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

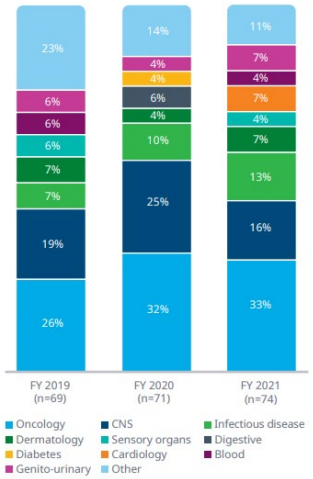


Highly Innovative pipeline -US

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

Exhibit 1. Cumulative number of launches, 2019–2021

Exhibit 2. Breakdown of launches by therapy, 2019-2021



Source: National Sales Perspective, Center of Launch Excellence, IQVIA; publicly available information from the FDA

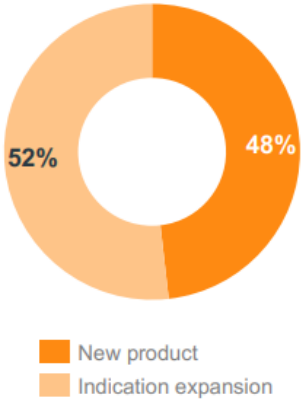
IQVIA Institute- global trends in R&D 2023

*ATTRIBUTES KEY: 1 = Oral, 2 = Biologic, 3 = Specialty, 4 = Next-gen biotherapeutic, 5 = Orphan, 6 = First-in-class, 7 = Expedited review, 8 = U.S Patent to launch ≤5 years 9 = EBP originated, 10 = EBP launched

THERAPY AREA	INDICATION	MOLECULE	BRAND	ATTRIBUTES* 1	2	3	4	5	6	7	8	9	10
Oncology	Acute myeloid leukemia	olutasidenib	Rezlidhia	●		●		●			●	●	●
	FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	mirvetuximab soravtansine	Elahere		●	●		●	●	●		●	●
	Hepatocellular carcinoma	tremelimumab	Imjudo		●	●		●		●			
	Myelofibrosis	pacritinib	Vonjo	●		●		●		●		●	●
	Neutropenia	eflapegrastim	Rolvedon		●	●							●
	Non-small cell lung cancer (NSCLC)	adagrasib	Krazati	●		●		●		●	●	●	●
	Prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC)	lutetium (177lu) vipivotide tetraxetan	Pluvicto			●			●	●		●	
	Relapsed or refractory multiple myeloma	ciltacabtagene autoleucel	Carvykti		●	●	●	●		●		●	
		teclistamab	Tecvayli		●	●		●	●	●			
	Unresectable or metastatic melanoma	nivolumab + relatlimab	Opdualag		●	●		●	●	●			
	Unresectable or metastatic uveal melanoma	tebentafusp	Kimmtrak		●	●		●	●	●		●	●
Neurology	Amyotrophic lateral sclerosis (ALS)	sodium phenylbutyrate + taurursodiol	Relyvrio	●		●		●		●		●	●
	Cerebral adrenoleukodystrophy	elivaldogene autotemcel	Skysona		●	●	●	●	●	●		●	●
	Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)	ganaxolone	Ztalmy	●		●		●	●	●		●	●
	Insomnia	daridorexant	Quviviq	●								●	●
	Myasthenia gravis	efgartigimod alfa	Vyvgart		●	●		●	●	●		●	●
	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	vutrisiran	Amvuttra		●	●	●	●		●		●	●
Immunology	Atopic dermatitis	abrocitinib	Cibinqo	●		●				●			
		tralokinumab	Adbry		●	●			●			●	
	Plaque psoriasis	deucravacitinib	Sotyktu	●		●			●				
	Pustular psoriasis	spesolimab	Spevigo		●	●		●	●	●	●		
	Severe asthma	tezepelumab	Tezspire		●	●			●	●			
Hemat-ology	Hemolytic anemia	mitapivat	Pyrukynd	●		●		●	●	●		●	●
	Hemophilia B	etranacogene dezaparvovec	Hemgenix		●	●	●	●	●	●		●	
	Cold agglutinin disease	sutimlimab	Enjaymo		●	●		●	●	●		●	
	β-thalassemia	betibeglogene autotemcel	Zynteglo		●	●	●	●	●	●		●	●
Infectious diseases	COVID-19	bebtelovimab			●	●					●		
	Dengue fever	dengue tetravalent vaccine	Dengvaxia		●					●		●	
	Recurrent vulvovaginal candidiasis (RVVC)	oteseconazole	Vivjoa	●						●		●	●
Anti diabet.	Stage 3 and Stage 2 type 1 diabetes	tepilzumab	Tzield		●	●			●	●		●	●
	Type 2 diabetes mellitus	tirzepatide	Mounjaro		●				●	●			
Cardio vascular	Heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD)	inclisiran	Leqvio		●	●	●		●			●	
	Symptomatic obstructive hypertrophic cardiomyopathy	mavacamten	Camzyos	●		●		●	●	●		●	
Derma-tology	Plaque psoriasis	tapinarof	Vtama						●			●	●
	Pruritus associated with chronic kidney disease	difelikefalin	Korsuva			●			●	●		●	●
Others	Acid sphingomyelinase deficiency	olipudase alfa	Xenpozyme		●	●		●	●	●			
	Detection and visualization of lesions with abnormal vascularity	gadopiclenol	Elucirem			●				●			
	Irritable bowel syndrome with constipation (IBS-C)	tenapanor	Ibsrela	●					●			●	●
	Neovascular age-related macular degeneration (nAMD) or diabetic macular edema	faricimab	Vabysmo		●	●				●			
Totals				12	23	33	6	21	24	30	4	26	19

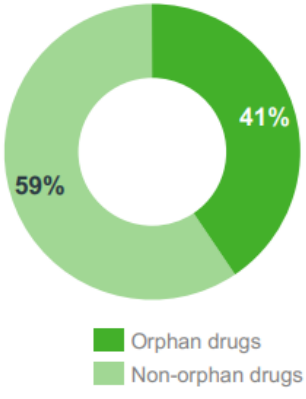
Highly innovative pipeline - EMA

Indication expansions vs new products



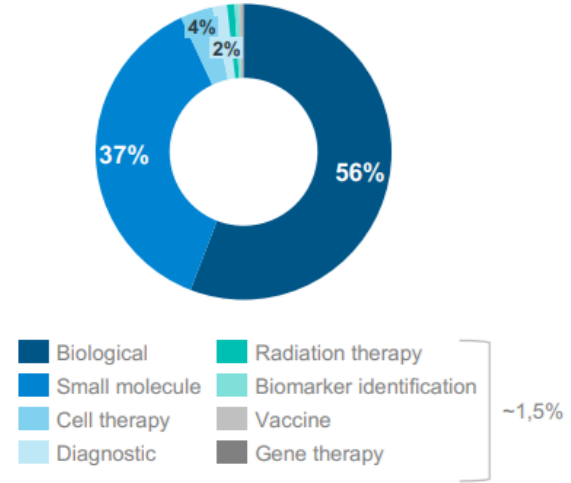
Source: IQVIA Launch Pipeline Database **June 2020**, active trials phase 2-3 for 56 pharmaceutical companies

Orphan vs non-orphan drugs



Source: IQVIA Launch Pipeline Database **June 2020**, active trials phase 2-3 for 56 pharmaceutical companies

Key categories



Source: Clarivate Analytics Cortellis, **Aug 2020**

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[1].

IQVIA_EFPIA Pipeline Review 2021 - Full Report

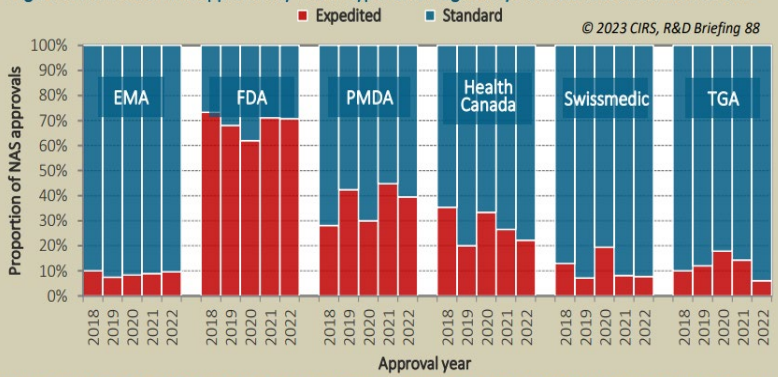
(1) 2019 R&D Achievements, IQVIA Institute, Mar 2020

A total of 55 New Active Substances EMA approvals in 2020

IQVIA-EFPIA pipeline review 2021

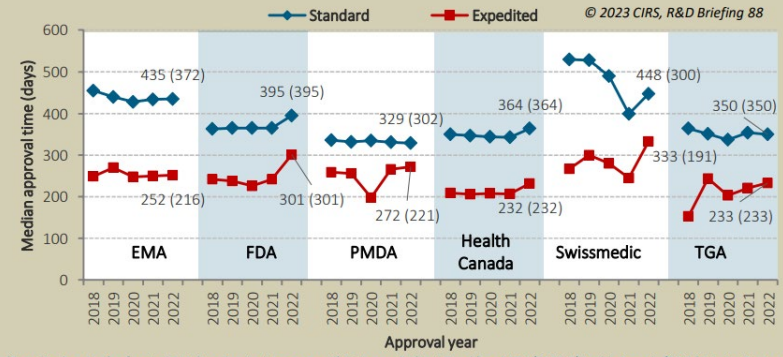
Some numbers from CIRS to start with…

Figure 5: Number of NAS approvals by review type for six regulatory authorities between 2018-2022



'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017.

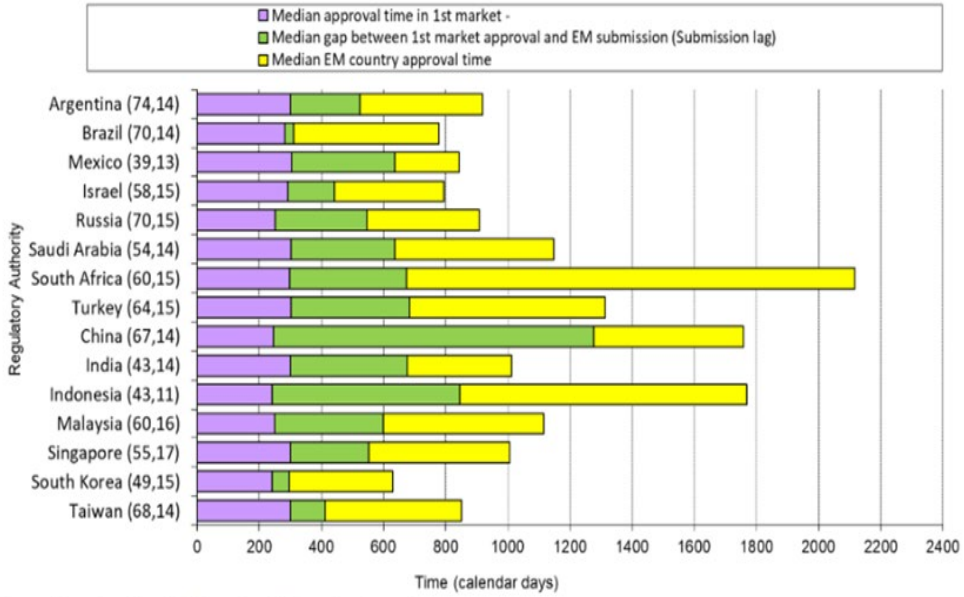
Figure 6: NAS median approval time by review type for six regulatory authorities between 2018-2022



'Expedited review' refers to EMA 'Accelerated Assessment', Swissmedic 'Fast Track' and FDA/PMDA/Health Canada/TGA 'Priority Review'. TGA introduced an expedited (priority) review programme in 2017. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = overall approval time for 2021; (N2) = time from submission until the end of scientific assessment (see p.28) for 2022.

Global Registration

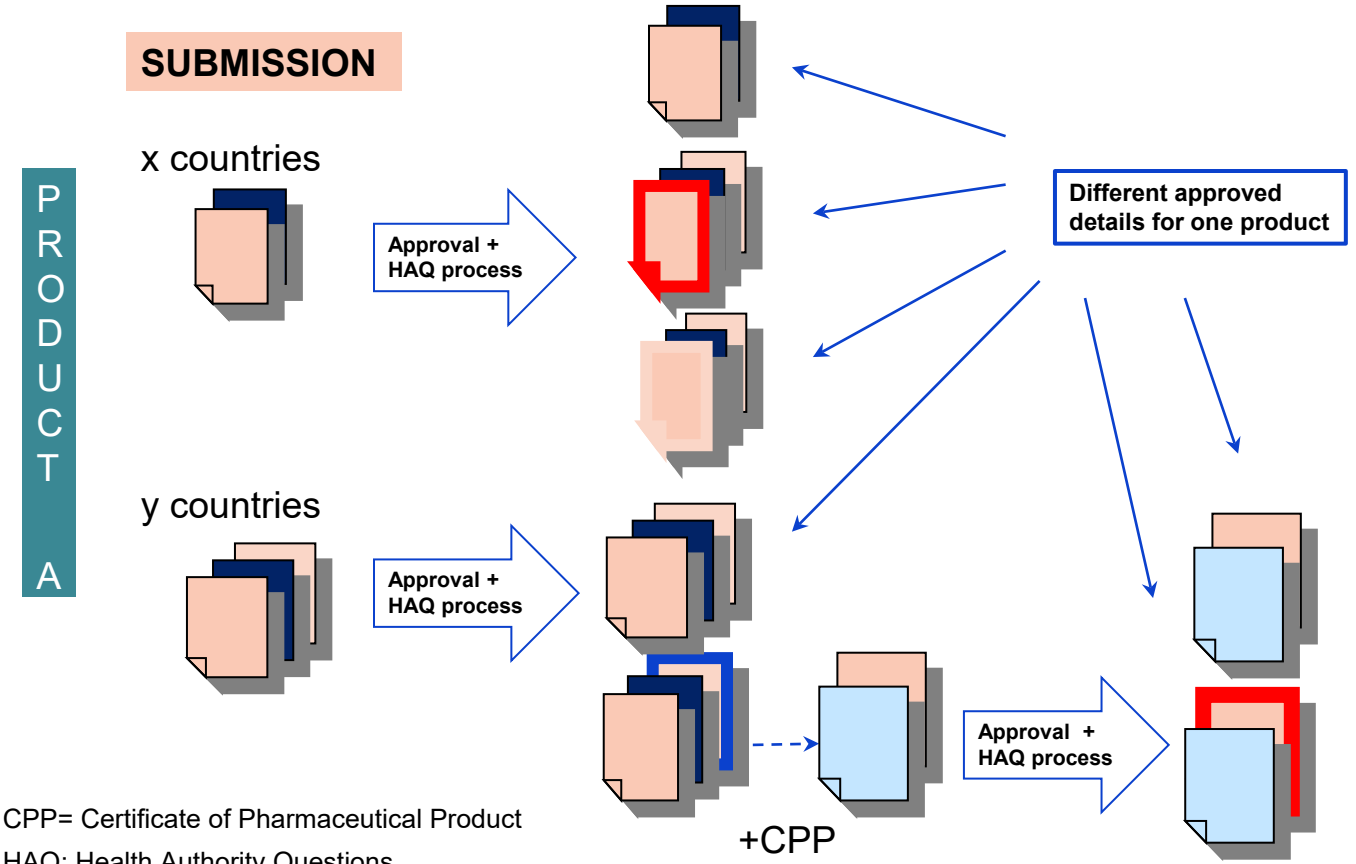
Median time to roll out New Active Substances (NASs) approved 2016-2020 to Emerging Markets (EM) approved



n in bar = median number of days; (n1,n2) = number of NASs, number of companies
NASs included in this analysis include those with first world submission, first world approval, application submission and application approval dates only. If n1 is less than 5 or if n2 is less than 3 data is not shown.
Source: CIRS Industry Metrics Programme

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

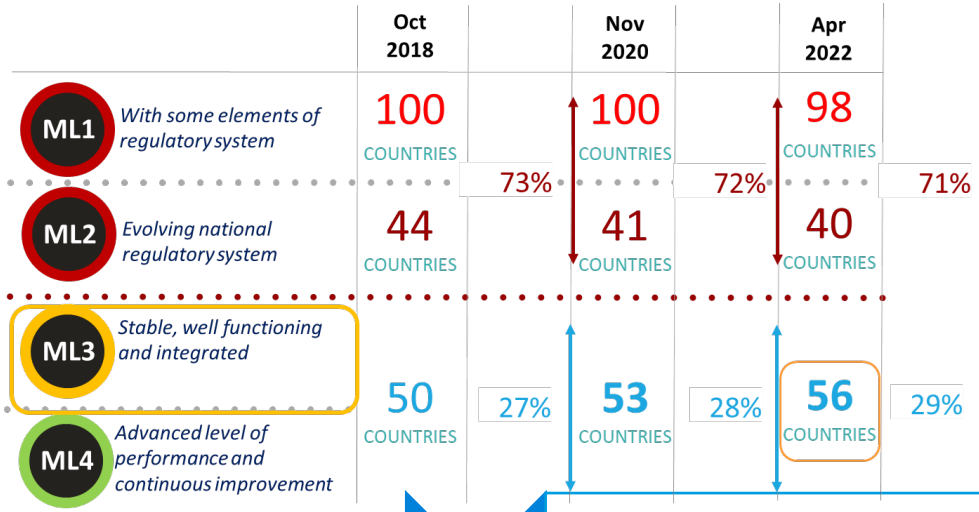
HAQ: Health Authority Questions

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



ML3 GOAL of WHA Resolution 67.20

ML: *(regulatory system) maturity level*

Why reliance?

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

Good regulatory practices, 2021

Good reliance practices, 2021

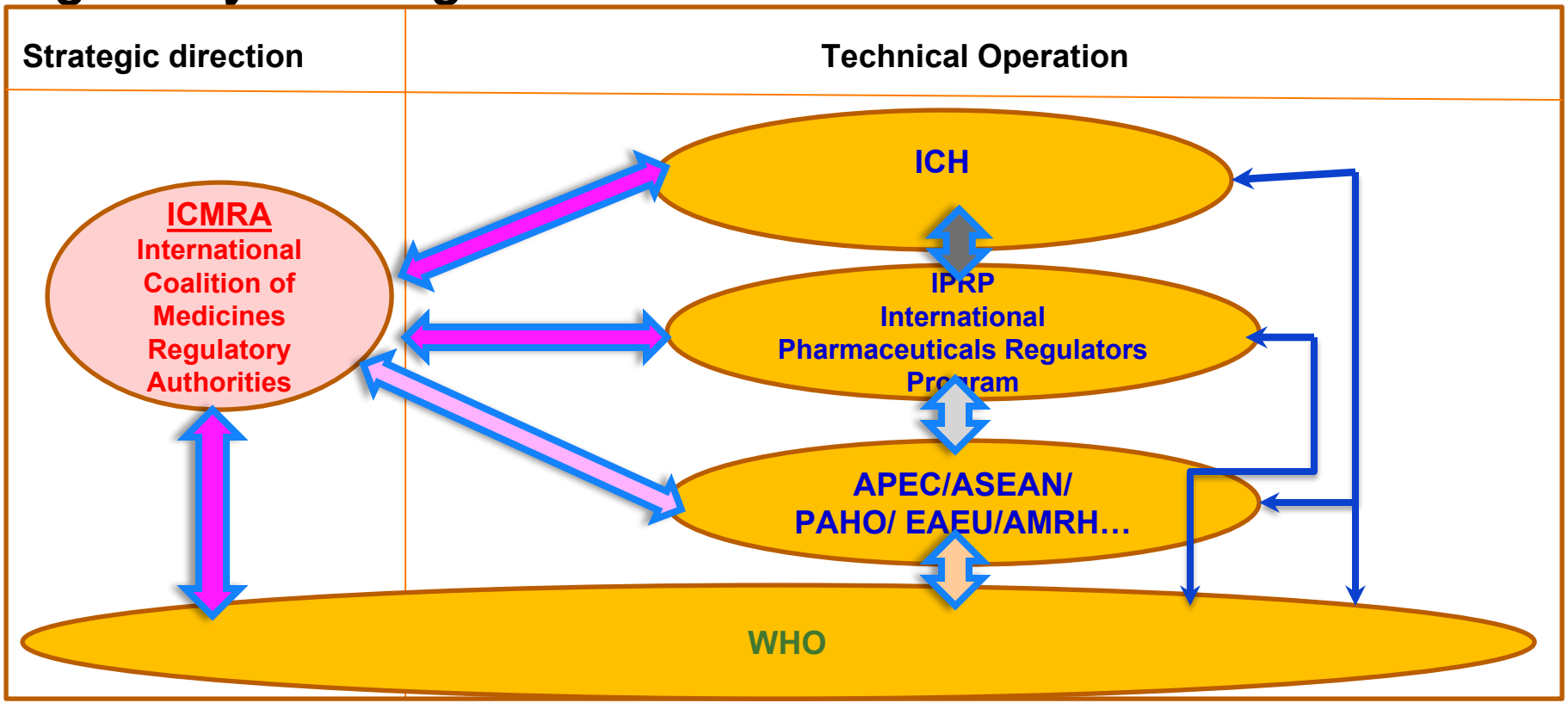
Slide adopted from M. Valentin, WHO presented at DIA CMC Conference, Sept., Sevilla 2022

Ultimate Goal: Global Convergence

- **One** product
- **One** regulatory standard

- **One** inspection
- **One** assessment

Global and regional initiatives driving regulatory convergence



International Coalition of Medicines Regulatory Authorities (ICMRA)

International Coalition of Medicines Regulatory Authorities

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.

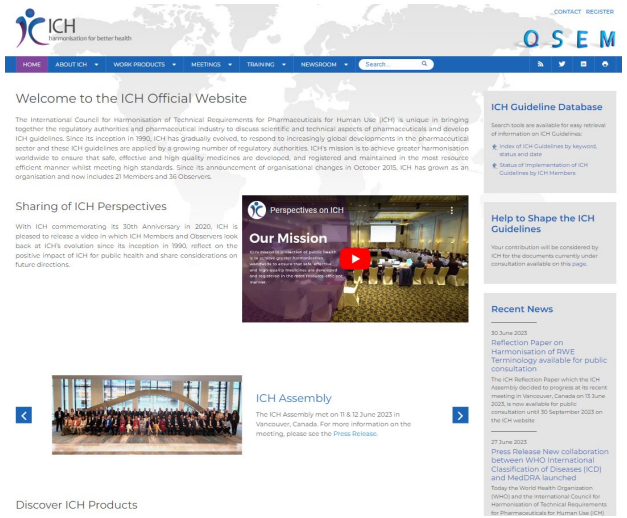
MAIN WORKING AREAS

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

International Council of Harmonization - ICH (www.ich.org)

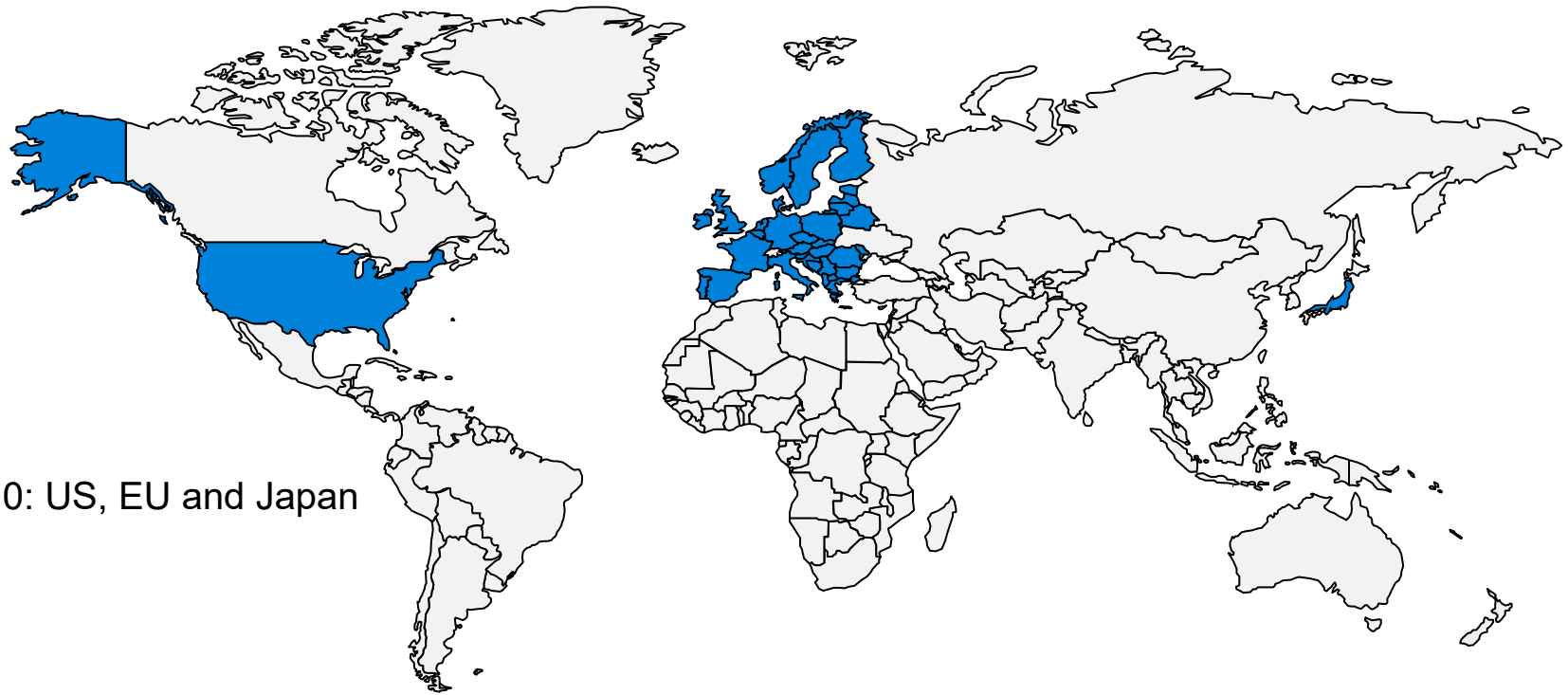


Mission

- 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

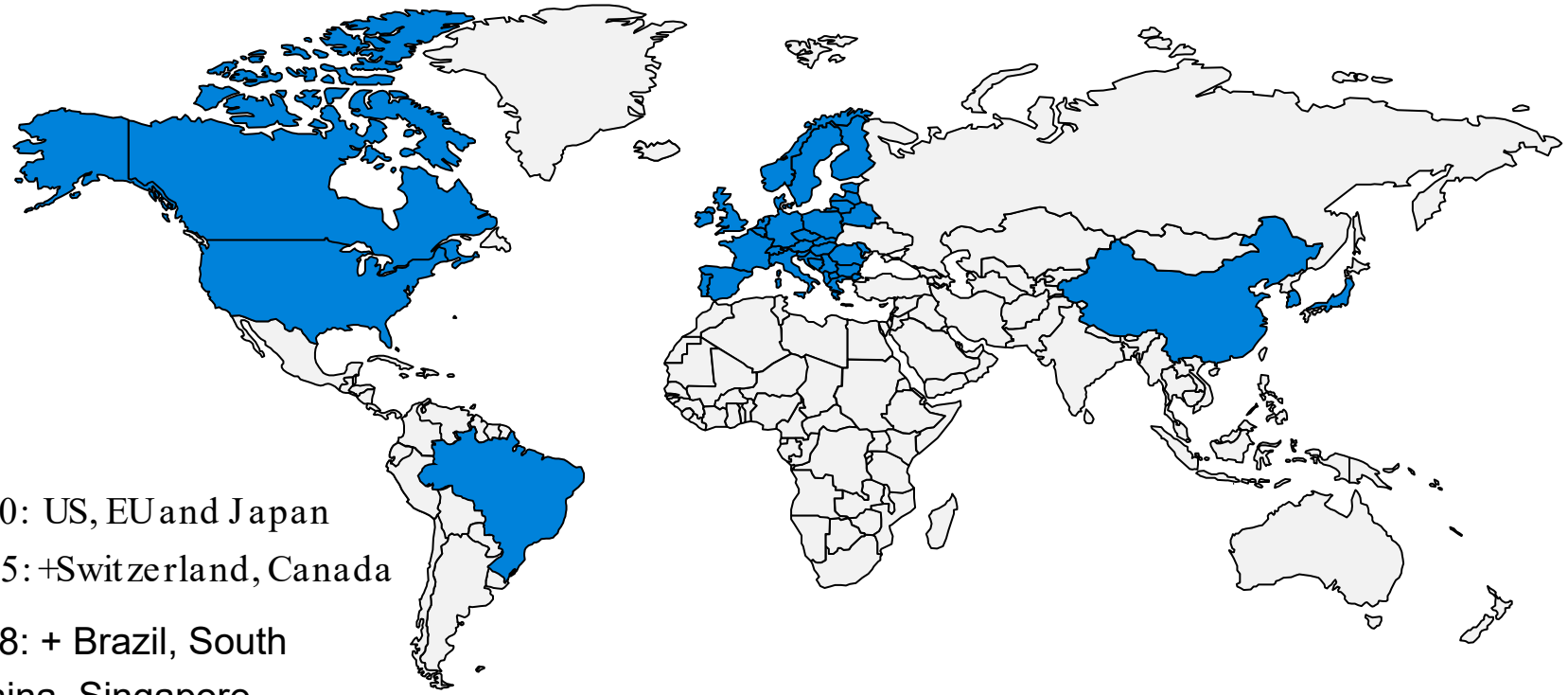


- 1990-2010: US, EU and Japan

Source: www.ich.org, Company reported data

ICH Membership until 2018

Health authorities

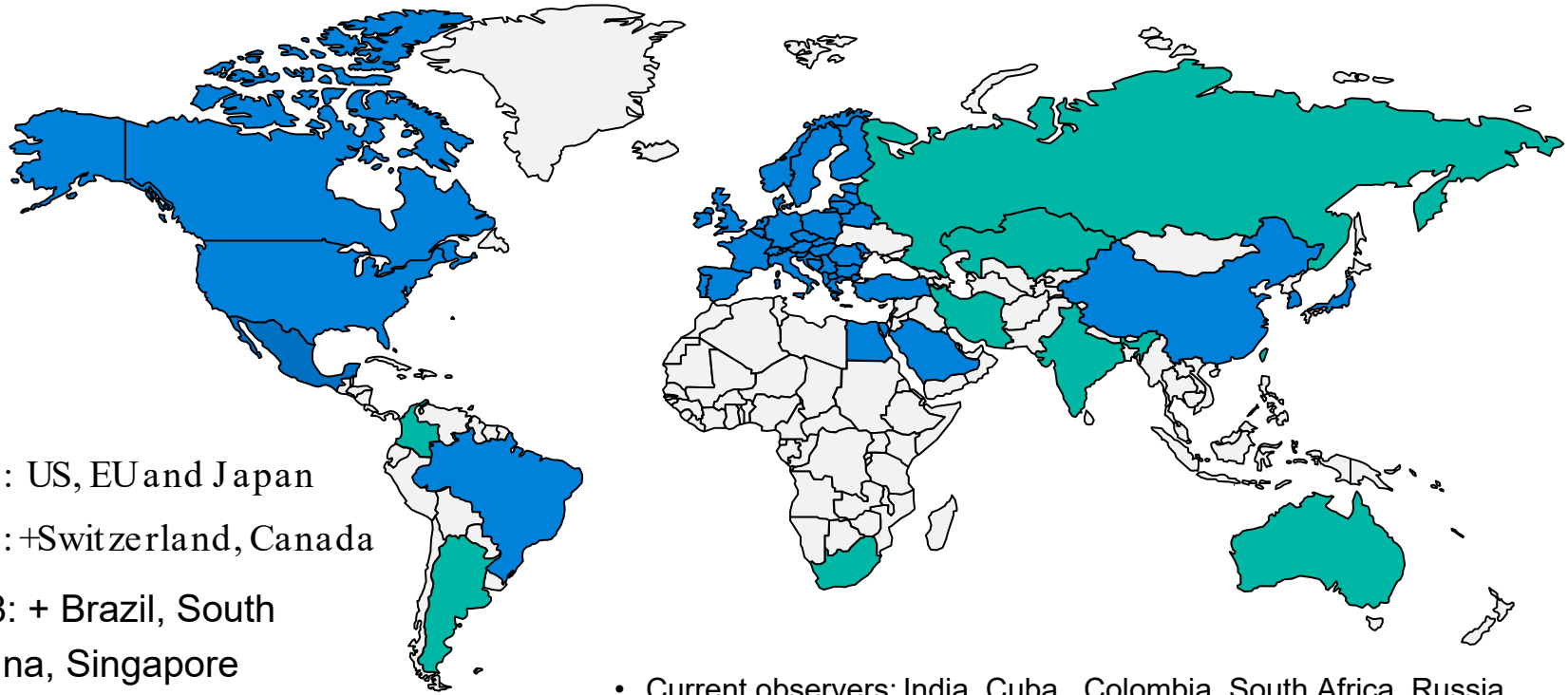


- 1990-2010: US, EU and Japan
- 2010-2015: +Switzerland, Canada
- 2015-2018: + Brazil, South Korea, China, Singapore

Source: www.ich.org, Company reported data

Current ICH Membership

Health authorities

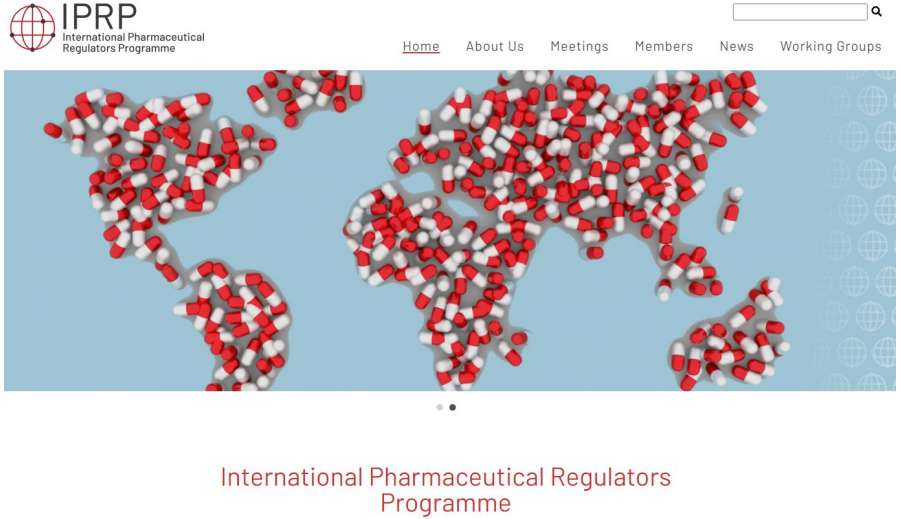


- 1990-2010: US, EU and Japan
- 2010-2015: +Switzerland, Canada
- 2015-2018: + Brazil, South Korea, China, Singapore
- 2018-2023: +Mexico, Egypt, MHRA, Saudi Arabia, Chinese Tapei, Turkey

- 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

International Pharmaceutical Regulators Programme - IPRP



30 June 2023

Updated IPRP Q&A documents on Reliance

The IPRP is pleased to share an updated Questions and Answers document on key aspects for reliance, that was revised by the IPRP Reliance Discussion Group to clarify the question on sameness of...

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

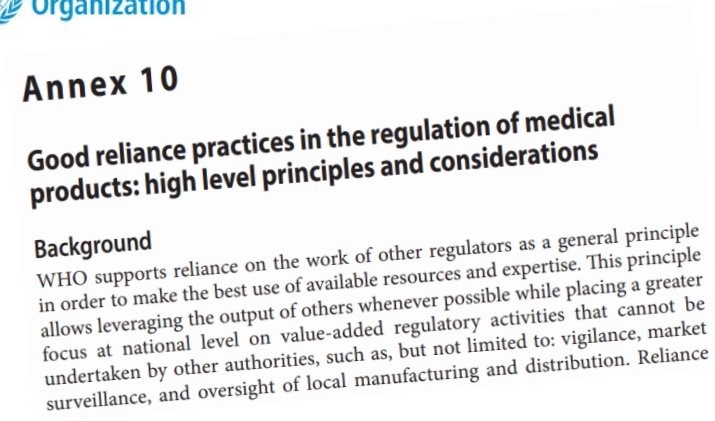
Increasing role of reliance

Promoting "informed" reliance

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

WHO Good Reliance Practices

World Health Organization



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.

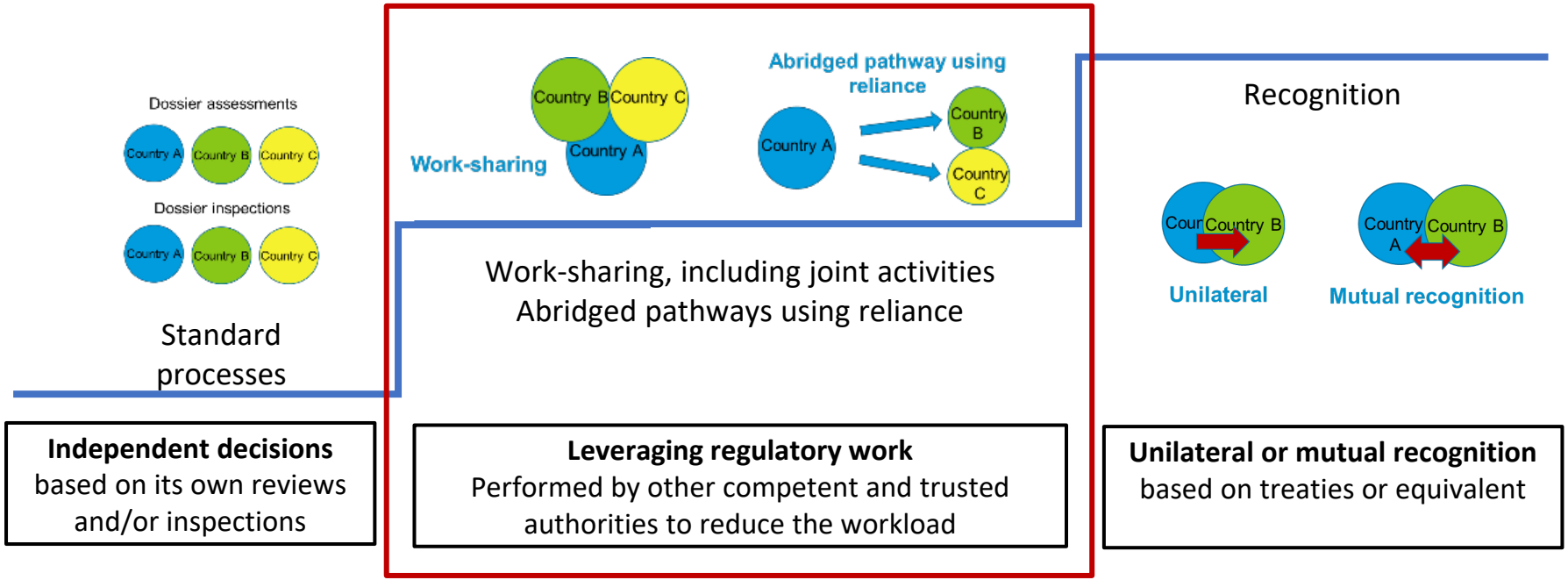
*The relying authority remains **independent, responsible and accountable** for the decisions taken, even when it relies on the decisions, assessments and information of others.*

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

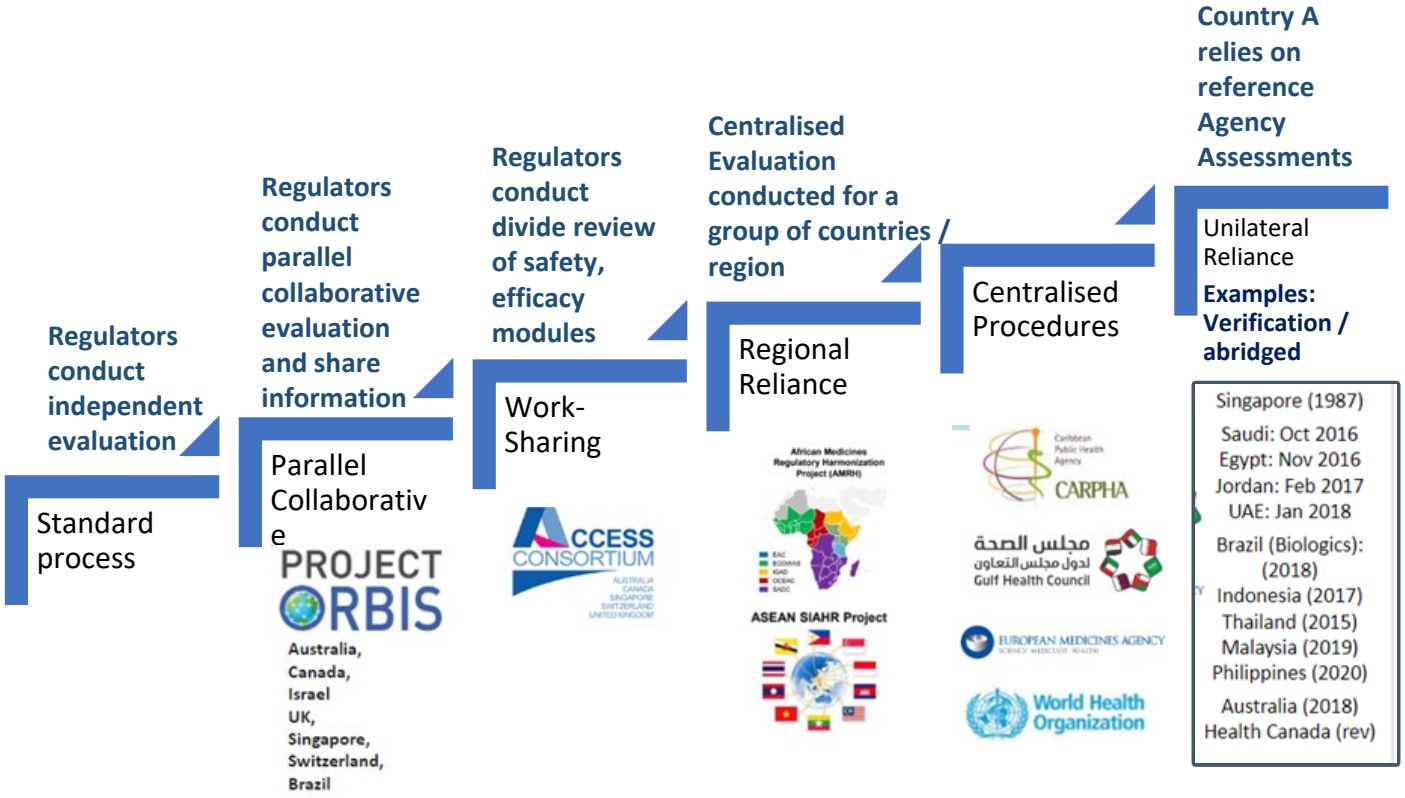
Options to facilitate good quality regulatory decisions – reliance in the focus



World Health Organization

Slide adapted from S. Azatyan, WHO, DIA CMC conference, September 2021

Risk Based approach – Examples of types of Models



Source: CIRS

Project Orbis -

A framework for concurrent submission and review of oncology products

Project Orbis Partners (POP)

TGA/Australia
ANVISA/Brazil
Swissmedic/Switzerland
MHRA/United Kingdom
IMoH/Israel
HC/Canada
HSA/Singapore

Orbis Type	Submission Timeline to POPs	Sharing of FDA reviews	Multi -country review meetings	POP Attendance at FDA review meetings	Concurrent review with FDA
Type A	⩽ 1 month of FDA submission	Yes	Yes	Yes	Expected
Type B	>1 month of FDA submission	Yes	Yes	Yes	Possible
Type C	Any time after FDA submission	Yes	No	Unlikely	Unlikely

SCOPE

High Impact Oncology products

- New Drug Applications (NDAs)
- Biologics License Applications (BLAs)
- Supplemental applications for new indications

PROJECT ORBIS

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

Median (range), in months	FDA		Orbis countries	
All applications	4.2 (0.9–6.9)	$N = 18$	4.4 (1.7–6.8)	$N = 20$
New molecular entities/New active substances	5.1 (3.9–6.9)	$N = 6$	5.9 (3.9–6.8)	$N = 7$
Supplements/Variations for new indications	3.6 (0.9–6.0)	$N = 12$	3.3 (1.7–6.4)	$N = 13$

https://aacrjournals.org/clincancerres/article/26/24/6412/82919/Project -Orbis-Global-Collaborative -Review

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

ACCESS Consortium

ACCESS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND
UNITED KINGDOM

Type of Collaboration:
Worksharing

Member Countries/ Regulatory authorities

Australia/ TGA
Canada/ HC
Singapore/ HSA
Switzerland/ SwissMedic
United Kingdom/ MHRA

Source: Access website

VISION

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

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

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

Streamlined process -
internationally coordinated review to reduce duplication and burden

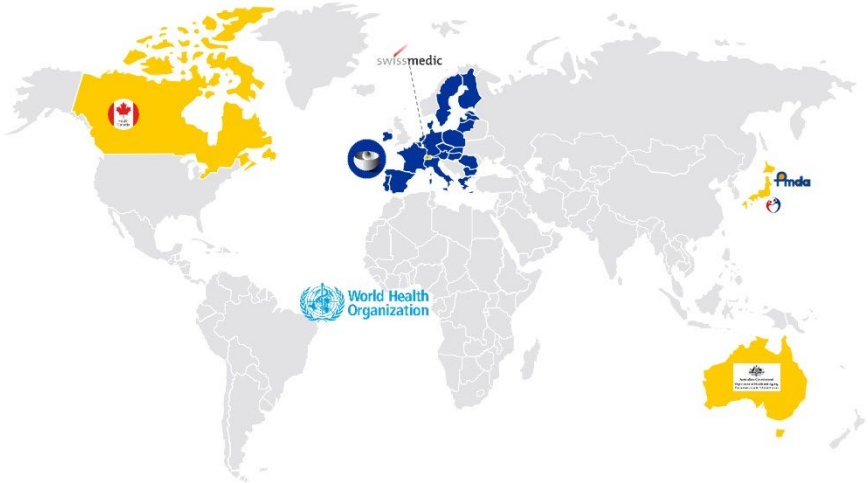
Increased access -
possibility of simultaneous access to markets of multiple countries

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

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

OPEN non-EU regulators

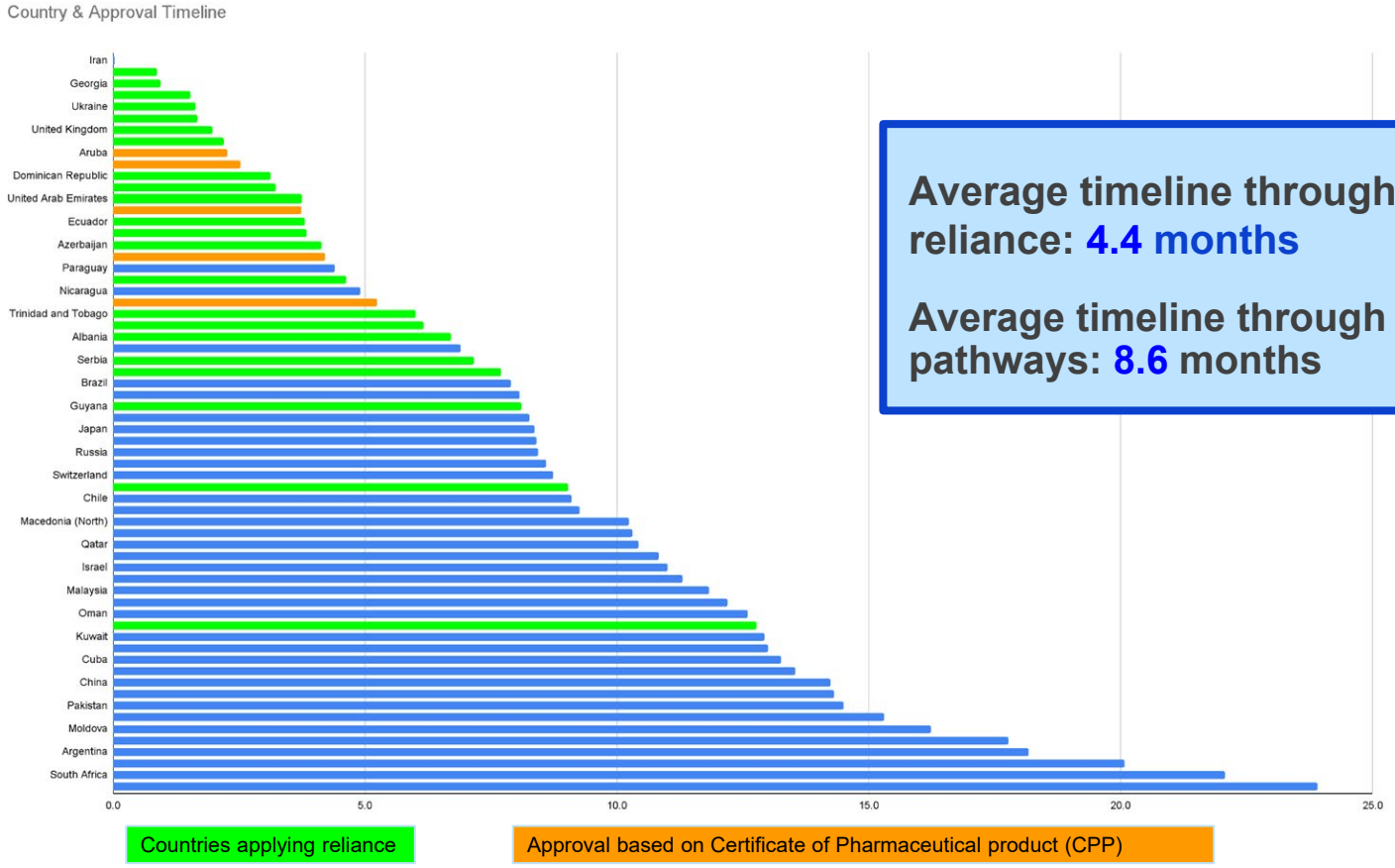
TGA Australia – Health Canada – MHLW/PMDA Japan – Swissmedic – WHO

Benefits : Accelerate approval in more countries

https://www.ema.europa.eu/en/documents/other/questions-answers-pilot-project-open_en.pdf

ETF: EMA pandemic Task Force

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:

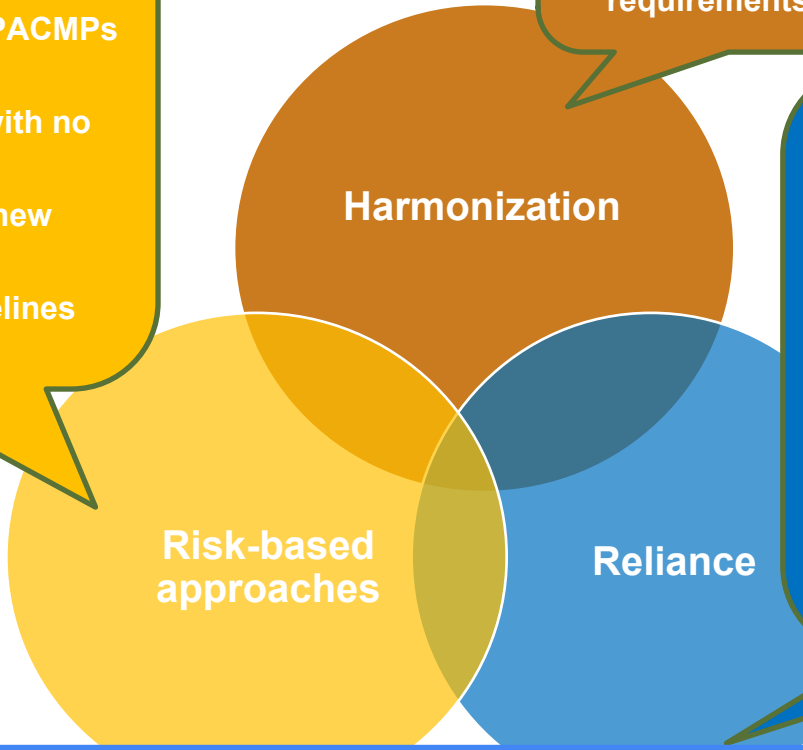
- Ensure market access and continuous supply of live-saving drugs to patients by reacting to supply demands, avoid drug shortages
- Support continuous improvement and optimization of manufacturing process and quality of the medicinal products
- Remain state-of-the-art with facilities, manufacturing methods 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?

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

- 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



- WHO Good Reliance Practice applied to life-cycle
- 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

efpia European Federation of Pharmaceutical Industries and Associations
IFPMA International Federation of Pharmaceutical Manufacturers & Associations
Vaccines Europe

Industry Position Paper: Optimising Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

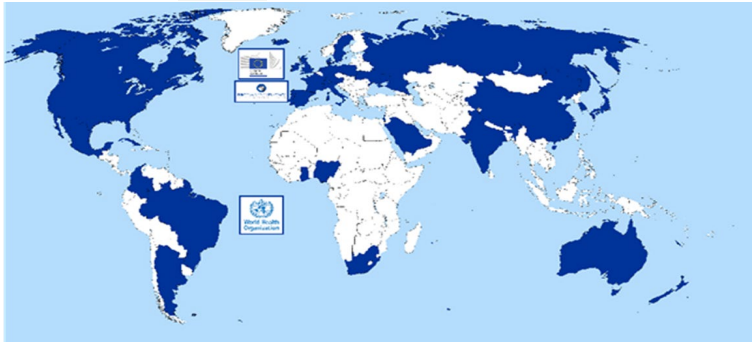
Path Forward to Optimise Post-approval Change Management and Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

RECENT PINK Sheet article

Prepare for a future health crisis by leveraging the above principles and learnings from the Covid-19 pandemic

ICMRA - Initiation of two regulatory collaboration pilots

The International Coalition of Medicines Regulatory Authorities (ICMRA)



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

European Medicines Agency
264,120 followers
21h • Edited •

Collaborative assessments of manufacturing sites can improve supply of medicines

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 Lunsumio, 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.

#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

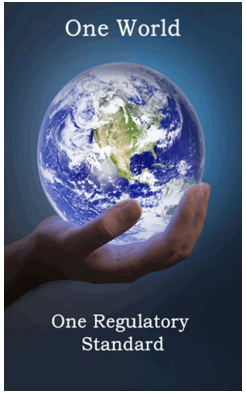
"Regulate through reliance" as the hallmark of a modern and efficient regulatory authority.

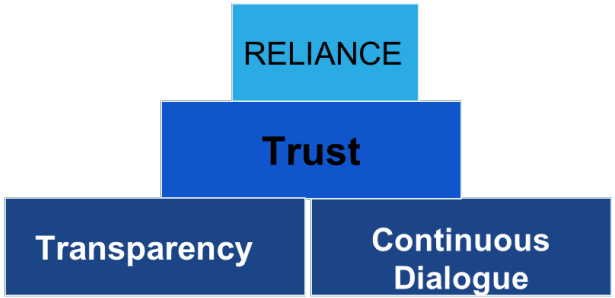
Increasing role of reliance

Promoting "informed" reliance

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

World Health Organization





EUROPEAN MEDICINES AGENCY

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

Reference NRA- FDA, EMA

Participating NRAs

WHO

Doing now what patients need next