, Colombia, South Africa, Russia, Australia, Kazakhstan, Argentina, Moldova, Armenia, Iran, Israel, Jordan, Malaysia, Indonesia, Ukraine, Lebanon, Nigeria, Tunisia, Azerbaijan

Source: www.ich.org, Company reported data
MISSION and STRATEGIC VISION

IPRP is a global forum of regulatory authorities and regulatory organizations at the operational level for issues related to the regulation of pharmaceuticals for human use. IPRP is committed to promote information sharing, facilitate the implementation of ICH and other internationally harmonised technical guidelines for pharmaceuticals for human use, promote collaboration and regulatory convergence of regulatory approaches to advance public health, facilitate access to medicines and address emerging regulatory challenges of mutual interest.
Reliance is not a new concept…

Long history of improving efficiency through reliance e.g. Certificate of Pharmaceutical Products Scheme (1969)

“Regulate through reliance” as the hallmark of a modern and efficient regulatory authority

Increasing role of reliance

Promoting “informed” reliance

COVID-19 as a strong accelerator for the use of reliance
WHO Good Reliance Practices

Annex 10

Good reliance practices in the regulation of medical products: high level principles and considerations

Background

WHO supports reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise. This principle allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to: vigilance, market surveillance, and oversight of local manufacturing and distribution. Reliance

The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision.

The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

International cooperation is key

- To ensure the safety, quality, efficacy or performance of locally used products
- To make the best use of available resources and expertise, avoid duplication and concentrate regulatory efforts and resources where they are most needed

Slide adapted from S. Azatyan, WHO, DIA Latin America Annual Meeting, March 2023
Options to facilitate good quality regulatory decisions – reliance in the focus

- Independent decisions based on its own reviews and/or inspections
- Dossier assessments
- Dossier inspections
- Standard processes
- Work-sharing
  - Country A
  - Country B
  - Country C

- Abridged pathway using reliance
  - Country A
  - Country B
  - Country C

- Leveraging regulatory work
  - Performed by other competent and trusted authorities to reduce the workload

- Recognition
  - Unilateral
  - Mutual recognition

Building trust between NRAs, increasing reliance and efficiency

Slide adapted from S. Azatyan, WHO, DIA CMC conference, September 2021
Risk Based approach – Examples of types of Models

- **Standard process**
- **Parallel Collaborative**
  - Regulators conduct parallel collaborative evaluation and share information
- **Work-Sharing**
  - Regulators conduct divide review of safety, efficacy modules
- **Centralised Evaluation**
  - Conducted for a group of countries/region
- **Regional Reliance**
- **Centralised Procedures**

**Examples:** Verification / abridged

- Country A relies on reference Agency Assessments
- Unilateral Reliance

Source: CIRS
Project Orbis -
A framework for concurrent submission and review of oncology products

**Project Orbis Partners (POP)**
- TGA/Australia
- HC/Canada
- ANVISA/Brazil
- HSA/Singapore
- Swissmedic/Switzerland
- MHRA/United Kingdom
- IMoH/Israel

**SCOPE**
High Impact Oncology products
- New Drug Applications (NDAs)
- Biologics License Applications (BLAs)
- Supplemental applications for new indications

**Orbis Type**
- **Type A** ≤ 1 month of FDA submission
- **Type B** >1 month of FDA submission
- **Type C** Anytime after FDA submission

**Key Features**
- Parallel/Collaborative review of dossier
- Use of Common Review Document (assessment Aid)
- Leverage FDA resource and expertise
- Each POP makes independent regulatory decision

**Table 2. Comparison of time-to-approval between FDA and Orbis countries for Project Orbis marketing applications.**

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<th>Median (range), in months</th>
<th>FDA</th>
<th>Orbis countries</th>
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<tbody>
<tr>
<td>All applications</td>
<td>4.2 (0.9-6.9)</td>
<td>N = 18</td>
<td>4.4 (17-6.8)</td>
</tr>
<tr>
<td>New molecular entities/New active substances</td>
<td>5.1 (5.9-6.9)</td>
<td>N = 6</td>
<td>5.9 (3.9-6.8)</td>
</tr>
<tr>
<td>Supplements/Variations for new indications</td>
<td>3.6 (0.9-6.0)</td>
<td>N = 12</td>
<td>3.3 (17-5.4)</td>
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**Concurrent review with FDA**
- **Expected**
- **Possible**
- **Unlikely**

[https://aacrjournals.org/clincancerres/article/26/24/6412/82919/Project-Orbis-Global-Collaborative-Review](https://aacrjournals.org/clincancerres/article/26/24/6412/82919/Project-Orbis-Global-Collaborative-Review)
ACCESS Consortium

**GOAL**
Maximizing international collaboration between member jurisdictions by aligning regulatory systems, reducing duplication, and increase agency’s capacity to ensure populations’ access to high quality, safe and effective health products

**VISION**
To provide faster access to safe, effective and high quality medicines for all our populations

**MISSION**
To align our regulations and policies to facilitate work-sharing and reduce duplication to ensure our populations have access to the health products they need for better health and wellbeing

**Type of Collaboration:** Worksharing

**Member Countries/ Regulatory authorities**
- Australia/ TGA
- Canada/ HC
- Singapore/ HSA
- Switzerland/ SwissMedic
- United Kingdom/ MHRA

**Streamlined process** - internationally coordinated review to reduce duplication and burden

**Increased access** - possibility of simultaneous access to markets of multiple countries

**Flexibility** - adaptability in how regulators organise collaboration amongst each other on a given review and which countries a company chooses to submit applications

**Predictability** - pre-determined milestones and targeted review timeframes

Source: Access website
EMA - The OPEN initiative

Opening our Procedures at EMA to Non-EU authorities

Non-EU experts are invited to attend and contribute to ETF discussions and CHMP evaluations of COVID-19 Vx and Tx but do not contribute to the conclusions. All regulators keep full scientific and regulatory independence.

OPEN enables to share scientific expertise to tackle common challenges regarding COVID-19 Vx and Tx while enhancing transparency on regulatory decisions and promoting EU Regulatory System.

Scope: COVID-19 Vx and Tx

Benefits: Accelerate approval in more countries

OPEN non-EU regulators
TGA Australia – Health Canada – MHLW/PMDA
Japan – Swissmedic – WHO

Accelerate Patient’s Access to a Rare Disease Medicine through Reliance Pathway

Average timeline through reliance: **4.4 months**

Average timeline through other pathways: **8.6 months**
Reliance concept beyond initial Marketing Authorization - Post Approval Changes

Introducing changes post-approval is an essential part of the lifecycle of a product to:

- Ensure market access and continuous supply of live-saving drugs to patients by reacting to supply demands, avoid drug shortages
- Support continuous improvement and optimization of manufacturing process and quality of the medicinal products
- Remain state-of-the-art with facilities, manufacturing methods and analytical techniques
- Implement safety label updates in a timely manner access to ensure up-to-date product information
- Fulfill regulatory agency requirements

Especially for products undergoing accelerated clinical and CMC development registered with expedited pathways, many changes will need to be implemented post-approval in a timely manner (e.g. to fulfill post-approval commitments)
Key messages: How to move forward?

- **Harmonization**
  - Adopt ICH CTD
  - Clear and consistent timelines
  - Reduce national requirements

- **Risk-based approaches**
  - Classification with risk-based approach
  - Maximize ICH Q12 tools (PACMPs as quick win)
  - Leverage PQS for changes with no quality impact
  - Explore novel approaches (new stability data approaches)
  - Flexible implementation timelines

- **Reliance**
  - WHO Good Reliance Practice applied to lifecycle
  - Leverage documents from reference agencies to shorten approval timelines
  - Establish principles for product sameness
  - Enable information sharing among regulators
  - Leverage and extend joint reviews & worksharing

Prepare for a future health crisis by leveraging the above principles and learnings from the Covid19 pandemic.
ICMRA - Initiation of two regulatory collaboration pilots

One focused on **collaborative assessments of post-approval CMC submissions (PACMPs)**, and the other on **collaborative hybrid inspections** are aiming to:

- facilitate convergence in assessment practices for key products
- develop collaborative assessment approaches
- promote multi-agency GMP inspections

This was an international premiere: on 12 May 2023, EMA and the US FDA concluded for the first time a collaborative assessment to add new manufacturing and quality control sites. These sites are linked to the production of the orphan medicine Lusimun, a cancer treatment. The collaboration could significantly contribute to the continuous supply of this medicine. The Japanese Pharmaceuticals and Medical Devices Agency, the PMDA, participated as an observer.

This work marks the beginning of an international pilot programme that aims to bring regulators together and build up regulatory reliance to allow faster supply of critical medicines. Future assessments under this pilot will involve more regulatory authorities worldwide.

Some key highlights of this procedure were that:

- All regulators involved were open and highly collaborative;
- The issues raised during the procedure were mutually agreed upon, confirming good alignment between the EU, the US and Japan;
- The pilot did not cause any delays in approval timelines;
- It received positive feedback from the industry.

Hashtags:

- #RegulatoryBreakthrough
- #GlobalCollaboration
- #EfficientMedicineSupply
- #PatientCare
- #QualityMedicines
Let’s bring reliance into action!

Reliance is not a new concept...

- Long history of improving efficiency through reliance, e.g. Certificate of Pharmaceutical Products Scheme
- "Regulate through reliance" as the hallmark of a modern and efficient regulatory authority.
- Increasing role of reliance
- Promoting "informed" reliance

COVID-19 response as a strong accelerator for the use of reliance

Making reliance and collaboration work

- COVID-19 showed that international collaboration is needed more than ever
- Reliance is a simple, useful and flexible tool for better cooperation
- Transparency, with openness to dialogue and sharing, are key to making it work
- Learning to trust others by being open and transparent, accepting challenges
- Benefit for regulators and industry who avoid duplication of work
- Benefits for patients who can have earlier access to high quality, safe and effective medicines

No one agency, no matter how big, can do it all by themselves.
Close Collaboration Among Stakeholders

Applicants

Participating
NRAs

Reference
NRA- FDA, EMA

WHO
Doing now what patients need next