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Innovative Approaches to Regulatory Reliance

Global Trends and Perspectives for Latin America and the Caribbean

Setting the scene

Reliance as a tool to promote stronger regulatory systems

Janis Bernat
Director, Scientific and Regulatory Affairs
IFPMA

Reliance | Different levels

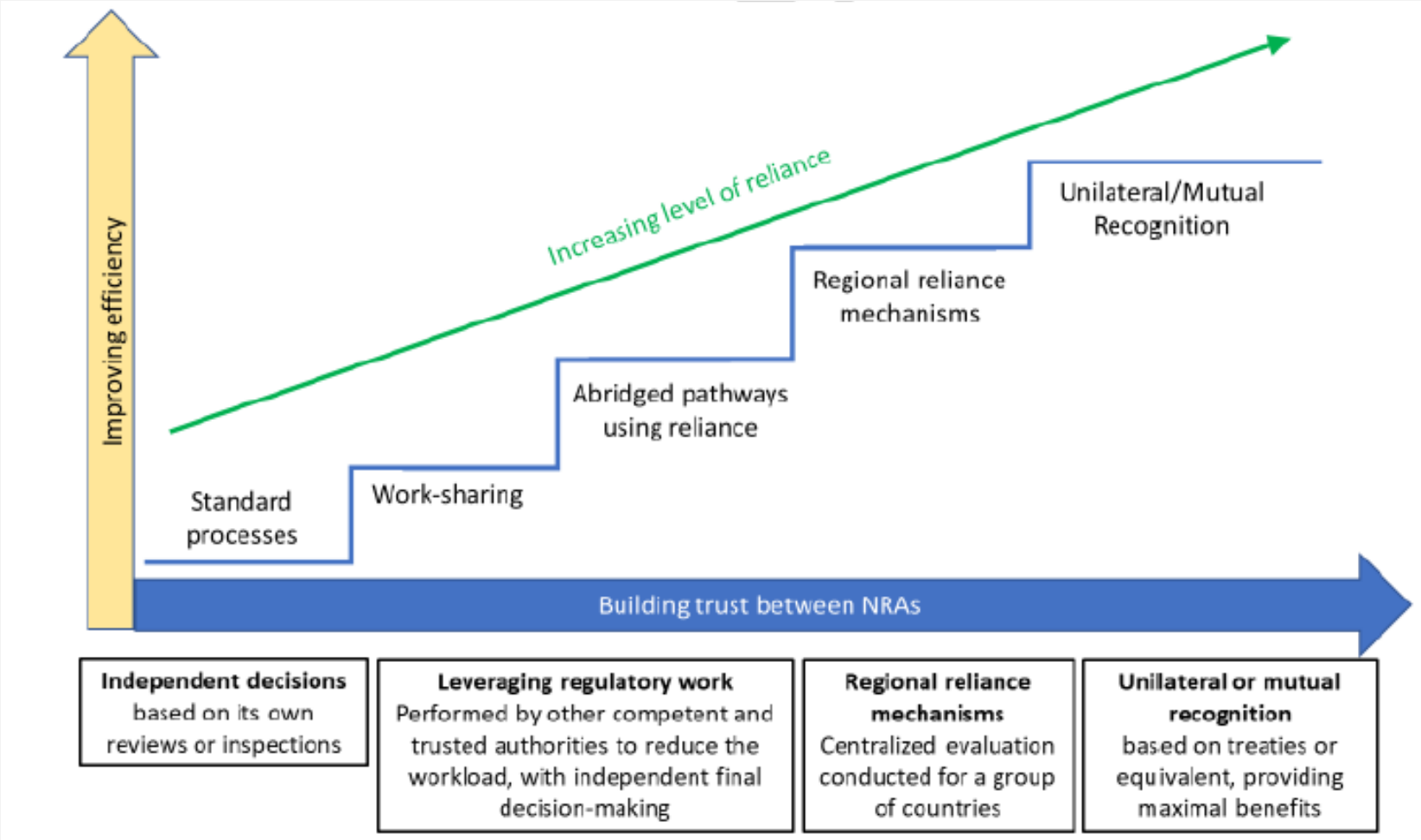

Image taken from WHO 'Good reliance practices in regulatory decision-making: high-level principles and recommendations' Working document QAS/20.851 June 2020

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Reliance | Multiple advantages

All stakeholders impacted by regulatory systems have the potential of benefiting from Regulatory Reliance

Patients & Healthcare Providers

Timely access to safe, effective and quality medical products.

Regulatory Agencies

Efficient utilization of resources by avoiding duplication of work and providing opportunities to strengthen the regulatory system, while maintaining sovereignty over decision-making.

Manufacturers

Streamlined management of regulatory submissions and global supply systems as well as predictable, timely approvals.

How to implement it?

Best practices?

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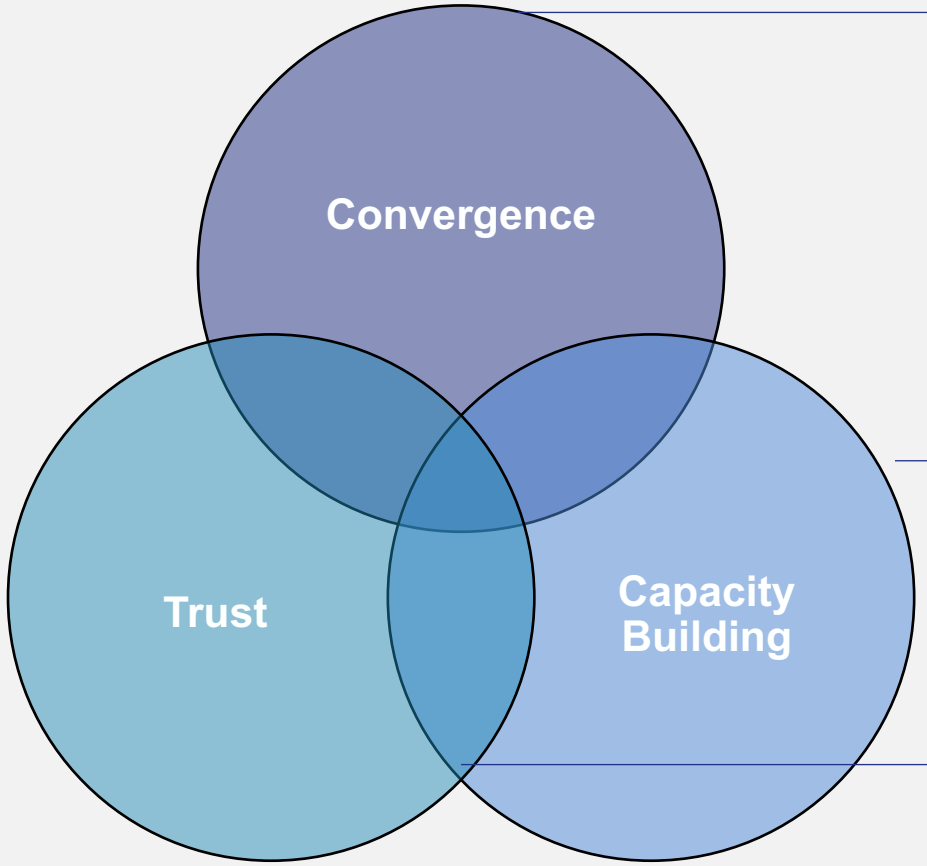
Reliance | Opportunities

Implementing regulatory reliance provides stakeholders with opportunities that go beyond regulatory processes.



Harmonization will foster regulatory reliance.
Implementing WHO and ICH guidance can facilitate the implementation of regulatory reliance mechanisms.

Changes to regulatory and legal frameworks should aim to leverage the benefits of regulatory reliance.

Regulatory reliance supports capability building
The learning and experience-sharing aspect of regulatory reliance will allow NRAs to address potential capability gaps in the longer term.

Strengthening trust between stakeholders
Collaboration and dialogue will help to create and build trust, which is the foundation of regulatory reliance.

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Thank you!

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International collaboration, reliance, and work-sharing

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Swissmedic, Swiss Agency for Therapeutic Products

International collaboration, reliance and work-sharing @ Swissmedic

IFPMA / FIFARMA Webinar: Innovative Approaches to Regulatory Reliance
8 May 2024

Lodovico Paganini, Scientific Officer Stakeholder Engagement

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Outline

- Principles of international collaboration
  - Multilateral cooperation
  - Bilateral agreements
- Reliance and work-sharing
  - Reliance @ Swissmedic / Art. 13 Therapeutic Products Act, TPA
  - Reliance on Swissmedic and WLA status
  - Access Consortium
- Swissmedic engagement in Regulatory Systems Strengthening
  - Marketing Authorisation for Global Health Products (MAGHP)
  - Capacity Building Activities
  - Coalition of Interested Parties (CIP)

Principles of cooperation

- Cooperation with all stakeholder groups according to their (divergent) interests

  → targeted approach
- Cooperation on the level of organization, association, etc. (not individual level)
- Open & transparent communication
- Balance of both active and passive communication
- Cooperation based on relation that creates and maintains trust and mutual understanding

Increasing workload for regulators

- ☞ How to address the increasing resource needs?
- ☞ Which approaches should be applied to address these challenges?
- ☞ Apply risk based approach

International collaboration (non-exhaustive list)

ICMRA
International Coalition of Medicines Regulatory Authorities

ICH
harmonisation for better health

IPRP
International Pharmaceuti
Regulators Programme

PIC/S

IMDRF

ACCESS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND
UNITED KINGDOM

Bilateral collaboration with partner authorities

Europe

- EMA, Europe
- AGES, Austria
- HPRA, Ireland
- PEI, Germany
- BfArM, Germany
- BVL, Germany
- MoH, Israel
- MEB, Netherlands
- MHRA, UK
- VMD, UK

Americas

- FDA, US
- Health Canada
- ANVISA, Brazil
- COFEPRIS, Mexico

African Region

- SAHPRA, South Africa

Western Pacific Region

- TGA, Australia
- PMDA, Japan
- MFDS, Korea
- Medsafe New Zealand
- HSA, Singapore
- NMPA, China
- TFDA, Chinese Taipei

Reliance and work-sharing

Reliance : the act whereby the regulatory authority in one jurisdiction **may take into account** and give 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 regarding the decisions taken**, even when it relies on the decisions and information of others […]

Work-sharing : a process by which regulatory authorities of two or more jurisdictions share activities to accomplish a specific regulatory task.

Reliance based on Art. 13 TPA - General considerations

If an applicant requests the authorisation, extension or a variation of an authorisation for a medicinal product or procedure for which **authorisation** has already been granted **in a country with a comparable control system for medicinal products***, Swissmedic will take into consideration the results of the assessments carried out by the foreign regulatory agency provided that certain requirements are fulfilled.

Scope

- New authorisation applications for medicinal products with known active substances
- New authorisation applications for biosimilars
- New authorisation applications for medicinal products with new active substances and their additional indications, provided that certain criteria are fulfilled
- Applications for extensions
- Variations

*according to List of all countries with comparable human medicinal product control

Implications of Swissmedic's WLA status

Enable efficient use of regulatory resources

by providing a robust framework to promote **trust, confidence** and **reliance**

Encourage continuous improvement of regulatory systems and **regulatory convergence**

Help procurement decisions

on medical products by UN and other agencies, as well as countries (especially LMICs)

Contributes to WHO PQ programme

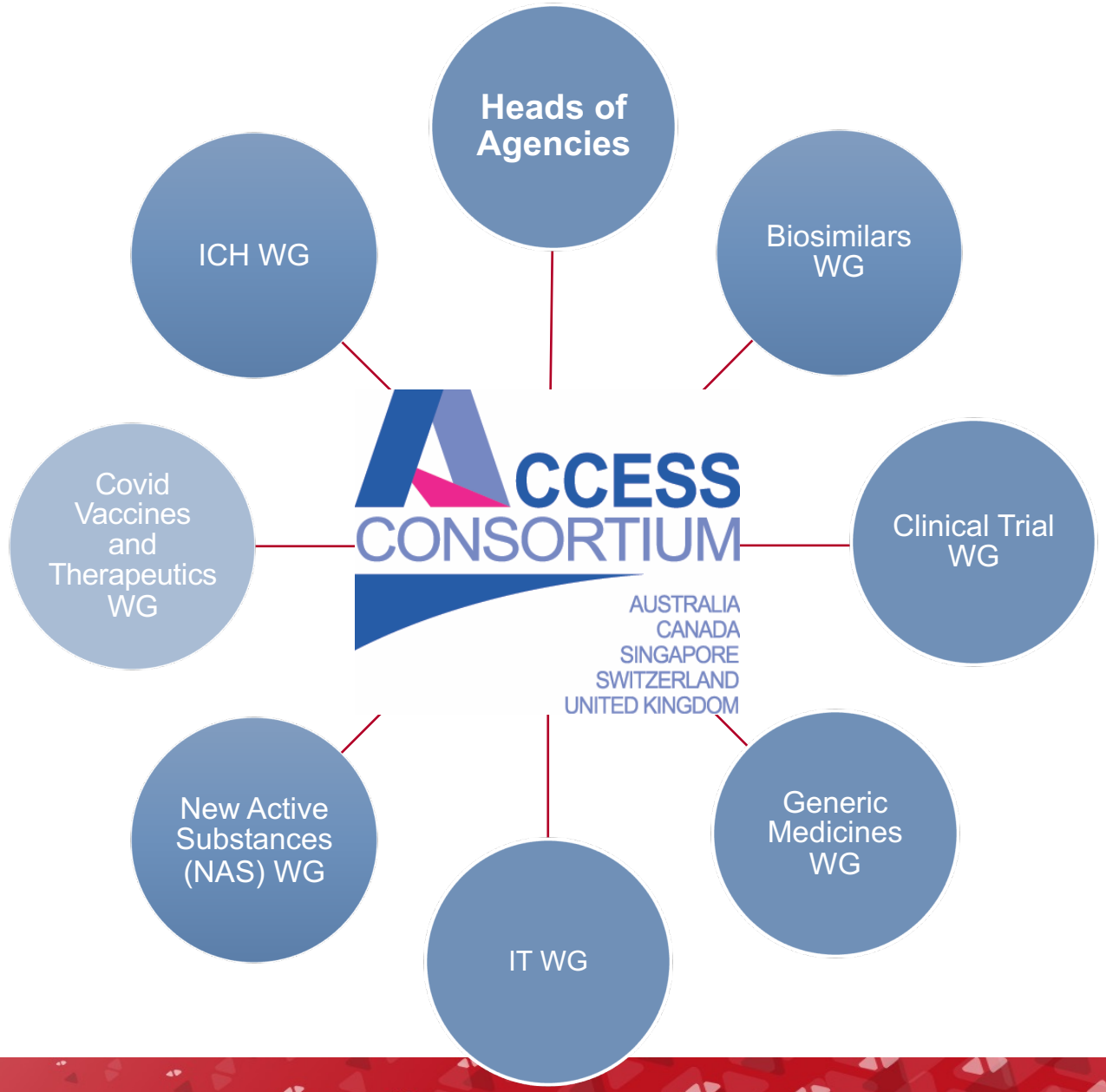
by expanding the pool of trusted regulatory authorities

Fosters health equity

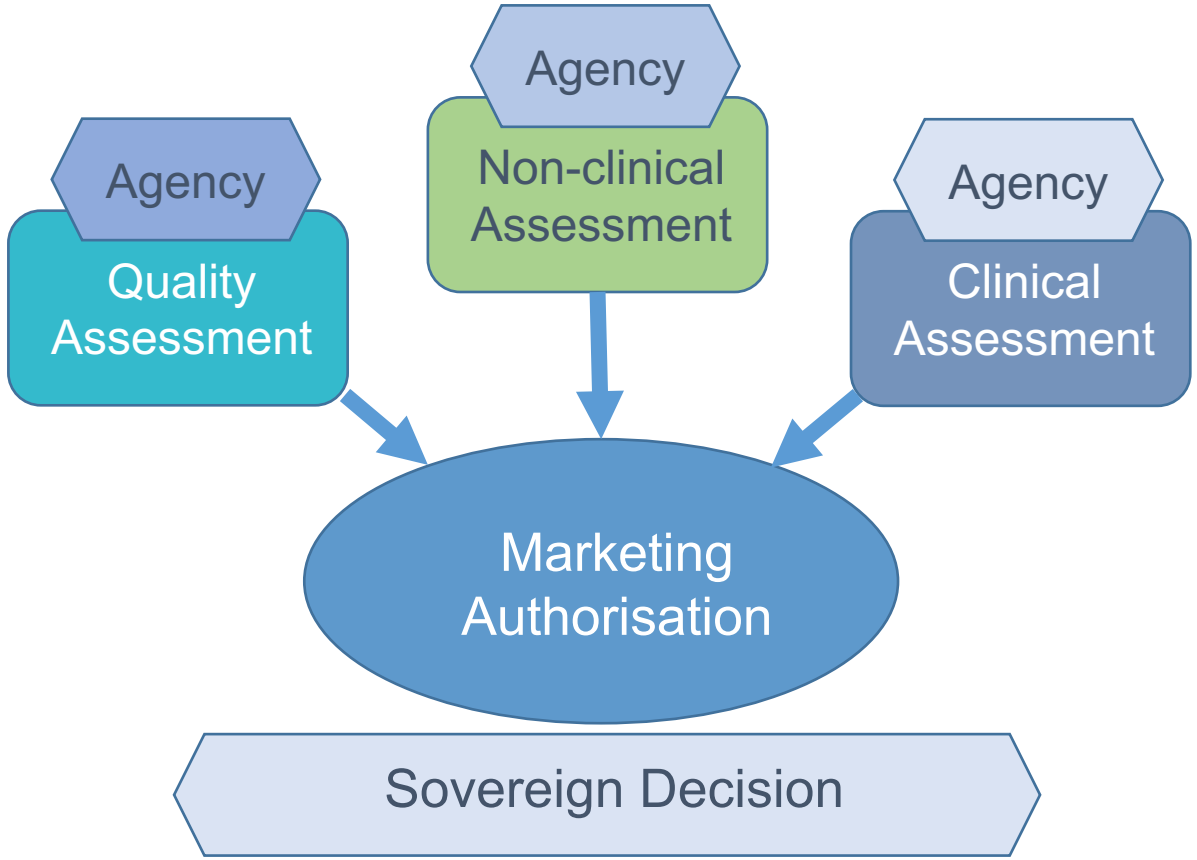
by enabling an environment for innovation and local production, and accelerating access to medical products

Access Consortium

- Therapeutic Goods Administration (TGA)
- Health Canada (HC)
- Health Science Authority (HSA)
- Swissmedic
- Medicines and Healthcare Products Regulatory Agency (MHRA)



New Active Substance Work-Sharing Initiative (NASWSI)



Swiss Health Foreign Policy 2019–2024

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

What drives access to quality medical products for all?

1 Research and Development (R&D)

Communicable diseases (e.g. malaria, addressing antimicrobial resistance, measles, HIV)

Non-communicable diseases (e.g. cardiovascular diseases, cancers, chronic respiratory diseases, diabetes)

Basic research and discovery | Early pre-clinical development | Clinical development

Push and pull incentive mechanisms, including intellectual property rights, market size and expected revenues

2 Regulatory Systems

Pre-clinical trials → Clinical trials → Production and scaling up

Market surveillance
Pharmacovigilance
Life-cycle management

Pre-market | Registration | Approval | Post-market

Establish, evaluate and maintain quality, safety and efficacy

Good Manufacturing / Clinical / Distribution / **Practice**

3 Financing

Supply side

Manufacturer price

Wholesaler price (mark-ups)

Demand side

- Health technology assessment (evaluation of benefits and costs of a new medical product)
- Price negotiations with the manufacturer
- Taxes and tariffs
- Reimbursement schemes (e.g. health insurance)
- Socio-economic status of patient
- Financial viability of the health system

4 Supply and Distribution

Production capacities

Transport system

Stock and storage management

National regulations

Substandard and falsified medical products

5 Healthcare Facilities, Equipment and Personnel

Facilities and equipment

Healthcare providers, including their technical knowledge and social skills

Treatment guidelines

6 Patients' Health-Seeking Behaviour and Adherence

Supply side

- Form, dosage, colour and taste of product
- Type and communication skills of providers

Demand side

- Patient literacy
- Guiding social and cultural norms and values
- Stigma of disease or health condition
- Preference for other medical products (e.g. traditional medicine)

Access to quality medical products for all

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

#A2M-Switzerland

A2M – Swissmedic implemented activities

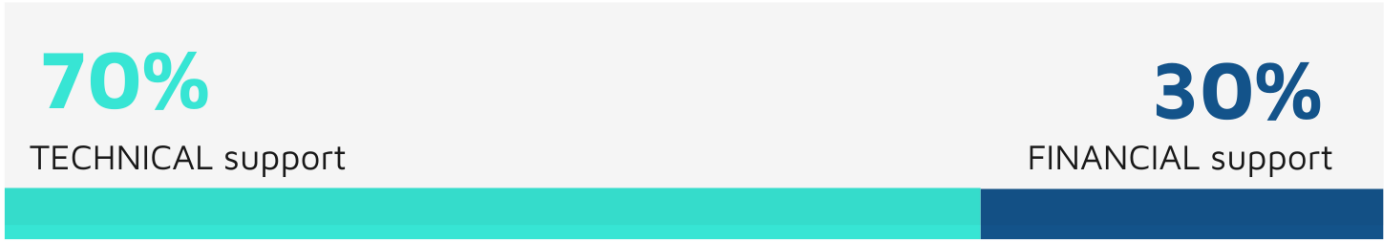
Harmonisation Since 2015	Support to implementation of the African Medicines Regulatory Harmonization (AMRH)
Access and Reliance Since 2015	Swissmedic procedure for scientific advice and for Marketing Authorization for Global Health Products (MAGHP Procedure)
Capacity Building Since 2018	Capacity building trainings/activities for NRAs (Regulatory Training, Swissmedic GMP Training, Guided Inspections)

Funding from the *Bill & Melinda Gates Foundation* secured through 2027

Coalition of Interested Parties (CIP)

- WHO coordinated network for regulatory systems strengthening
- voluntary collaborative mechanisms of organisations active in RSS
  - Government bodies, intergov. organisations, philanthropic organisations, NGOs, academic institutions, regional or international industry associations
- to establish and promote a unified, strategic and coordinated approach to national and regional RSS
- to enhance access to safe, effective and quality medical products

CIP Network support for regulatory system strengthening in 2023



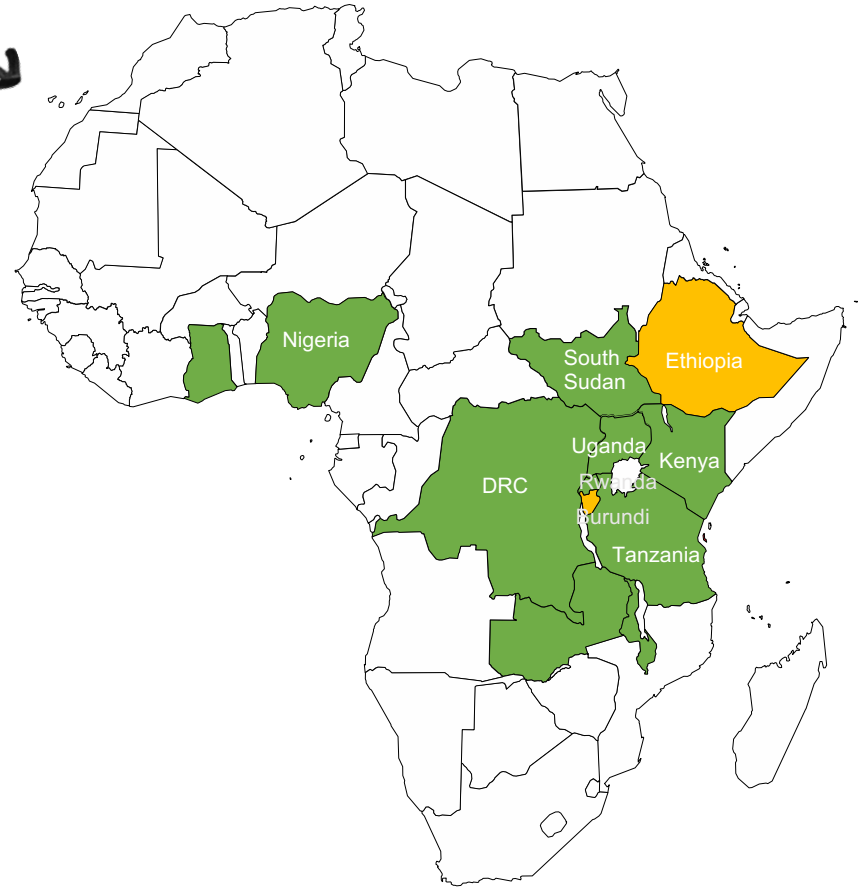
swissmedic Marketing Authorisation for Global Health Products

The MAGHP is based on the approach of involving regional National Regulatory Agencies (NRAs) and the WHO in the Swissmedic provision of scientific advice and assessment process

- helps building **trust** and **confidence** in the process.
- helps **building capacitiy** at the involved NRAs.
- is expected to **facilitate and speed up the granting of national marketing authorisations** following Swissmedic's approval (by "well-informed reliance").
- results in a Swiss Marketing Authorisation.
- **No restriction to specific indications**

MAGHP – Case Study

- 1 product for **prevention of postpartum uterine atony** following vaginal delivery registered
- 7 NRAs granted authorization, 3 of these within less than 90 days – **Median approval time = 5.5 months**
- Approval through **WHO SRA CRP** in Malawi, Ghana and Zambia
- Positive recommendation from **CARPHA's CRS**
- **WHO PQ**



- 4 Scientific Advice requests for other products elaborated
- Advocacy events
- Multiple feedbacks and lessons learned from Industry and targeted NRAs

Regulatory Training Courses

- Since 2018 Swissmedic conducts, in cooperation with WHO, **two training visits a year** for NRAs
- Goal: NRAs acquire new skills for developing and implementing standard practices according to country specifics, by getting insights into Swissmedic's operational processes and tasks → **Peer-to-peer**
- Outreach: **335 trained attendees** from **68 Countries**
  - All 6 WHO Regions covered
  - Participation from AMR: **Bolivia**, **CARPHA, Chile, Colombia, Costa Rica**, **Ecuador**, **El Salvador**, **Guatemala, Honduras**, **Panama**, **Peru**
- Publication of extensive **impact study:** Frontiers | Collaborative training of regulators as an approach for strengthening regulatory systems in LMICs: experiences of the WHO and Swissmedic (frontiersin.org)

Conclusion and considerations

- In a globalised environment, international **cooperation between regulators is paramount**
- Effective international cooperation is based on
  - **harmonised requirements**
  - **common standards**
  - **trust and confidence in regulatory systems and evaluation process**
- Prioritisation of activities aligned with overall strategy, driven by clear objectives and criteria
  - Which tasks need to be performed locally → **build capacity**
  - When can we rely on work already done by other regulators → **build trust**
  - There is no "one size fits all“ → **tailored approach**
- Need for a **balanced approach towards work sharing and reliance: Give and take!**

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Tools to facilitate the use of reliance

Jorge Azar
On behalf of IFPMA Reliance Taskforce

Overview

- Introduction. Why reliance is important?
- Ensuring Product sameness
- Use of assessment reports for reliance
- Q&A

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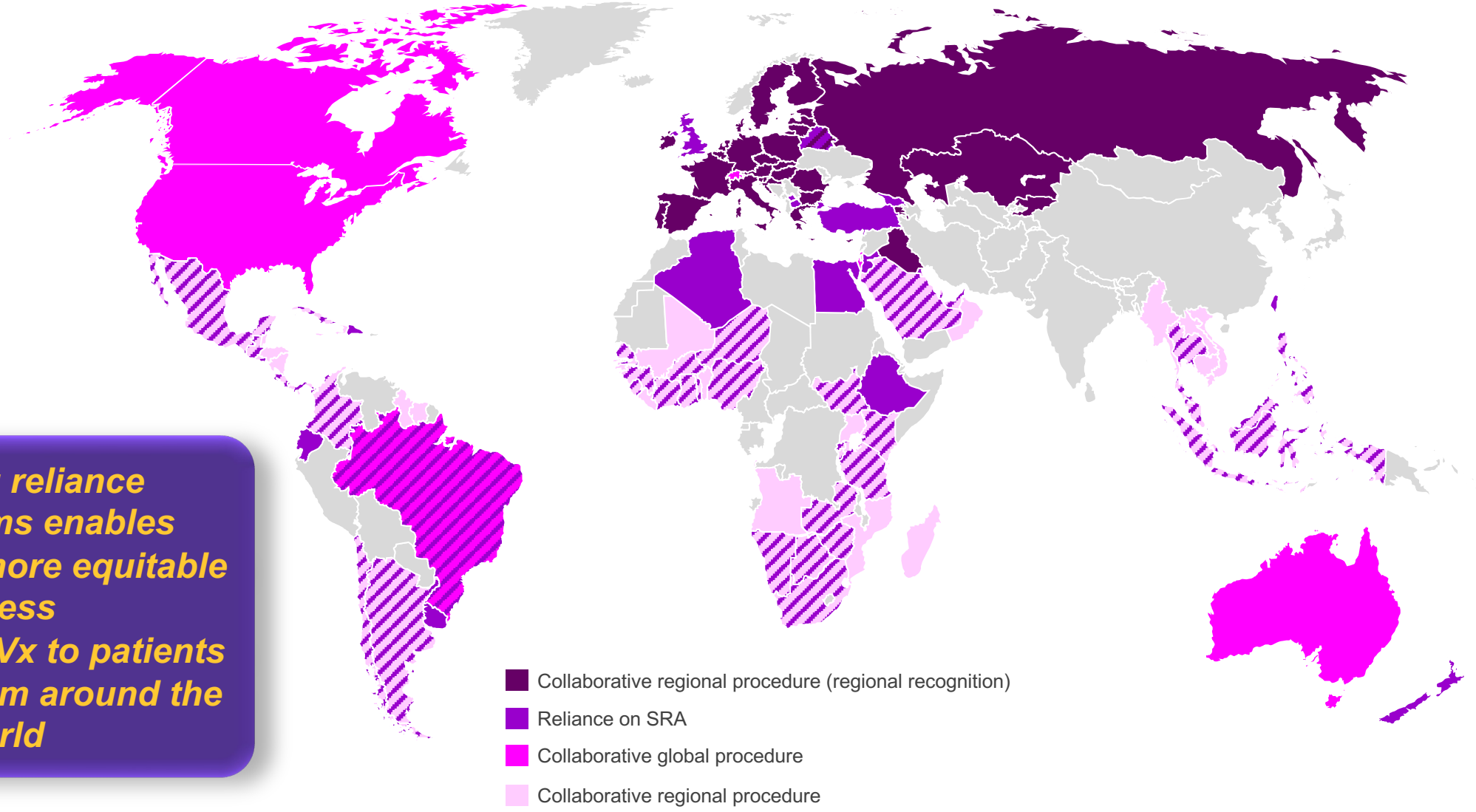
Introduction | Current Overview of Worldwide regulatory reliance pathways (MAAs)



Applying reliance mechanisms enables quicker and more equitable access of drugs and Vx to patients who need them around the world

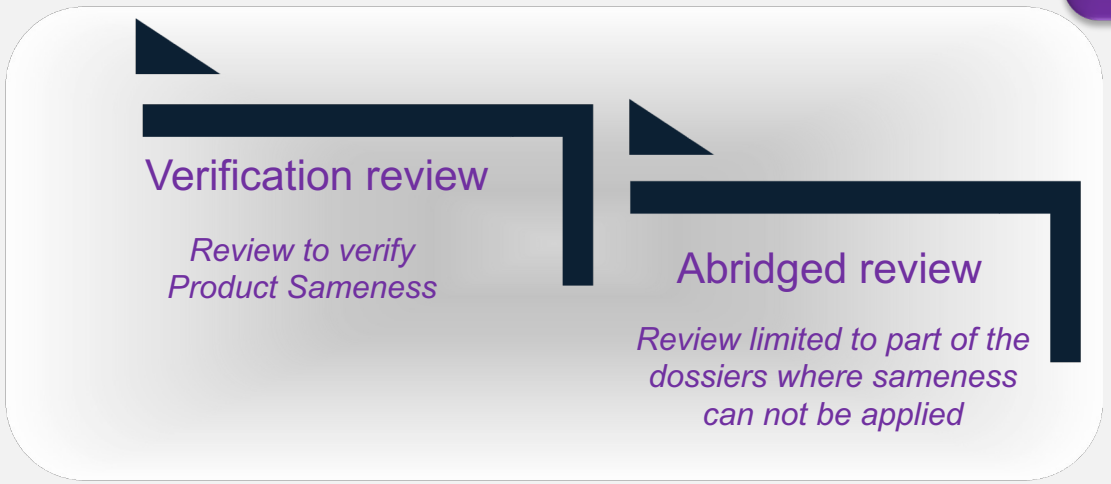
Source: Merck (2022)

Why is Reliance important ? Access to medical products is a global challenge

Applying reliance mechanisms enables quicker and more equitable access of drugs and vaccines to populations who need them around the world

RELIANCE

When a regulatory authority takes into account/gives significant weight to assessments performed by another regulatory authority in reaching its own decision



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

Ref - WHO (2016) Good Regulatory Practices Guidance

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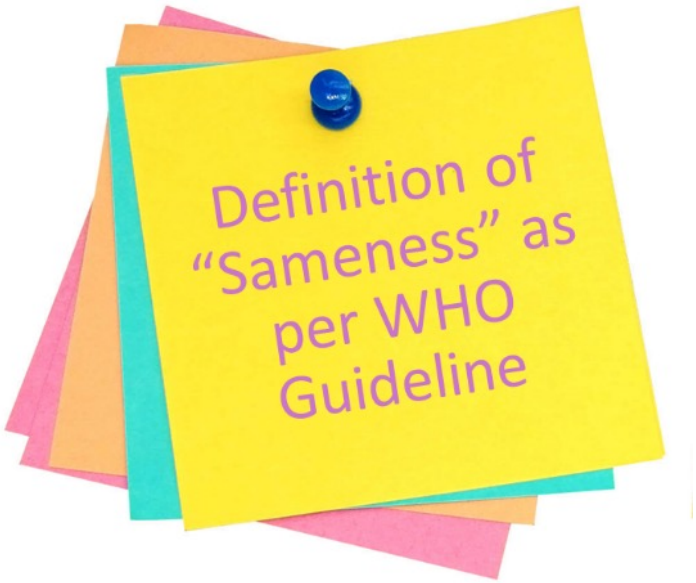
Ensuring product sameness

National Regulatory Authorities should verify that the medical product being assessed is the same or essentially similar to that approved by the reference authority



All relevant aspects are to be considered e.g.:

- Same qualitative and quantitative composition
- Same strength
- Same pharmaceutical form
- Same intended use
- Same manufacturing process
- Same suppliers of active pharmaceutical ingredients
- Same quality of all excipients

Multinational companies (MNCs) develop innovative products under ICH guidelines to ensure sameness in product quality supplied to the globe- ONE product to the globe

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Linking sameness of Product to Dossier Content and Manufacturing supply chain

Sameness of product does not mean

identical dossiers documentation and manufacturing sites

MCNs provide **dossiers that comply with each jurisdiction's** specific requirements.

There are differences in the level of detail provided between SRA and NRA dossier but essentially the **same quality attributes apply.**

This should not preclude using reliance approaches. Transparency is key during the dossier evaluation

More than one manufacturing site is often used to **ensure uninterrupted supply of medicines**

All sites operates under the same quality standards, procedures, and practices (Pharmaceutical Quality System- ICH Q10 plus ICH Q8 and 9)

- Minor manufacturing adjustments may occur without impacting product quality or sameness
- For the drug product, the emphasis is on the manufacturing process & not the manufacturing site.

New applications:
Dossier submitted to relying authority will be **embedding variations** submitted after **initial SRA approval** and may differ from the assessment report due to the time Δ in submissions

Post-Approval changes:
Divergence on classifications and timelines for variations globally may lead to dossier lag and supply issues
More **changes needed prior approva**l (including minor changes) with slower approvals compared to SRA so these dossiers lag behind SRA
Potential supply **shortages if changes are not approved** before reserved supplies are depleted.

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What else can be done to build trust and ensure mutual understanding on verification of sameness?

IFPMA believes that **mutual trust between all parties is the foundation of reliance.**
Transparency between all parties is a key principle for good regulatory practice and fundamental to reliance.

Highlighting differences	Build a Shared Mutual understanding	Regulatory convergence
Critical for Industry to highlight any differences of concern to the NRA, and justifying why such differences have no impact on the quality, efficacy and safety of the product.	Workshops to explain the ICH quality standards managed under the PQS. Industry practical insights and case studies on how MNCs apply the "sameness" definition.	Support Convergence to ICH and WHO requirements and reduction in national requirements

IFPMA Points to consider on the importance of product sameness in the context of regulatory reliance

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IFPMA Template for description of differences

Intended use:

Review aid for reliance-based procedures. The template serves as an **optional tool** that applicants can submit along with the necessary documentation for review. It highlights and **justifies** potential differences so that NRAs can easily find information needed to make a decision on how to apply reliance.

Benefits:

- **Simplify** and **harmonize** documentation submitted to NRAs in reliance-based procedures
- **Increased transparency** without additional review burden
- **Provide guidance** on where to focus the review, thus **expediting** review times and improving the **efficiency** of review processes
- **Reduce** the number of ancillary and redundant document requests

Ultimately, this document will accelerate trust-building through improved transparency.

It is not intended to replace any document already being used, but it will provide an opportunity to standardize current approaches – MCNs are already using similar templates, with different levels of detail to keep track of differences.

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IFPMA Template for description of differences

Example:

COLUMN A	COLUMN B	COLUMN C	COLUMN D
Module 3/Submodule	**Documents included in this application**	**Dossier sameness as compared to Reference NRA (Yes/No)**	**Brief discussion and justification that the difference has no impact on product quality (including reference to supporting data as appropriate)**
3.2.P: DRUG PRODUCT			
3.2.P.1 Description and Composition of the Drug Product	Y	Y	
3.2.P.2. Pharmaceutical Development	Y	Y	
3.2.P.2: Manufacture			
3.2.P.2.1: Manufacturer	Y	N	Finished drug product release site is different from EU. EU regulations specify that the qualified person shall certify that each batch underwent analysis in an EU Member State. Therefore the finished product release site for the EU market has to be in EU territory, which is different from that for rest of the world. The same release criteria and release procedure are applied to all release sites to ensure that the products have identical quality
3.2.P.2.2: Batch Formula	Y	Y	

Use of Assessment Reports | Introduction

Assessment reports detail and explain how the reviewing national regulatory authority (NRA) assessed the safety, efficacy and quality data within a submission dossier to inform its final decision on a regulatory action.

What types of reports are issued by NRAs?

- **Product-focused** assessment reports from initial registration of new products or major post-approval changes (new indications or dosage forms) . It can be **redacted or unredacted assessment report**.

- **Manufacturing site focused inspection** reports related to the **adherence** to good manufacturing practice (GMP) **verified** via **inspection** of the manufacturing site either **physically or via desk-based** assessment. Usually, they are issued by the national inspectorate within the NRA that has performed the inspection or occasionally by a regional/district inspectorate within a country (e.g. within China).

Key considerations

- **Assessment reports varies between NRAs**, and **there is no commonly accepted international standard.**
- Public assessment reports are **produced following the approval of a medicine** to **provide transparency** on the review and demonstrate how NRAs are **fulfilling** their **responsibilities to safeguard public health**.
- **Assessment reports contain data** on the product generated by the pharmaceutical industry applicant.

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Use of Assessment Reports | Best Practices

Best Practice Point:

- No need to agree Memorandum of Understanding (MOU) /confidentiality agreement
- PARs will help expand pool of reference NRAs

1 **Encourages NRAs to issue & share Public Assessment Reports, (PAR)**

Best Practice Point:

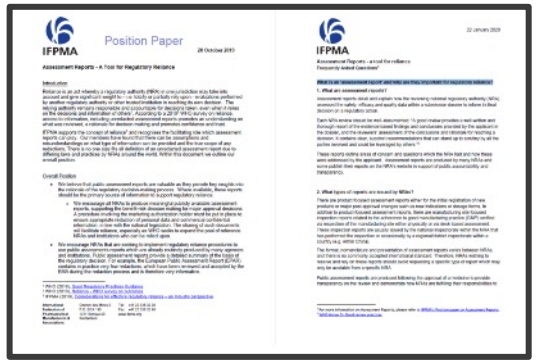
- Ideal exchange = NRA to NRA via secure platform to safeguard IP/confidentiality
- MOU or Confidentiality agreement need to be in place

2 **If no PAR or more information needed, then *confidential review documents can be shared**

Best Practice Point:

- Needs controls to avoid inadvertent entry of confidential information into the public domain

3 **If no MOU and NRA can't share documents, then individual companies may ** share case by case**


IFPMA Position Paper

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Assessment Reports – A Tool for Regulatory Reliance

[IFPMA Position paper & F.A.Q. - Assessment Reports as a Tool for Regulatory Reliance]

*Unredacted assessment Report +List of Questions
** Summary basis of Approval (public) for US

US- Section 552(b) of title 5
***According to CFR Part 20- Public Information

***EU- Regulation (EC) No 726/2004
Regulation (EC) No 1049/2001

Use of Assessment Reports | Considerations & Recommendations

- **NRAs** should **establish regulatory reliance procedures** based on what is actually possible for reference NRAs to provide, **recognising** that **assessment reports vary across different jurisdictions** due to national legislation that determines what type of information can be provided.

- We believe that the provision of assessment reports to support regulatory reliance should **speed up and not slow down approval process** in comparison to a conventional review, thus enabling patients to have faster access to new treatments as a result.

- We believe that **only one assessment report from one agency** being relied upon should be requested and supplied. Provision of reports from multiple NRAs who arrived at the same approval decision and for the same conditions of use for the product is not value added, because it is not providing any additional information to inform the decision.

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Thank you!

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