USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTaPS) PROGRAM

Improved Access. Improved Services. Better Health Outcomes.

Strengthening Pharmaceutical Regulatory Systems in Asia

SESSION 2

Thursday, July 13, 2023

2pm – 4.30pm

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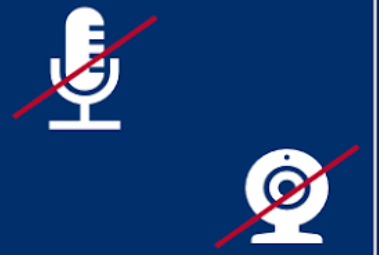
WELCOME

Andrew Brown
Principal Technical Advisor, Governance and Capacity Building
USAID MTaPS Program

Housekeeping

Please remember to sign in using the link to the attendance sheet in the chat.

				
Ensure that your audio and video connection are in working order	Mute your microphone during the presentation Turn off your camera while the presentation is ongoing	Reserve questions for the Q&A; or you may write your questions in the chat box Should you wish to make a comment or feedback, kindly make a note in the Chat Box and you will be recognized	Indicate that you are done sharing or speaking by saying, ‘**Over**’ Avoid interrupting other people when they’re speaking (or attempt to speak over them)	This event is being recorded.

Agenda Session 2

2.00 – 2.05 pm	**Welcome and Overview** Welcome, *Andrew Brown, MTaPS* Housekeeping, *Shahreen Haq, MTaPS* Overview of the Program, *Andrew Brown, MTaPS*
2.05 – 2.20 pm	**Enhancing Regional Collaboration Through Convergence and Harmonization of Medicine Regulation,** *Dra. Togi Junice Hutadjulu, Apt, MHA, SEARN Steering Group*
2.20 – 2.35 pm	**Case Study – Convergence and Harmonization,** *Petra Bismire, TGA, Australia*
2.35 – 2.50 pm	**Facilitated Questions,** *Andrew Brown, MTaPS*
2.50 – 3.05 pm	**Convergence of Technical Standards,** *Rochapon Wacharotayankun, MTaPS*
3.05 – 3.20 pm	**Developing Joint Assessment Procedures for Product Registration,** *Jeyakhandan E, PQM+*
3.20 – 3.35 pm	**Lessons on Convergence and Harmonization from Regional Implementing Partners,** *Vivian Rakuomi, MTaPS*
3.35 – 3.50 pm	**Facilitated Questions and Stretch,** *Andrew Brown, MTaPS*
3.50 – 4.05 pm	**Effective Medicines Registration Systems and Collaboration with Regional Networks: Country Experiences,** *Md. Salahuddin, DGDA, Bangladesh*
4.05– 4.20 pm	**Facilitated Questions,** *Andrew Brown, MTaPS*
4.20 – 4.30 pm	**Closing,** *Vivian Rakuomi, MTaPS*

South-East Asia Regulatory Network

Enhancing Regional Collaboration through **Convergence and Harmonization** of Medicine Regulation

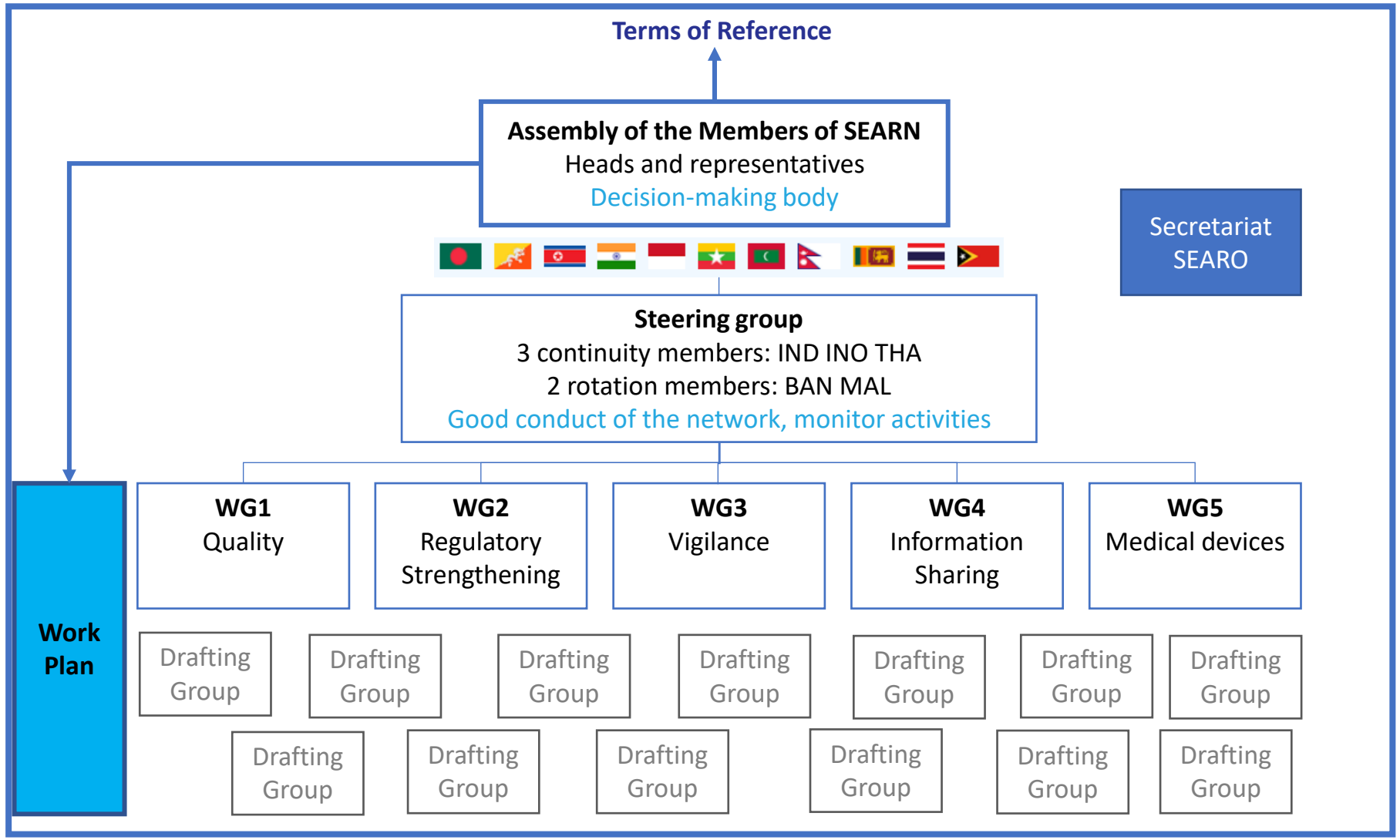
searn-network.org
13 July 2023

Dra. Togi Junice Hutadjulu, Apt, MHA,
Chair of SEARN Steering Group

What is SEARN?

- **SEARN** (South-East Asia Regulatory Network)
  - Volunteer association of the NRAs of 11 countries from the WHO South-East Asia Region
  - Launched in April 2017 to enhance:
    - information sharing,
    - collaboration and
    - **convergence** of medical product regulatory practices
    - across the Region to guarantee access to quality medical products.
  - Supported by Ministers of Health: 2018 Delhi Declaration on improving access to essential medical products
  - June 2022: adoption of new terms of reference (v5) and 2022-2023 workplan by the Heads of NRAs during the meeting of the Assembly in New Delhi, India

What is SEARN?



Working method

- Workplan driven by the **needs** expressed by the SEARN Members
- For each action point, a **Rapporteur** is nominated from one of the members of the working group to lead the related work.
- the Rapporteur is supported by a **drafting group** constituted by other working group members, experts, and the secretariat

Key issues/gaps: an analysis based on the 2022-2023 workplan

14 Action points

Capacity building	**Experience Sharing**	**Information Sharing**	**Public website and internal platform**	**Reliance**	**Sustainability of the Network**	**Lessons from COVID-19 for preparedness**
Access to reference standards for NCLs	**Strengthen NCLs**	**Increase the number of reports**	**Integration of vigilance**	**Regulatory intelligence during public health emergency**	**Gaps in medical devices regulation**	**Integrity of excipients**

Collaboration to build capacity
Information sharing
Defining and addressing common challenges

SEARN activities to address identified issues

- Young network
- At the moment, focus on:
  - Building trust
  - Information sharing
  - Developing collaboration
  - Reliance
  - Convergence
- Some worksharing activities may be initiated in the next work plan
- Harmonization may come at a later stage

- The following example (strategy to strengthen reliance) illustrates how SEARN has been using convergence to address the identified issues

SEARN activities to address identified issues

Example – Reliance awaiting further discussions and adoption

- 2021 Good reliance practices. Definition of 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.'

- Reliance may be used for
  - **any of the medical products** in the scope of SEARN
  - for **all regulatory functions**,
  - in the **full life cycle** of a medical product.

- Some conditions are required to enable reliance,
  - including having **access to sufficient information** from the reference NRA.

SEARN activities to address identified issues

Example – Reliance awaiting further discussions and adoption

- **Survey**: a useful tool to facilitate convergence through
  - Common definition of how the issue is captured and questioned
  - Developing a shared understanding of the issue
  - Developing a shared vision on the goals
- The survey allowed to map:
  - Where reliance is currently used
  - Where reliance could be used

Outcomes of the strategy

Based on the survey, the drafting group has proposed:

- Some prioritized areas for reliance (MA, VL, RI, LT)
  - and agreed on the types of decisions for which reliance can be used in each of these areas
- Convergence on the identification of reference authorities, through a guidance to NRAs on:
  - The principles guiding reliance
  - The criterion for selecting a reference regulatory authority

SEARN activities to address identified issues

Example – Reliance awaiting further discussions and adoption

Proposed actions in the next workplan

- Convergence on the minimum information required for each decision for reliance
- Worksharing on identifying and mapping reference authorities and organisations for prioritised regulatory decisions
- Initiate work on reliance for MC

Possible indicators to measure the impact of the strategy:

- Number of SEARN Members countries reporting using reliance for
  - MA
  - VL
  - RI
  - LT
- Number of SEARN Members countries for which the guideline(s) on reliance are aligned with the SEARN principles and criterion for identifying reference regulatory authorities

SEARN activities to address identified issues

Other examples awaiting further discussions and adoption

Capacity building: convergence on the definition of capacity development, its dimensions, and the methods – **support by MTaPS**

Information sharing: convergence on which information should be shared and how

Strengthening NCLs: proposition of worksharing to identify reliable laboratories

Integration of vigilance: definition of integration and proposition of a method

Medical devices: survey conducted to identify the gaps and build a common understanding of the issues in the region

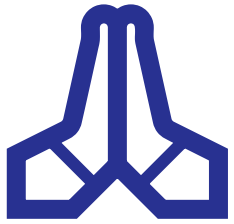
Integrity of excipients: sustained discussions to frame the issue and develop solutions tailored to the region

Next steps

- The proposed outcomes from the 2022-2023 work plan will be presented for discussion and adoption to the **Assembly** of the Members (Jakarta, 24-27 July 2023)

- When appropriate, the outcomes of the 2022-2023 workplan will be published on the SEARN website: searn-network.org

- The Assembly will also adopt the 2023-2024 workplan



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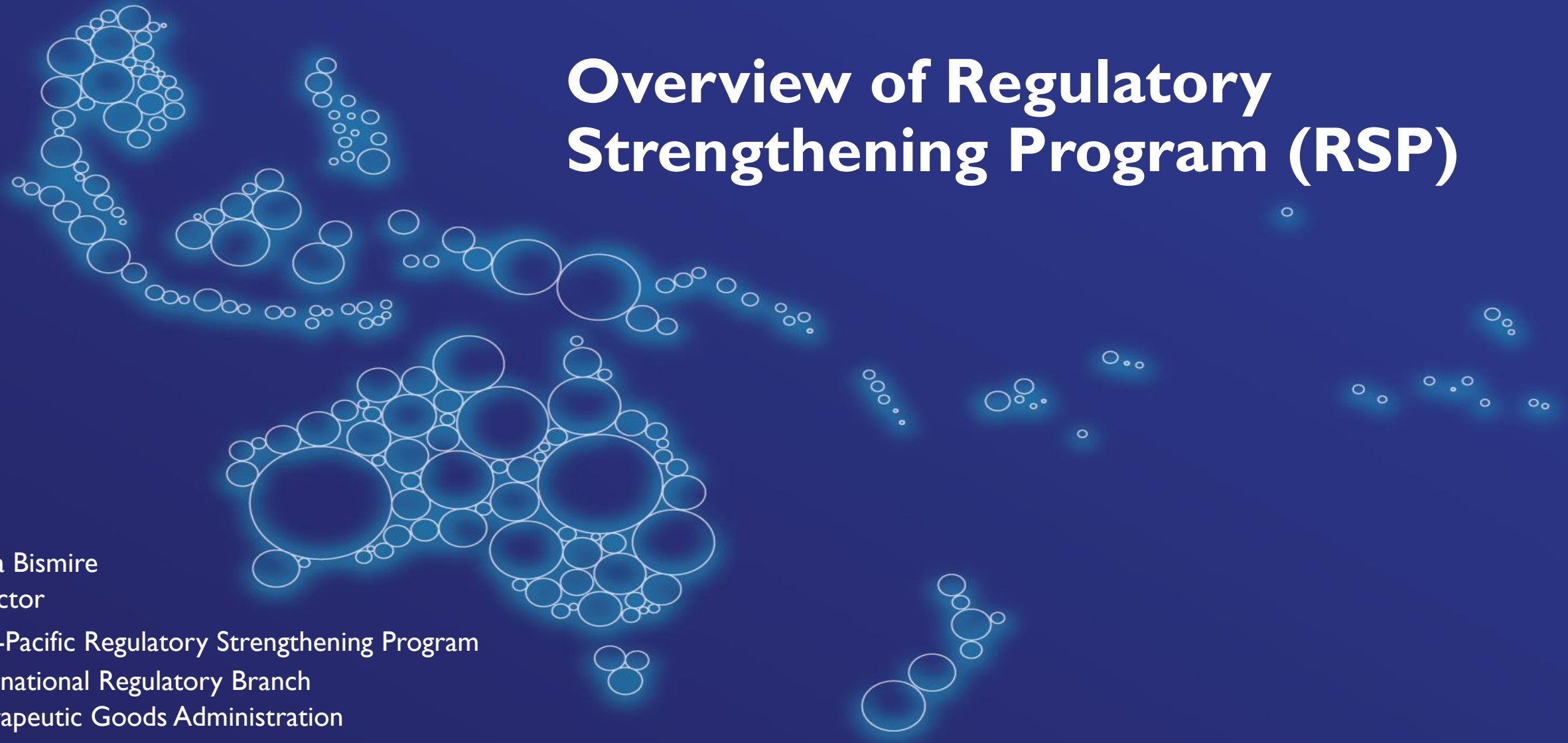
Overview of Regulatory Strengthening Program (RSP)



Petra Bismire
Director
Indo-Pacific Regulatory Strengthening Program
International Regulatory Branch
Therapeutic Goods Administration

Therapeutic Goods Administration (TGA)

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

The TGA is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods.

Responsibilities include evaluating, assessing and monitoring products that are defined as therapeutic goods, so the Australian community has access to quality, safe and effective products. This includes:

- prescription medicines
- complementary medicines, (e.g., vitamins, herbal and traditional medicines)
- medical devices
- products used to test for various diseases or conditions
- vaccines, blood products, and other biologics

The TGA does not regulate veterinary medicines, food, health insurance, cosmetics, chemicals, or healthcare professionals.

Regulatory Strengthening Program (RSP)

Department of Foreign Affairs and Trade (DFAT) has partnered with the Department of Health and Aged Care, through the Therapeutic Goods Administration, to implement the Indo-Pacific Regulatory Strengthening Program (RSP) under the Partnerships for a Healthy Region initiative.

Commenced 1 July 2023

- Committed to deliver technical assistance throughout the Indo-Pacific region in the area of regulation of medical products, to promote access to quality-assured, safe and efficacious medical products.
- The Program has been designed to be an extension of the 2018-2023 TGA-led regulatory strengthening and support Programs.
- In partnership with National Regulatory Authorities (NRAs), regulatory systems will be *strengthened*, and regulatory *support* provided, for the control of therapeutic products that support the management of:
    - communicable and noncommunicable diseases
    - sexual reproductive health
    - assistive technologies

RSP Participating countries

- Indonesia
- Laos
- Cambodia
- Fiji
- Malaysia
- Papua New Guinea
- he Philippines
- Timor-Leste
- Thailand
- Vietnam
- Federated States of Micronesia
- Kiribati
- Nauru
- Niue
- Palau
- Republic of Marshall Islands
- Samoa
- Solomon Islands
- Tonga
- Tuvalu
- Vanuatu
- Myanmar (on hold)

Regulatory Systems Strengthening

Targeted health systems *strengthening*, capacity building activities for 11 countries

Indonesia, Laos, Cambodia, Fiji, Papua New Guinea, Timor-Leste, the Philippines, Thailand, Vietnam, Malaysia and Myanmar (on hold)

Responsive Regulatory Support

'On call' *support* will be offered to address specific regulatory needs at a point in time for 22 countries

Indonesia, Laos, Cambodia, Fiji, Papua New Guinea, Timor-Leste, the Philippines, Thailand, Vietnam, Malaysia, Federated States of Micronesia, Kiribati, Nauru, Niue, Palau, Republic of Marshall Islands, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu and Myanmar (on hold)

Regulatory Systems Strengthening

Targeted capacity building activity themes

Quality

- Pre-market assessment of quality and manufacturing controls
- Good Manufacturing Practice (GMP)
- Laboratory testing
- Substandard and falsified medicines
- Lifecycle management of products (variations)

Safety and Efficacy

- Pre-market assessment of safety & efficacy and post-market surveillance
- Risk Management Plans
- Medicine defects (may also involve product quality)
- Adverse event reporting
- Causality assessments
- Recalls

Risk Communication

- Role of regulators in keeping external stakeholders appropriately informed
- Promotion of the Quality Use of Medicines (may relate to quality, safety or efficacy of a medical product or combination of these aspects)

Cross Cutting

Tools required to perform regulatory functions effectively (i.e., the legal, policy, IT and operational framework)

Opportunities to engage in **Reliance and Cooperation** for the purpose of:

- saving resources
- avoiding unnecessary duplication
- building a knowledge base by learning from other agencies

Design of inclusive & participatory **GEDSI** approaches and systems, including incorporation of GEDSI considerations in legal, policy and operational frameworks such as those outlined under 'tools'

Responsive Regulatory Support Technical Assistance

Undertake program awareness activities, to ensure Ministries of Health are aware of the programs offering

Collaborate with the Pacific Medicines Testing Program (PMTP) to determine if there are other regulatory support activities these countries desire

Concurrently look to engage Pacific Island Countries (PICs) through the Pasifika Medpro Regulatory Collaboration

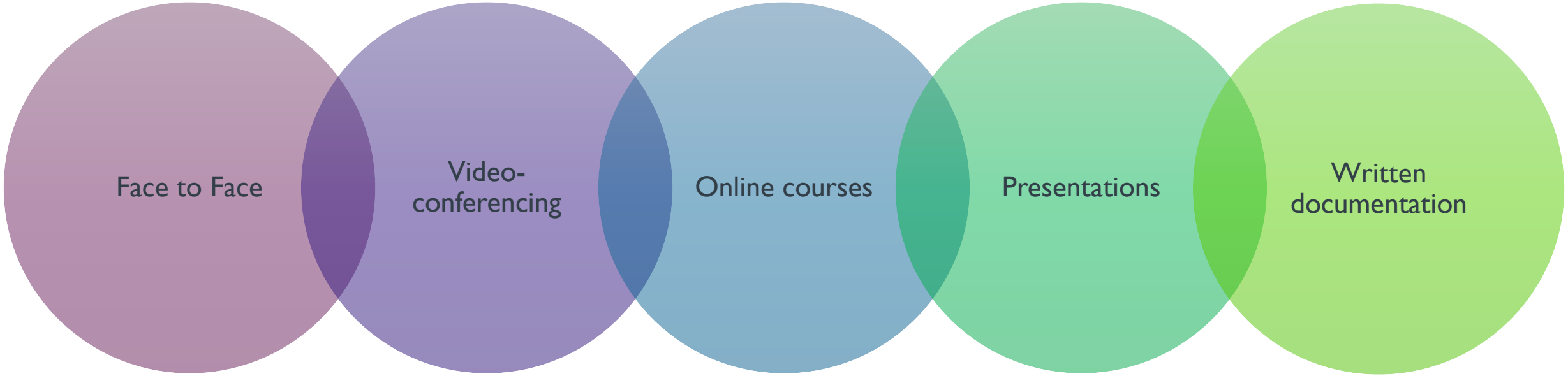
Australia-Indonesia Contaminated Medicines and Vaccines Program

TGA will undertake regulatory strengthening activities in partnership with the Indonesian Food and Drug Authority (BPOM) to address the systemic regulatory challenges highlighted by recent contamination of paediatric medicines with EG and DEG, which has led to hundreds of deaths in children in Indonesia, and worldwide.

- Strengthening **laboratory** capacity for the detection of contaminants
- Reviewing national and regional **Good Manufacturing Practice** requirements and controls for medicines and vaccines
- Reviewing **compliance and enforcement powers** and identifying areas within the policy and legislative/ regulatory framework
- Strengthening **pharmacovigilance** (safety monitoring)

How will support be delivered?

Highly integrated, multi-modal delivery of regulatory strengthening and support activities spanning theoretical training and hands-on capacity building



These functions all serve to transfer technical regulatory understanding to staff across the region, and to enhance regulatory systems.

Collaboration in the region is encouraged and supported.

Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Questions?

rsp@health.gov.au

FACILITATED Q&A

Andrew Brown
Principal Technical Advisor, Governance and Capacity Building
USAID MTaPS Program

Convergence of Technical Standards: Policy Convergence of Regional Technical Requirements for Medicines Registration Among Asian Countries: Nepal & Bangladesh

Assist. Prof. Rochapon Wacharotayankun, Ph.D., R.Ph.

Executive Director

Establishment of Mahidol University Bio-industrial Development Center, Thailand

Mahidol University
Establishment of Mahidol University
Bio-industrial Development Center

Agenda

1. Overview of convergence of technical standards
2. WHO guidance on good reliance for medical products registration
3. Application of reliance mechanisms for improved efficiency for product registration
   - *Country case studies*
4. Benefits of reliance to regulatory authorities
5. Next steps and priorities for NRAs
6. Resources

Good Practices for Registration Procedure under Good Regulatory Practice

GRevPs: Documented best practices for any aspect related to the process, format, content and management of a medical product review. GRevPs helps any National Regulatory Authority to achieve:

GOOD REVIEW PRACTICES (GRevP)

GOOD SUBMISSION PRACTICES (GSubP)

GOOD RELIANCE PRACTICES (GRelP)

GOOD REGISTRATION MANAGEMENT: TIMELINE & TARGET

Criteria:

1. Scientifically sound
2. Within targeted timeline
3. Predictable procedure
4. Legally & scientifically consistent

Timely Access of Medicine/Vaccine of Assured QSE To Patients

RELIABLE, and TRANSPARENT DECISION- MAKING PROCESS

(RISK BASED APPROACHES: B/R ASSESSMENT)

Overview of convergence of technical standards - GRP, GRelP and GRevP

1

One of the rationale on the development of GRP, GRelP, GRevP is insufficiency of regulatory capacity including the capacity to conduct medicine/vaccine review or evaluation

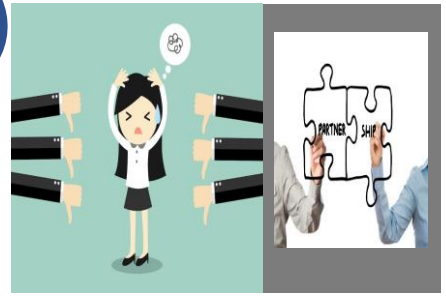
2

WHO is supporting reliance pathway to conduct the review as to make the best use of available resources and expertise → regulatory collaboration (work-sharing, Joint Assessment)

3

The need of technical capacity building as regulatory science is evolving with time → basis of regulatory decision → specific and more elaborated by conducting scientific BR assessment → focus on extrapolating for local medical needs (e.g., outcome of Phase III CT)

4



Regulatory principles on biologicals incl vaccine review follows the GRevP, but has a specific consideration, such as, disease background, age, type of antigen, epidemiological factors etc

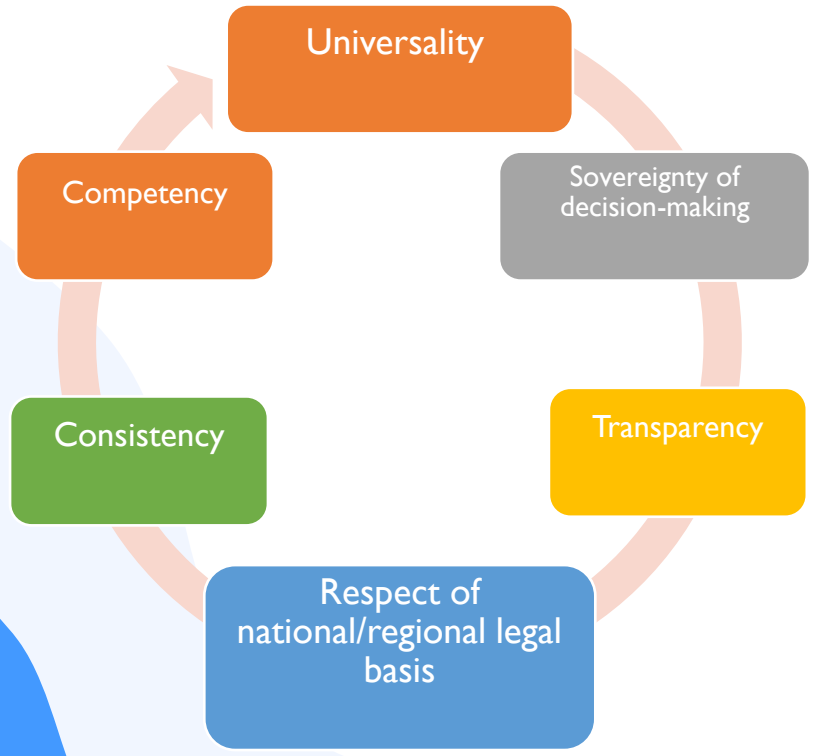
5

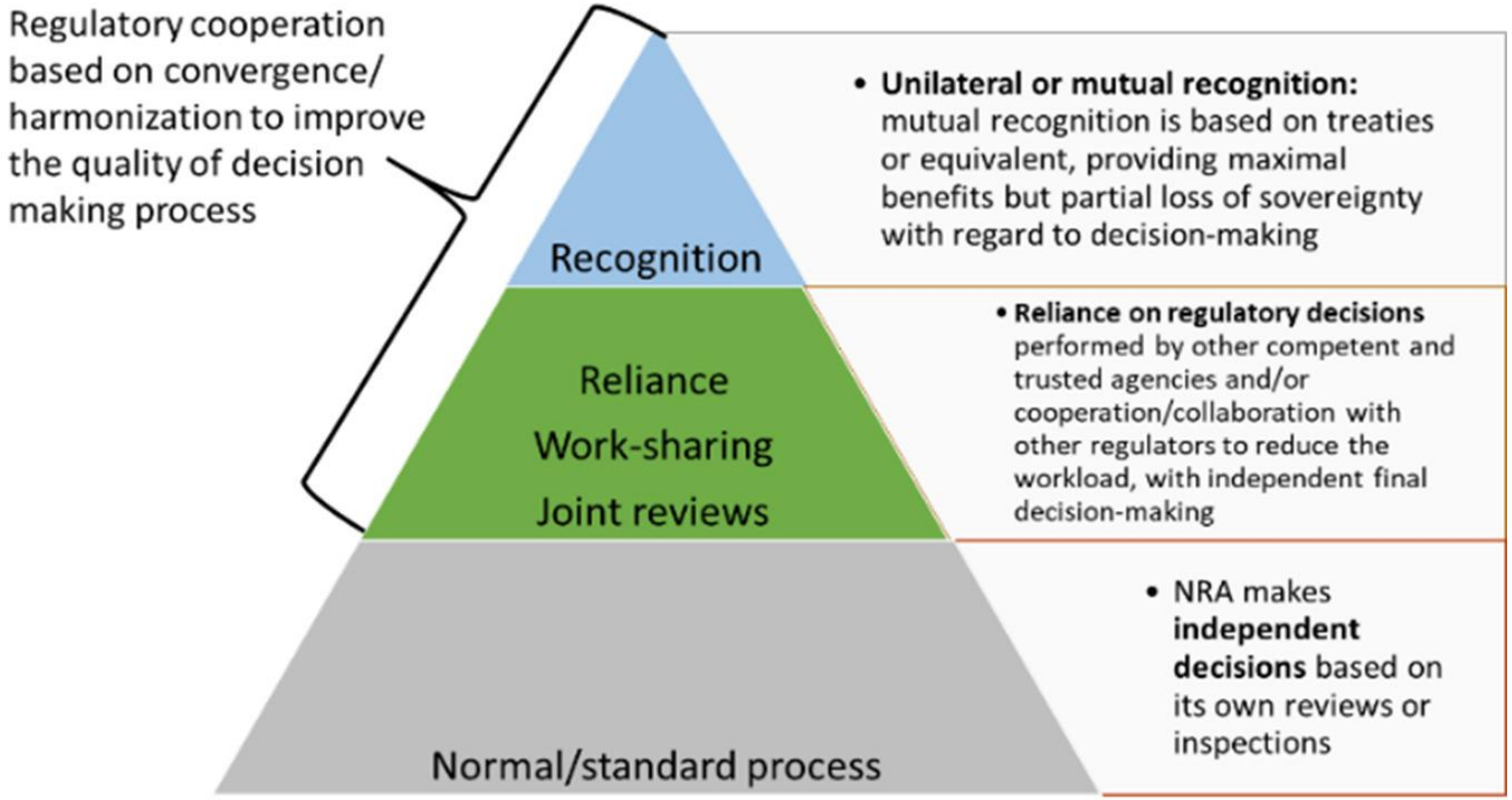
The implementation of GrelP & GRevP in PHE must be supported by a legal mandate, science- based decision making, sufficient resources, and making use of the current global and regional collaboration

WHO Good Reliance Practices (WHO TRS 1033 – ANNEX 10, 2021)

Promote a more efficient approach to regulation, thereby improving access to quality assured, effective and safe medical products

Option for Regulatory Decision via Reliance Scheme





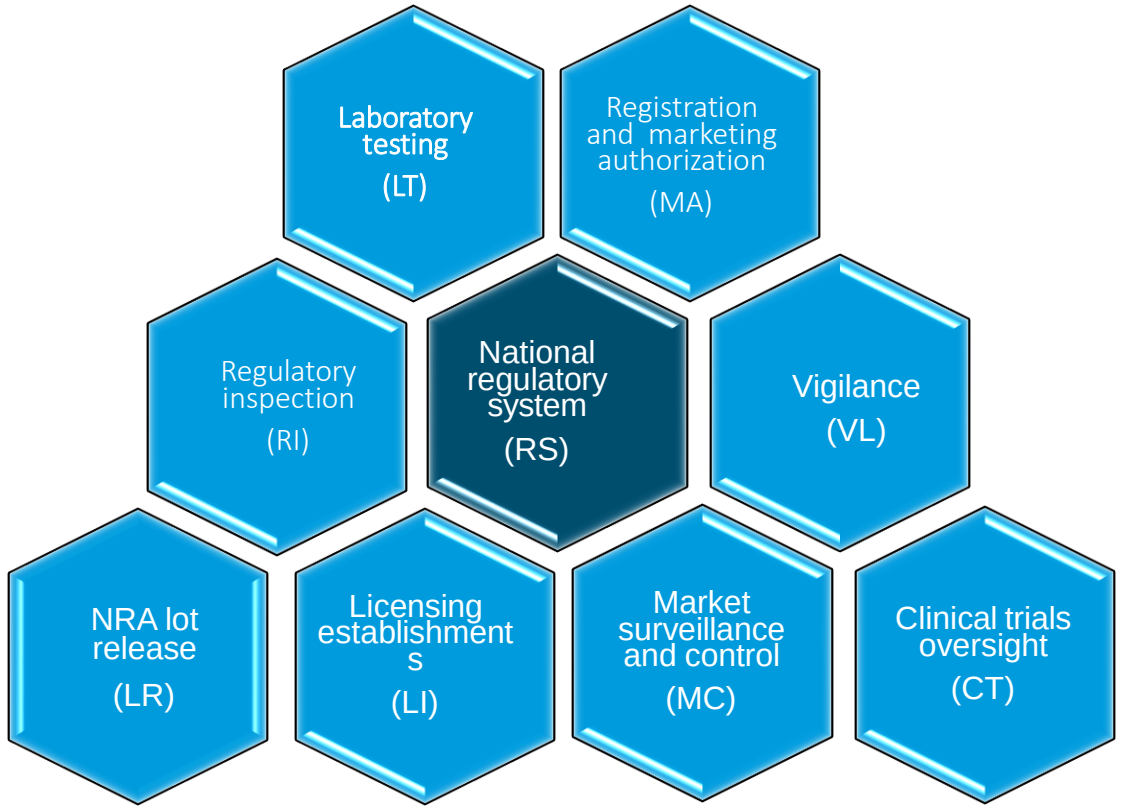
WHO Strategic Plan Relevant to Regulatory System Strengthening

DELIVERING QUALITY-ASSURED MEDICAL PRODUCTS FOR ALL

2019–2023

WHO's five-year plan to help build effective and efficient regulatory systems

GLOBAL BENCHMARKING TOOL



Regulatory System Strengthening:
Good Regulatory Practices and Global Benchmarking Tool

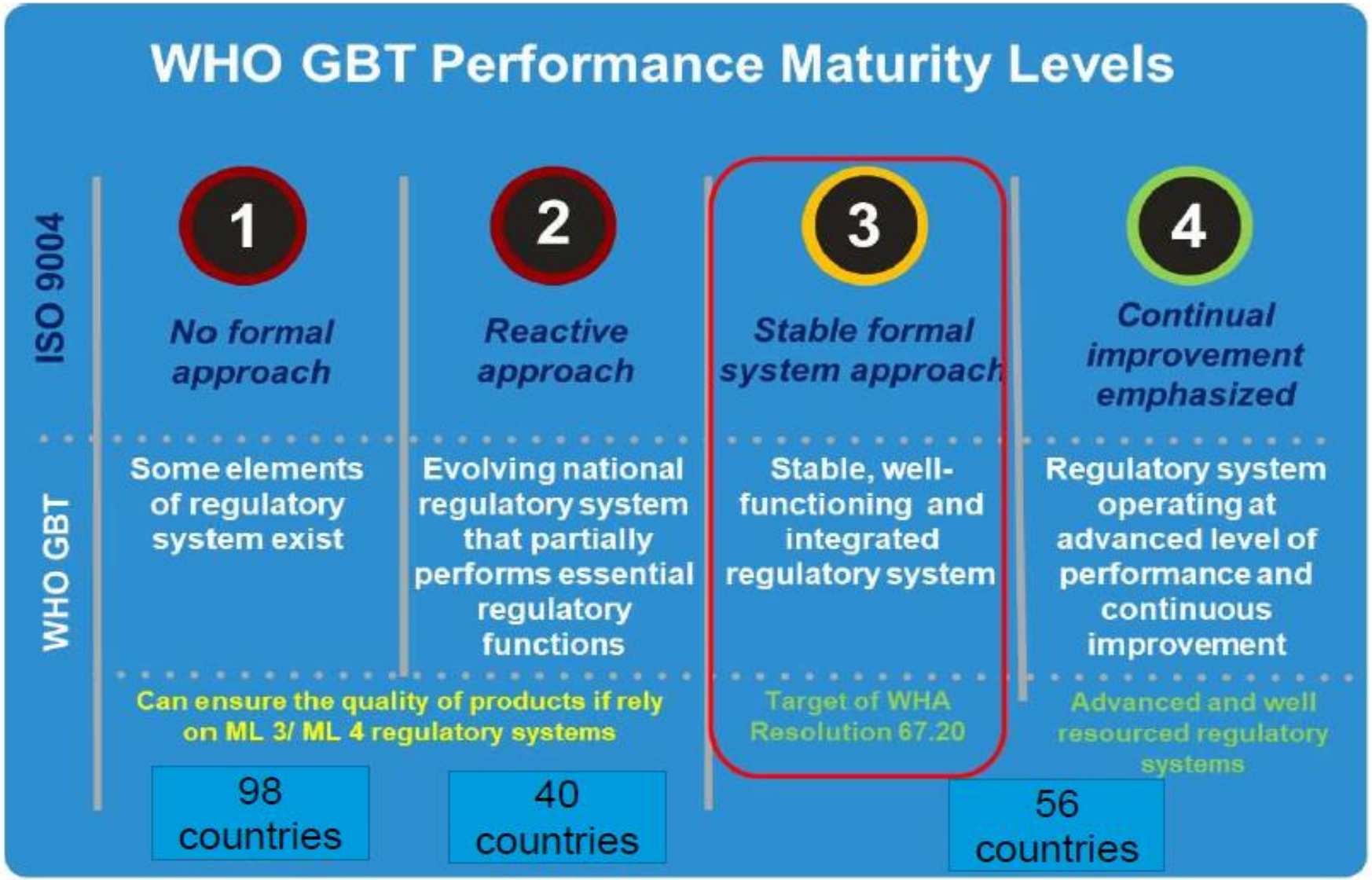
GRP Principles

1. Legality
2. Impartiality
3. Consistency
4. Proportionality
5. Flexibility
6. Effectiveness
7. Efficiency
8. Clarity
9. Transparency

GBT Indicators

1. Legal provisions, regulations and guidelines
2. Organization and governance
3. Policy and strategic planning
4. Leadership and crisis management
5. Transparency, accountability and communication
6. Quality and risk management system
7. Regulatory process
8. Resources (HR, FR, Experts, Infrastructure, Equipment and IMS)
9. Monitoring progress and assessing

Sources : Alireza Khadem, WHO / RSS


WHO GBT Performance Maturity Levels
ISO 9004
WHO GBT
1
2
3
4
No formal approach
Reactive approach
Stable formal system approach
Continual improvement emphasized
Some elements of regulatory system exist
Evolving national regulatory system that partially performs essential regulatory functions
Stable, well-functioning and integrated regulatory system
Regulatory system operating at advanced level of performance and continuous improvement
Can ensure the quality of products if rely on ML 3/ ML 4 regulatory systems
Target of WHA Resolution 67.20
Advanced and well resourced regulatory systems
98 countries
40 countries
56 countries

Application of Reliance Mechanisms for Improved Efficiency for Product Registration

Country Case studies - Bangladesh and Nepal (as of July 2022)

Capacity building workshop held on facilitating convergence of technical standards for medical products registration.

Legal mandate or Act and regulations requiring RMA of all medical products before placing the product on the market.

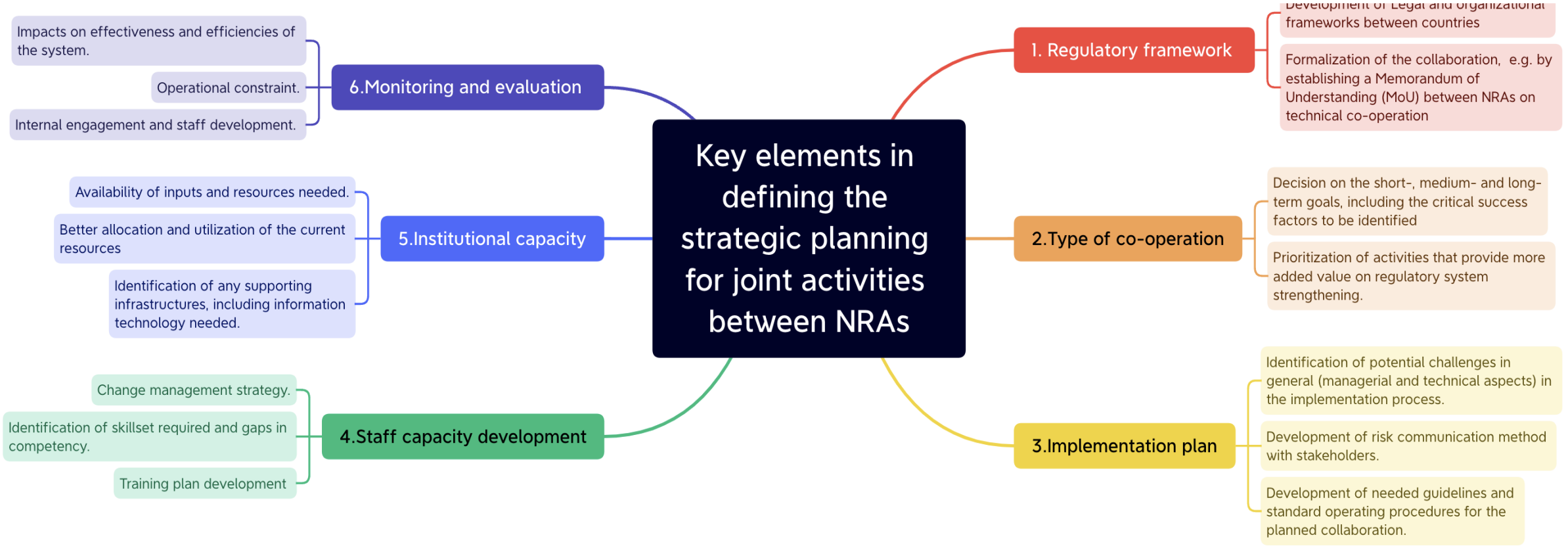
- To withhold, suspend, withdraw, or cancel an MA if there are concerns regarding QSE issues.
- Legal implementation supported by governance and leadership structures.
- Nepal's NRA still finalizing their QMS improvement.

Dossier evaluation regulations and guidelines available which mimic WHO GRevPs but need to be updated e.g.

- NRA of Nepal to adopt CTD format for MA application.
- NRAs of both countries to have provision that allows them to recognize and/or rely on MA-relevant decision, reports or information from other NRAs or regional and international bodies.
  - Could be done between NRAs of Bangladesh and Nepal as both NRAs are members of SEARN that support closer collaboration and cooperation for joint assessment.
  - A formal agreement between NRAs of Bangladesh and Nepal, for example, in the format of an MoU should be established.

Strategic Planning for Regulatory Convergence or Joint Activities between the two NRAs on Evaluation of Dossiers

- Implementing convergence, collaboration and networking based on reliance and trust, as well as built through joint activities, particularly for NRAs in LMICs.
- In this regard, the NRAs of Bangladesh and Nepal agreed that it is important to include key elements in defining the strategic planning for joint activities between NRAs.



Conclusion of the Workshop:
Benefits of reliance to regulatory authorities

- Regulatory cooperation and harmonization/convergence on evaluation of medical products is important to improve the performance of RMA function by NRAs of Bangladesh and Nepal.
  - This is possible since both NRAs of Bangladesh and Nepal are members of SEARN.
- Implementation of GRevPs and other common technical guidelines will help improve regulatory performance.
- Collaborations will contribute to the advancement of convergence. This could potentially lead to the application of facilitated regulatory pathways to accelerate regulatory review processes by condensing the elements considered in the review process and ultimately meet patients' expectations of timely access to medicines.

Challenges

- Adequate number of competent staff dedicated to performing RMA activities, particularly for innovative medicines, biologicals, and vaccines.
  - Currently, there are limited dedicated staff, although officers from other departments are also involved in supporting MA activities. Therefore, joint training and sharing experiences on MA activities between the two NRAs are of particular importance to build-up the trust for regulatory reliance.
- Differences in general aspects of regulatory system design i.e., legal and organizational structures, differences in processes and systems.
- Lack of existing framework for collaboration mechanism.

Recommendations: Next steps and priorities for NRAs

1. Establishment of a proposed **framework for joint assessment of medical products** between Bangladesh and Nepal covering components that support FRPs and utilizing the collaborative network through SEARN platform.

2. Provision of operational support for the implementation of collaboration between the NRAs of Bangladesh and Nepal:

   a) Preparation of a short-term plan for the visit of NRA, Nepal staff to NRA, Bangladesh for further in-depth discussion on the proposed framework, including the drafting of an MOU between both NRAs.

   b) Development of country ownership on the collaboration by outlining a return on investment of the new networks for both NRAs, and the importance of strengthening systems in parallel to convergence for the function of RMA.

   c) Continuation of regulatory capacity building to both NRAs to identify gaps and deficiencies in the process of RMA, and to help both NRAs prioritize areas for collaboration.

Resources

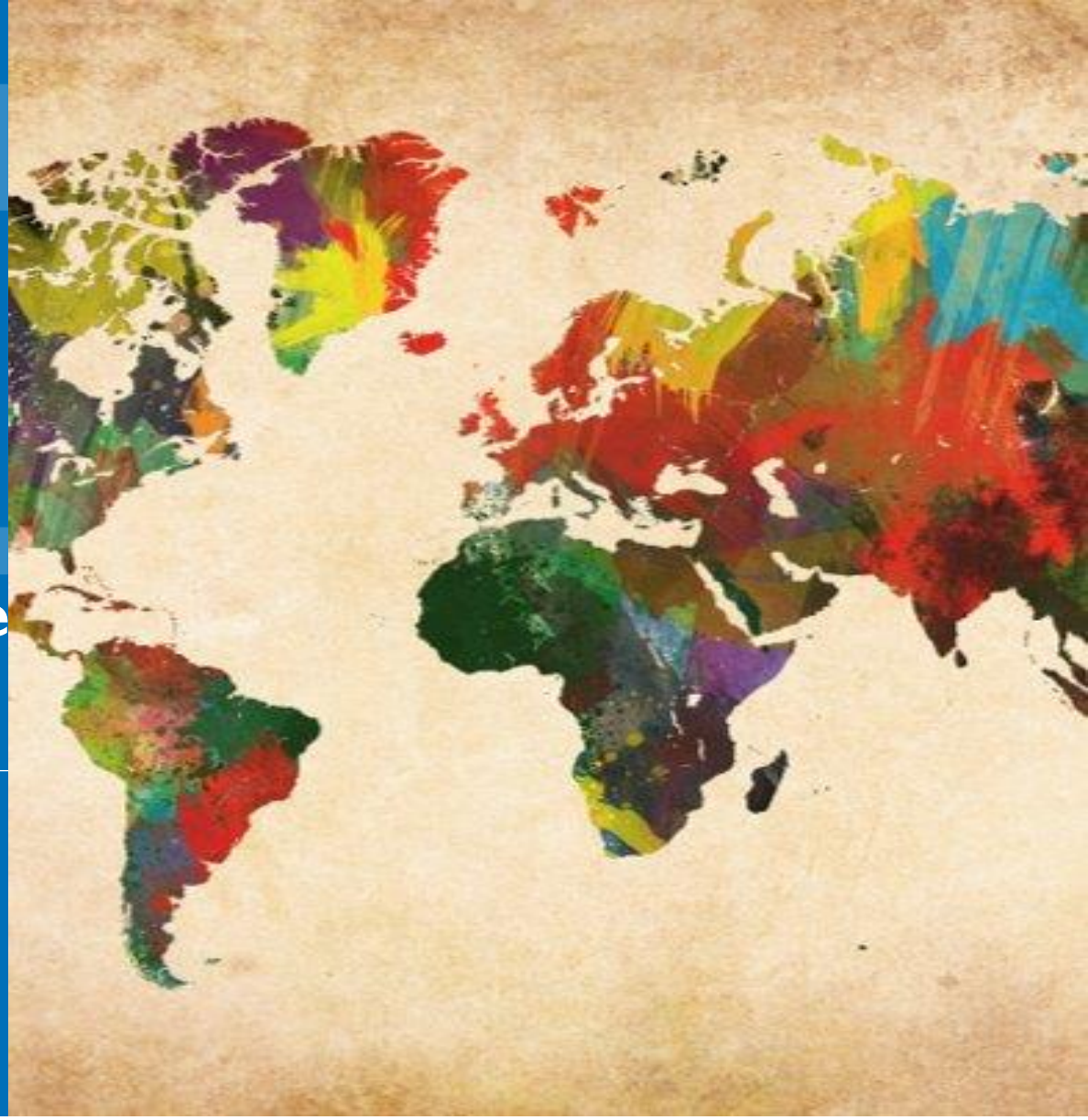
- Lucky S. Slamet, and Vivian Rakuomi: Capacity Building Workshop Report for Facilitating the Convergence of Technical Standards for Medical Products Registration for Bangladesh and Nepal, MTaPS, July 2022.
- Loice Kikwai : Training on Good Review Practices: Good Reliance Practices WHO GBT – Registration and Marketing Authorization, February 2023.
- Rochapon Wacharotayankun: Training on Good Review Practices: Good Review Practices: Overview and Principles, February 2023.
- WHO Technical Report Series No. 992, 2015, Annex 9: Good review practices: guidelines for national and regional regulatory authorities.
- WHO Technical Report Series No. 1033, 2021, Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations.

Promoting the Quality of Medicines Plus

Joint Assessment Procedures: Challenge and Opportunities

Mr. Sultan Ghani, Senior Technical Advisor, PQM+ Program

Mr. Jeyakhandan, Technical Advisor, PQM+ Program



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Outline of the presentation

- What is joint assessment procedures?
- Overview of product registration procedures
- Benefits of joint assessment for regulatory authorities
- Phases of Joint Review
- Reliance and Recognition
- Conclusion
- Next steps and priorities for NRAs
- Resources

What is Joint Assessment ?

- Joint assessment is a formal procedure in which simultaneously application is submitted to all participating National Medicines Regulatory Authorities (NMRAs).
- This Joint assessment (JA) procedure is an arrangement of work sharing by two or more NMRAs, where timelines and work allocation are negotiated in advance and decisions are communicated to the applicant.
- One NMRAs will serve as a Project Lead with responsibility for preparing, tracking and coordinating the JA plan.
- Each participating regulator is assigned a technical section of the dossier (e.g., Quality, safety, efficacy), and each review report is peer-reviewed by the other countries' regulators.

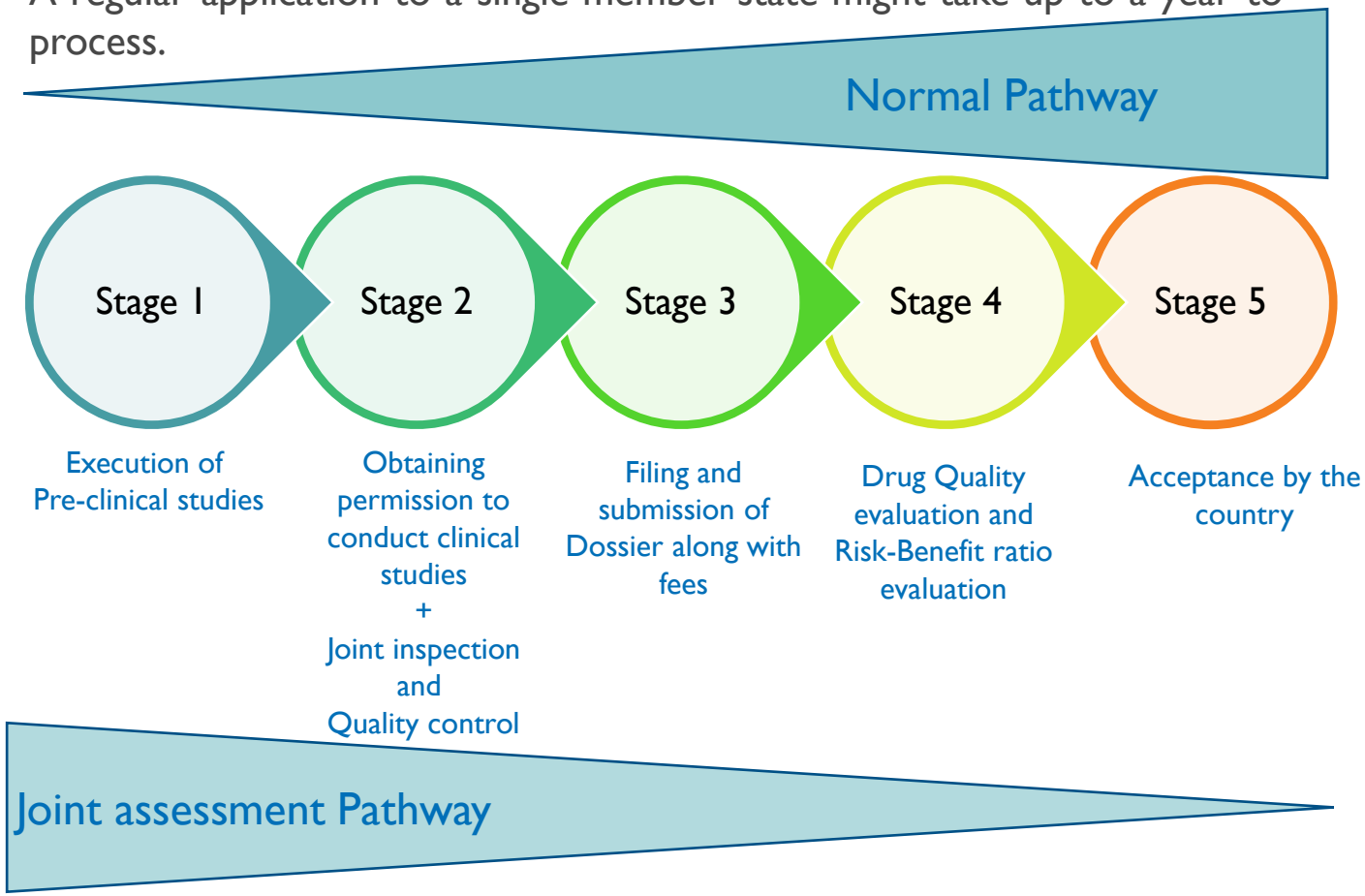
General Overview of Product Registration Procedures

- To improve public health by increasing rapid access to safe and effective medicines of good quality for the treatment of priority diseases.
- Focus on in-country registration as one factor in the time it takes for beneficial therapies to reach patients in need.

Registration Process in 5 stages

Time it takes for beneficiary to access the medicine – Longer.

A regular application to a single member state might take up to a year to process.

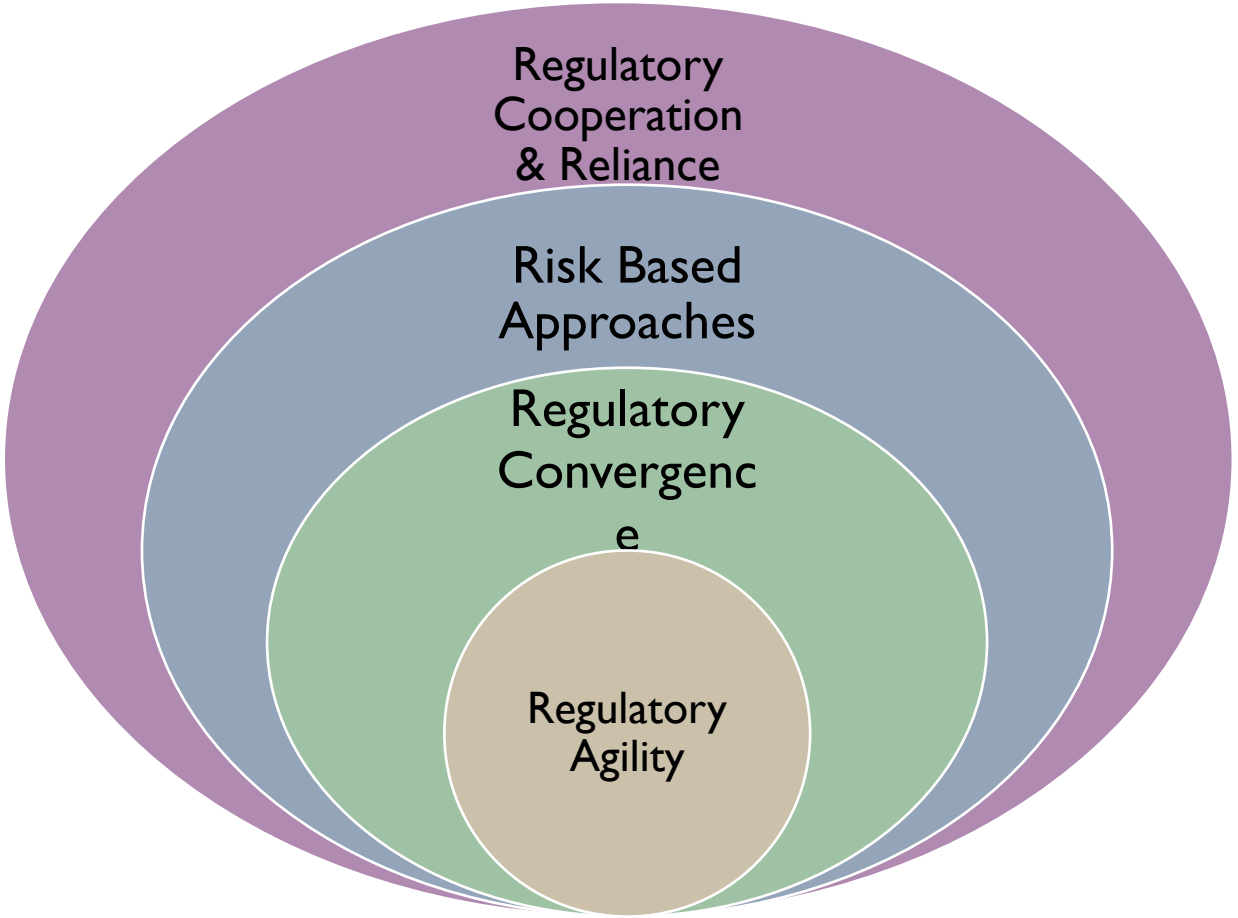


Time it takes for beneficiary to access the medicine – Relatively Short

Joint assessment take a maximum of 60 days—and fewer for expedited or emergency reviews.

Building Regulatory Agility

Regulatory agility should become part of regulatory "new normal" to support innovation and future public health challenges



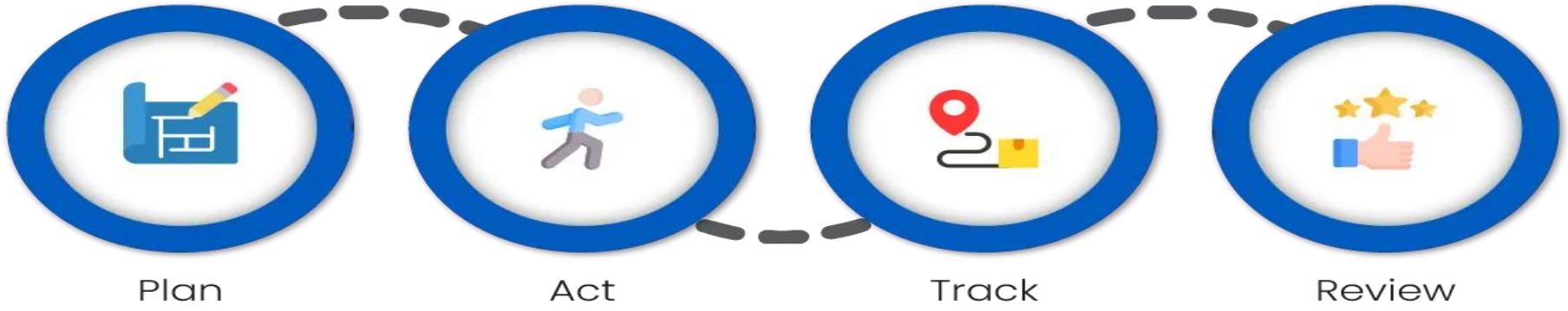
Convergence supports Regulatory Agility

Regulatory requirements become more aligned over time with adoption of internationally recognized technical guidance documents, standards and scientific principles, while considering distinctive national legislative, demographic and risk-tolerance factors

Topics applicable to all regulatory agilities

Reference taken from presentation 11th Asia Regulatory Conference - Regulatory Agilities Co-hosted by IFPMA & SAPI #ARC2022 17-21 October

Employing Range of Regulatory and Scientific Tools



Regulatory Tool/ Work Practices

- Rolling reviews
- Emergency Authorization
- Conditional Authorization
- Continuous communication
- Virtual Inspection.
- Post Approval Changes

Scientific Tool

- Alternative process validation approaches
  - Concurrent Validation
  - Decoupling DS & DP PPQ
- Prior knowledge/Platform
- Predicted Shelf life
- Reliance on data to be provided post approval

Benefits of Joint Assessment Procedure

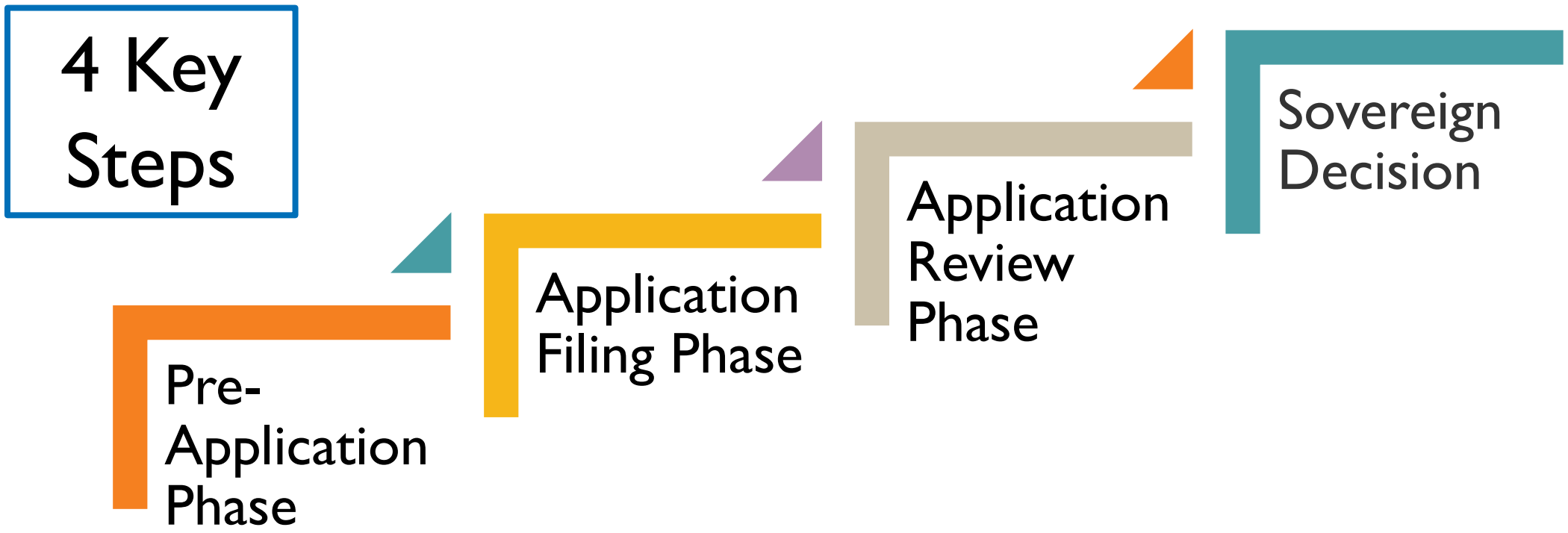
Benefits

- Reduced workload for NRA experts due to reduced need for in-country evaluations.
- Shorter regulatory approval times.
- Consistent and robust regulatory decisions.
- Maximizes efficiency by sharing the work.
- Builds a stronger global review community.
- Share knowledge and expertise.
- Independent, sovereign decision-making.
- Reduces administrative burden for industry.
- Simultaneous access to multiple major markets.

Factors contributed delays include:

- In country registration requirements such as mandatory submission of samples and repetitive in country performance evaluation.
- Inadequate communication between key participants.

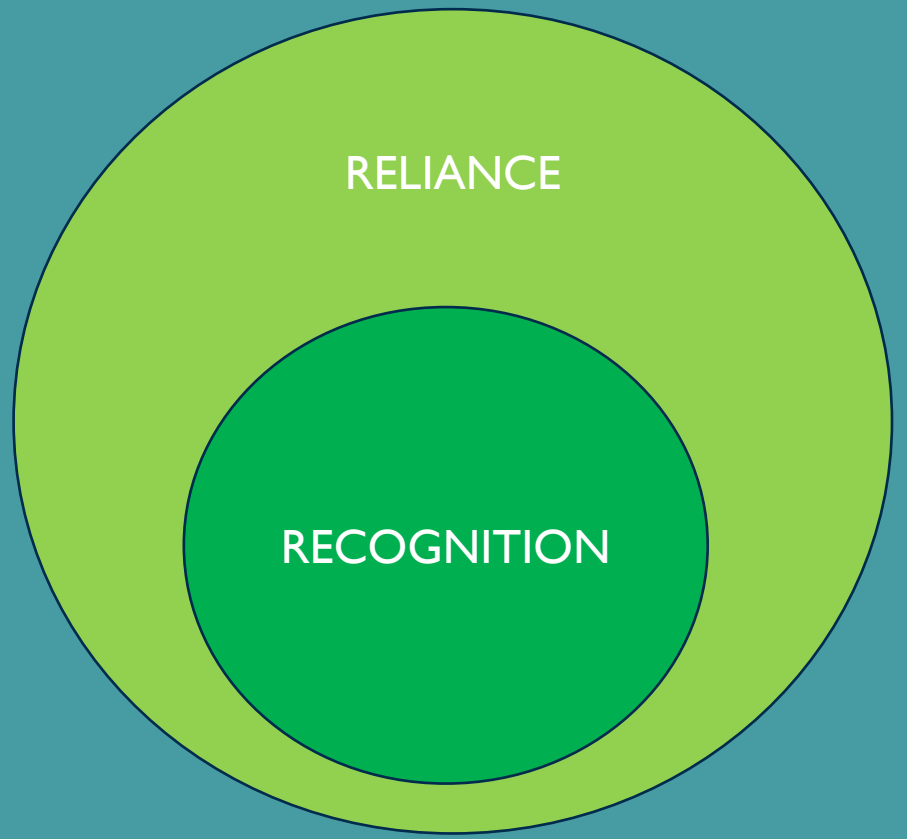
Phases of Joint Review



Documents	Location in ICH CTD	Location in ACTD
Administrative documents	Module 1	Part I
Common technical document overview and summaries	Module 2	Incorporated in Parts II, III and IV
Quality documents	Module 3	Part II
Non-clinical documents	Module 4	Part III
Clinical documents	Module 5	Part IV

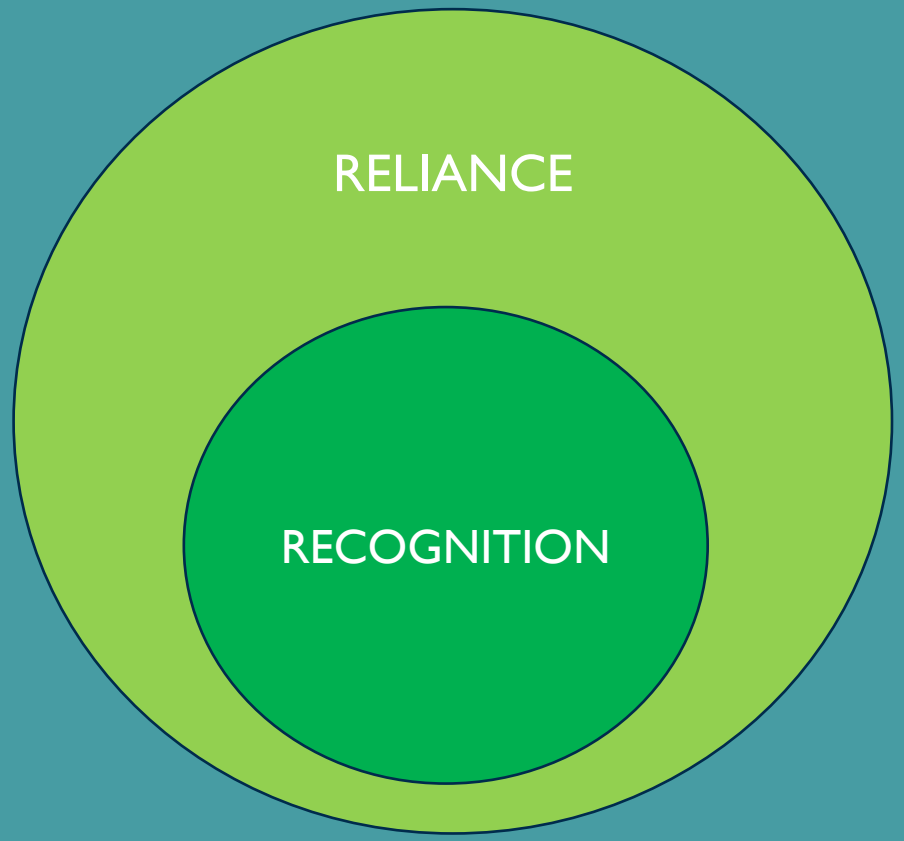
Reliance and Recognition

- Recognition is the acceptance of one regulatory authority dossier assessment by another authority.
- Recognition indicates the evidence of regulatory conformity requirement between the authorities.
- Recognition may be unilateral, bilateral, or multilateral.



Reliance and Recognition

- Reliance is the act whereby the regulatory authority in one jurisdiction give significant weight to the work (totally or partially) of another regulatory authority.
- The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions of other authorities.



- JA promotes harmonization and cooperation and develop reliance and recognition among regulatory authorities.
- JA have been successfully performed in several countries' regulatory authorities with different capacity, resources, and skills.
- JA improves access to essential medicines and building regulatory capacity and trust.
- JA promotes regulatory functions at higher level of competence, efficiency, and effectiveness.

Useful Reference

- https://globalforum.diaglobal.org/issue/september-2021/joint-assessment-of-marketing-authorization-applications-cooperation-among-asean-drug-regulatory-authorities/
- Health Canada: Guidance on Veterinary Drug Joint Reviews.
- BMJ Global Health: Regulatory reliance for convergence and harmonisation in the medical device space in Asia-Pacific Ming Xu ,1 Li Zhang,2 Xiangning Feng,1 Zhenyu Zhang,1 Yangmu Huang1
- Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators (2020) https://doi.org/10.17226/25594.


THANK
YOU

PROMOTING CONVERGENCE AND HARMONIZATION OF MEDICINE REGULATION IN ASIA

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USAID MTaPS Program

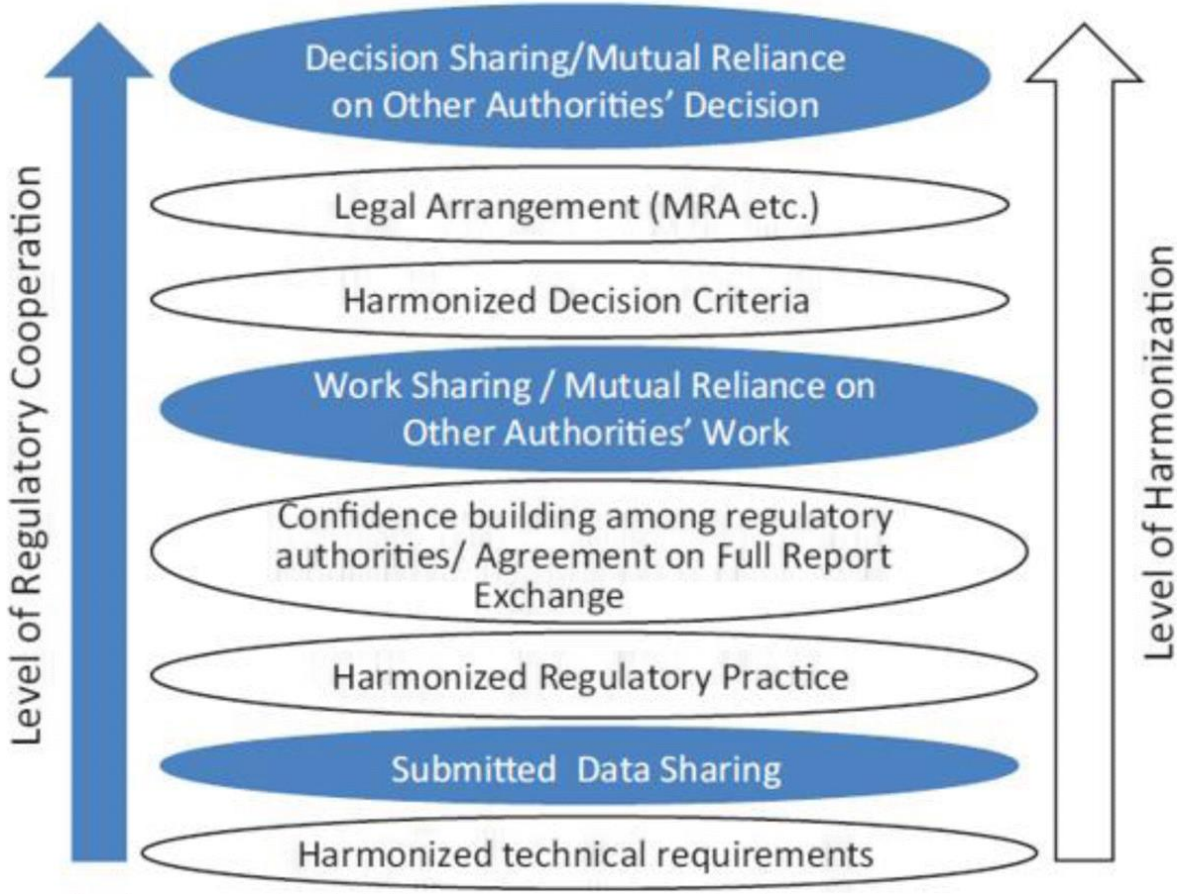
Outline

- Convergence and harmonization: What is it and why is it important?
- Cornerstone for convergence
- Application of reliance mechanisms for improved efficiency for product registration
- Facilitating registration system convergence within SEARN
- Capacity strengthening for product registration in ASEAN
- Challenges encountered
- Consideration for the future
- Resources

Overview of convergence and harmonization of regulatory standards

- **Convergence:** regulatory requirements in different countries or regions become more similar or 'aligned' over time (voluntary).

- **Harmonization**: uniformity of technical requirements across differing organizations within defined legal framework.



Tominaga T (2013) The ICH, the GHTF, and the future of harmonization initiatives. Therapeutics Innov Regul Sci 47:572

Why convergence and harmonization?

- Reduced amount of human and animal experimentation: One source code for the products.
- Reduced cost of development which can lead to lower prices (regulatory documentation both for new drugs and multisource/generic medicines is reduced).
- Common regulatory standards for scientific evaluation and inspection facilitate regulatory communication and information sharing.
- Local products are more likely to be acceptable for export to other countries.
- Faster access to medicines of high public health value (pediatric medicines, medicines for major diseases or for emergencies in national settings etc.).
- Increased competitiveness resulting from newly developed common markets.
- Enhanced regulatory capacity for participating NRAs.

Cornerstone of Convergence and Harmonization: Good Regulatory Practices and Global Benchmarking Tool

GRP Principles

1. Legality
2. Impartiality
3. Consistency
4. Proportionality
5. Flexibility
6. Independence
7. Efficiency
8. Clarity
9. Transparency

GBT Indicators

1. Legal provisions, regulations and guidelines
2. Organization and governance
3. Policy and strategic planning
4. Leadership and crisis management
5. Transparency, accountability and communication
6. Quality and risk management system
7. Regulatory process
8. Resources (HR, FR, Experts, Infrastructure, Equipment, and IMS)
9. Monitoring progress and assessing impact

Sources : Alireza Khadem, WHO / RSS

Cornerstone of convergence and harmonization
Regulatory Processes and Competencies

Regulatory Processes

1. Product registration
2. Licensing of establishments
3. Market surveillance and control
4. Regulatory inspections
5. Vigilance
6. Clinical trials oversight
7. Laboratory inspections
8. Lot release

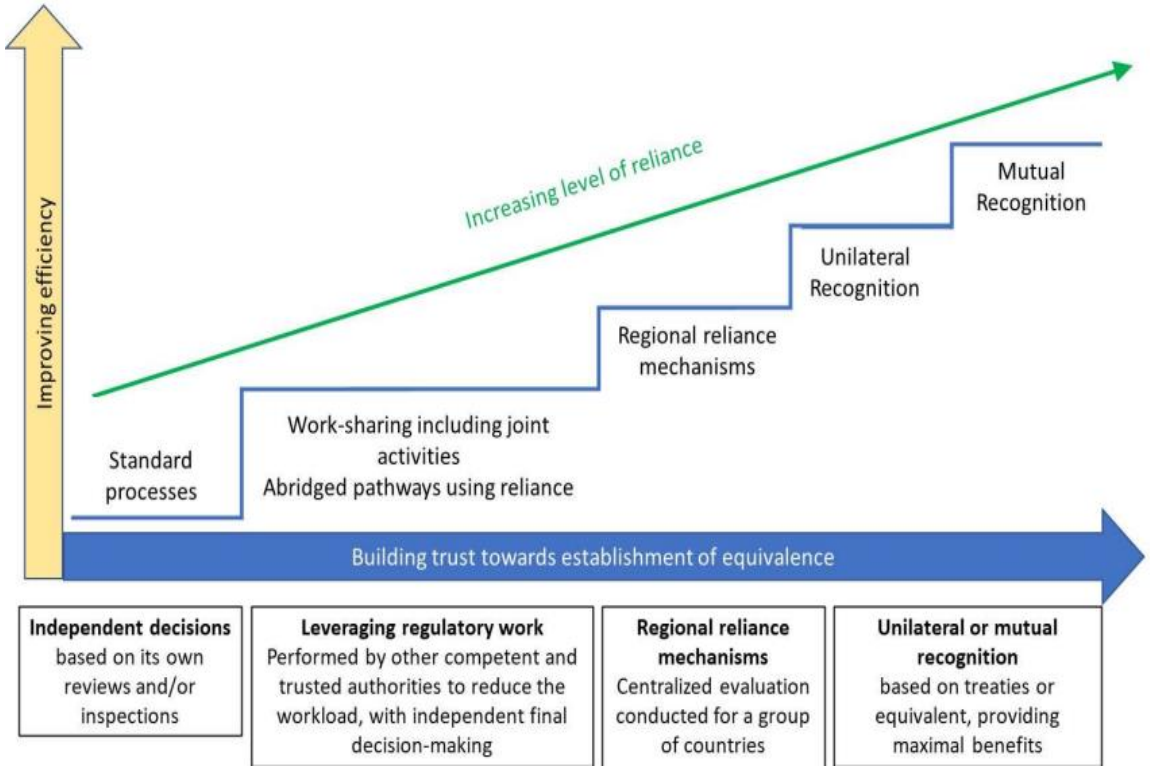
Regulatory Competencies

Meta competencies
Core competencies
Role-specific competencies

1. Collaboration
2. Communication
3. Decision-making
4. Evidence-informed practice
5. Personal conduct

Reliance as an aspect of convergence

Option for Regulatory Decision via Reliance Scheme



Facilitated participation of Bangladesh, Nepal and the Philippines in a course on application of good reliance practices organized by CORE Singapore (MTaPS partner).

Principles of reliance:

- Universality
- Sovereignty of decision-making
- Transparency
- Respect of national/regional legal basis
- Consistency
- Competency

Application of Joint Learning for Improved Knowledge Base for Product Registration

Case studies: Bangladesh and Nepal

- Capacity strengthening on Assessment of COVID-19 Vaccine Dossiers
  - Key principles related to joint assessment on evaluating vaccines, with a special focus on COVID-19 vaccines.
  - Practical skills on how to evaluate a dossier and develop a systematic approach to preparing interim and assessment reports with the recommendation for approval or rejection of the registration and MA application.

- Joint assessment processes
  - Defining the minimum requirements for submission of information on non-clinical, clinical, and quality data in a registration and MA dossier using the International Council for Harmonization (ICH) CTD format.
  - Implementing a systematic approach to evaluate the critical evidence of non-clinical and clinical data and the evidence of consistency of production, quality assurance, and compliance with existing standards regarding quality data.
  - Compiling a record of the evaluation process and findings.
  - Preparing an evaluator's report of the findings.
  - Preparing a recommendation for registration/rejection.

Convergence Mechanisms for Improved Product Registration Systems
Case studies: Bangladesh and Nepal (as of July 2022)

Capacity building workshop held on facilitating convergence of technical standards for medical products registration.

- Legal mandate or Act and regulations requiring marketing authorization of all medical products before placing the product on the market.
  - To withhold, suspend, withdraw, or cancel an MA if there are concerns regarding quality, security, and equiomент (QSE) issues.
  - Legal implementation supported by governance and leadership structures.
- Quality management systems(QMS) implementation for product registration function.
  - Nepal's NRA still finalizing their QMS improvement.
- Product registration regulations and guidelines aligned to WHO standards.
  - DDA Nepal to adopt CTD format for MA application.
  - NRAs of both countries to have provision that allows them to recognize and/or rely on MA-relevant decision, reports or information from other NRAs or regional and international bodies.
    - Could be done between NRAs of Bangladesh and Nepal as both NRAs are members of SEARN that support closer collaboration and cooperation for joint assessment.
    - A formal coordination framework for example an MoU should be established.

Capacity Strengthening of Regulatory Workforce
Case studies - ASEAN

Training of trainers on evaluation of biological products, including vaccines.

- Current global regulatory requirements for product registration and evaluation of biological products
  - General regulatory framework especially for vaccines.
  - Regulatory and scientific challenges during the evaluation of biological products.
  - The principles for developing biological products and the key elements to be considered (quality aspects, preclinical aspects, and clinical aspects).

- Expected outcomes
  - Understanding of various guidelines being used by the regulatory authorities in ASEAN and internationally.
  - Establishing a structured level of proficiency for evaluation of vaccines by NRAs.
  - Improve access to COVID-19 vaccine of assured quality, safety and efficacy/immunogenicity.
  - Promote convergence of application of technical standards for registration of biologics and vaccines and build trust and confidence among the ASEAN NRAs.

Application of Good Review Practices in ASEAN Member States
Case studies: ASEAN

Training on Good Review Practices

- Improving knowledge on the essential principles of WHO guidance on GRevP guidelines in ASEAN nations
  - WHO good practices to enhance regional capacity to review applications for market authorization.
  - Application of GRevP principles and adopting GRelP within a regional context.
  - Promote adoption of international regulatory standards.
  - Benefits of WHO CRP for NRAs.

- Framework for implementation of GRevP in line with WHO recommendations
  - Policies to govern implementation of regional GRevP.
  - Responsibilities and procedures for participation by NRAs.
  - Process to evaluate the regional need for GRevP.
  - Implement GRevP at a regional level.
  - Evaluate the effectiveness of GRevP implementation.

Challenges

- Differences in general aspects of regulatory system design i.e. legal and organizational structures, differences in processes and systems
  - Resources (Human, Technical)
- Lack of existing framework for collaboration mechanism
  - Confidentiality requirements for review of dossier
  - Joint Assessments
  - Work-sharing
  - Reliance

Future Considerations

- The NRAs should benchmark their regulatory activities against the WHO recommendations. A gap analysis for improvements should be developed, and recommendations for implementation should be outlined and executed.
- NRAs should implement training plans on key principles of regulatory functions through developing action plans, SOPs, and evaluation metrics for key indicators.
- Develop and implement frameworks on collaborative activates on convergence and harmonization including CRP and GReIP.
- Enhance regulatory capacity through a phased level of proficiency:
  - Foundational, Intermediate, Advanced

Resources

- Lucky S. Slamet, and Vivian Rakuomi: Capacity Building Workshop Report for Facilitating the Convergence of Technical Standards for Medical Products Registration for Bangladesh and Nepal, MTaPS, July 2022 (currently being finalized)
- Loice Kikwai, Rochapon Work: Training on Good Review Practices (currently being finalized)
- WHO Competency Mapping Framework and Implementation Tool
- MTaPS/PQM+ Course Evaluation and Training Report: Training of trainers on evaluation of biological products, including vaccines (currently being finalized)
- WHO Technical Report Series No. 992, 2015, Annex 9 : Good review practices: guidelines for national and regional regulatory authorities https://www.who.int/publications/m/item/annex-9-trs-992
- WHO Technical Report Series No. 1033, 2021, Annex 10 : Good reliance practices in the regulation of medical products: high level principles and considerations https://www.who.int/publications/m/item/annex-10-trs-1033

FACILITATED Q&A AND STRETCH

Andrew Brown
Principal Technical Advisor, Governance and Capacity Building
USAID MTaPS Program

Effective Registration System for Medical Products and Collaboration with Regional Network

Md. Salahuddin
Director, DGDA, Bangladesh

DGDA

Directorate General of Drug Administration is the national regulatory authority of drugs and Medical Devices in Bangladesh

Regulatory Inspection in Bangladesh

As per Drug (Control) Ordinance 1982:

(1) Every manufacturer of drugs shall follow the good practices in the manufacture and quality control of drugs recommended by the World Health Organization.

(2) If any manufacturer does not follow such good practices its manufacturing license may be cancelled or suspended.

GMP implementation is ensured through inspection by the competent inspector of DGDA on regular basis.

Standards, Guidelines followed by DGDA:

- DGDA follows WHO guidelines which is supported by our law. Also, we follow ICH & PIC/S Guidelines.
- For GMP main concept TRS 986 (Annex-II)
- For Sterile Products TRS 961 (Annex-VI).
- For Biological Products TRS 822 (Annex-I) replaced by TRS 996 (Annex-III).
- For GMP for API 957 (Annex II).
- For evaluation of Water System TRS 970 (Annex II).
- For Stability Testing TRS 1010 annex 10.
- For Validation TRS 937 (Annex IV).
- For Quality Risk Management (QRM) TRS 981 (Annex II), ICH Q9
- For Data requirement for change of approved vaccine TRS 993 Annex 4.
- Preclinical evaluation of vaccines TRS 927 annex 1.
- Clinical Evaluation of vaccines TRS 1004 annex 9.
- ICH M4, Common Technical Document (CTD).
- Guidelines for Registration of Biosimilar Products, 2018 etc.,

Product Registration:

Products are categorized as:

(a) new product (Unintroduced Product)

(b) introduced product.

New product (Unintroduced Product) registrations issued on the basis of recommendation of Drug Control Committee (DCC).

For Vaccine Registration : additional 2 (two)- Expert committees are in place.

1. Expert committee on Chemistry, Manufacturing & Control (CMC)

2. Expert committee on Toxicology and Clinical Trial. For Medical device registration an expert committee consist of members of biomedical engineering and specialists of different medical fields.

Registration of Local Products:

For registration of local products DCC considers whether the product has been registered by USFDA, UKMHRA or included in British National Formulary (BNF). Registrations and Marketing Authorizations are issued for 5 years.

Registration Requirements

- **Vaccines-Biologics:** It is a standardized and harmonized system. An applicant has to apply in CTD format using RIMS software/ Apps and to submit hard copies of CTD format of dossier. Vaccines and Biosimilar registration guidelines are in place.

- **Generic Drugs**: Applicants for Generic Drugs have to submit application by filling up and submitting documents as per DA-form 1/88 for introduced molecules and DA-form 2/88 for unintroduced molecules, data according to these checklists together with details information of R/M, excipients, test protocol, process validation protocol and accelerated and real time stability study data for 6 months of 3 consecutive R&D/ pilot batches.

Registration Procedure

- Recipe Approval/ Pre-registration approval : Unintroduced all molecules (chemicals, biologicals) are reviewed and recommended by Drug Control Committee (DCC).

- Introduced molecules are reviewed by DGDA officials of generic drug evaluation department.

- Registration of Generic Drugs: After getting Pre-registration/ Recipe approval applicant has to apply for registration with all documents as Dossier. Applicant has to submit commitment letter for real time stability data to be submitted.

- Evaluation of submitted data/ dossier is being performed by DGDA officials of Generic drugs.

- Evaluation also made the manufacturers' capacity interims of production and Q/C facilities and HR . This is not harmonized system.

Continuation

- **Testing** : Samples are tested in DGDA lab (non pharmacopeial INN products, Vaccines, Biosimilars are tested before registration and BP/USP generics are tested of 1st commercial batch in DGDA lab).
- **Medical Devices** and **Invitro Diagnostics** registrations are based on the guidance given in "DGDA Medical Devices registration guidelines" on the basis of risk based classification such as class B (moderate risk), C (moderate high risk) and D (high risk) are registered, Class A (low risk) devices are not registered.
- For imported medical devices are registered on the basis of reliance mechanism on other and listed regulatory authorities.
- **Class B** is registered on the basis of Free sale certificate (FSC) from country of origin, ISO/IEC 13485 compliance certificate and CE marking certificate.

Continuation

- **Class C and D a**re registered on the basis of Free sale certificate (FSC) from country of origin, ISO/IEC 13485 compliance certificate and CE marking certificate and FSC from EU countries, USFDA, PMDA, TGA, UK MHRA, Health Canada.
- Locally manufactured medical devices are approved on the basis of their production and quality control facilities as well as ISO/IEC 13485 compliance.
- Registration and Marketing Authorization for Vaccines and Biologics department is responsible for registering and issuing MA certificate of a vaccine-biologics/ biosimilar Products as well as vaccines, biologics/biosimilar bulk, post market variation approval for Vaccines and Biological products, legal mandate, established procedures and guidelines are in place. Similar Generic Drug department is responsible for generic drug registration related issues.

Continuation

- Licensing of Premises (LI) dept. is issuing premises license for registering vaccines plant, established procedures and guidelines are in place. Inspection takes place by competent team of inspectors.
- Vigilance dept. is responsible for taking care of adverse event and regulatory decision on the basis of vaccines related SAEs.
- Market surveillance and control dept. is taking sample for testing and oversee market for post-marketing surveillance, control SF drugs through Risk based sampling, screen by mini-lab, regularly surveillance activities by sudden operation gathering information and take punitive action by lodging cases in Drug and Magistrate courts.

For Imported Drugs Registration

- DCC considers whether the drugs/ Vaccines and Biologics are registered in the same brand name out of one of the following countries- USA, UK, Switzerland, Germany, France, Japan and Australia or the product is registered by EMA. CoPP from any of the said NRAs.
- WHO PQ products are considered case to case basis.
- For Public health emergency Covid -19 vaccines are expeditely issued EUA if it got EUA from country of origin and having satisfactory safety and efficacy data of Phase iii trial and recommended by Public Health Emergency Committee on Covid-19 vaccine, IVD, IND, new biologics to combat Covid-19 infection.

Harmonization and Standardization of Regulatory System and Cooperation, Collaboration with other NRAs, DPs and Regional Network

- DGDA has been working since 2016 for strengthening of Drug Regulatory system, Harmonization of Drug Registration system. We are on the verge of achieving WHO maturity level 3.
- Vaccines, Biologics/Biosimilars registration system is harmonized with ICH / WHO standards.
- Reliance on reference stringent regulatory authorities: DGDA adopts reliance mechanism for import medical products registration.

MTaPS Cooperation to DGDA

- DGDA- RIMS, a registration software provided by MTaPS, a platform to submit application for Registration.
- CTD dossier Evaluation of vaccine products combinedly took place with Nepal and Indonesia.
- Competency mapping for DGDA officials.
- 5-year Strategic Plan.
- PV support.
- IT support.

Collaboration, Cooperation, and Continuation

- For approving a new molecule (unintroduced molecule) for local manufacture, it also reliance on USFDA and UKMHRA (if a molecule is approved by FDA and MHRA , DGDA considers).
- DGDA is very active member of SEARN.
- We are one of regulatory agencies for collaborative evaluation of NIPAH and Chikun Gunya Vaccines Dossier supported by CEPI
- For Public health emergency issue DGDA is always looking forward for collaboration and cooperation with other NRAs and leading International health related organizations including WHO.

Website links

- DGDA website : http://www.dgdagov.info
- DGDA Guidance Guidance documents: http://www.dgdagov.info/index.php/information-center/guidance-documents
- DGDA Checklist for application for introduced molecule:DA-1 Form /88 da1-88.pdf
- DGDA Checklist for application for introduced molecule:DA-1 Form /88 da2-88.pdf

FACILITATED Q&A

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CLOSING

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