World Health Organization

WHO's Approach to Promoting Reliance

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WHO's Regulatory Activities:

Aiming to assist countries in building efficient sustainable regulatory systems

- Global Benchmarking Tool (GBT) to assess NRA capacity and identify gaps, followed by assisting NRAs to develop Institutional Development Plan (IDP)
- Moving from the concept of "Stringent Regulatory Authority (SRA)" to "WHO Listed Authorities (WLA)" based on the GBT
- Promoting reliance and facilitated market authorization, including joint assessment and Collaborative Registration Procedures (CRP)
- Supporting convergence/harmonization and regulatory networks:

  e.g., AMRH, ASEAN, ICH, ICMRA, IPRP, SEARN

- International Conference of Drug Regulatory Authorities (ICDRA)
  18th ICDRA recommendations (Dublin, Ireland: 3-7 September 2018)
- Coalition of Interested Partners (CIP)
- Pharmacovigilance preparedness

Current regulatory challenges:

- Regulatory authorities under mounting pressure to improve performance and facilitate timely access to safe, effective and quality innovative medical products
- Task has become more challenging due to globalization, increasingly complex technologies and growing public expectations
- No where are these challenges more acute than in low and middle income countries (LMICs)

“Reliance” is gaining recognition

- No longer a question of ‘if’, but when and how
- About smart regulation and investment
- Occurring amongst even most resourced regulatory agencies
- Benefits don’t accrue by magic – requires framework and planning
- One element of a larger international strategy and toolkit

Definitions:

Reliance:

act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.

Recognition:

the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

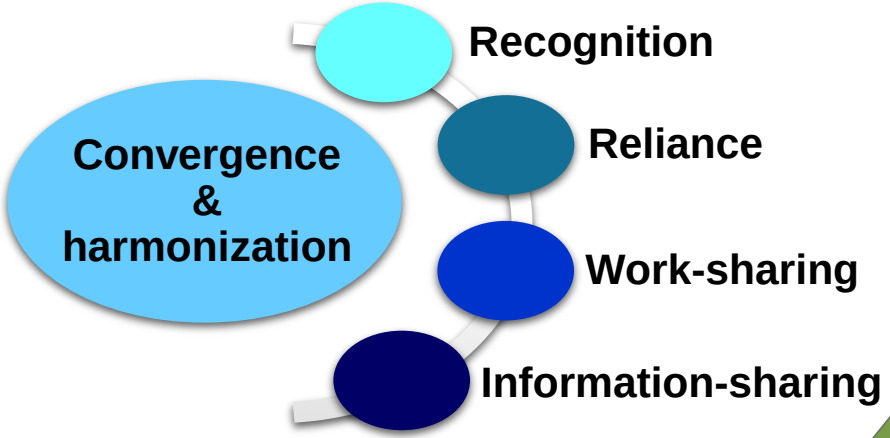
From Reliance to Recognition

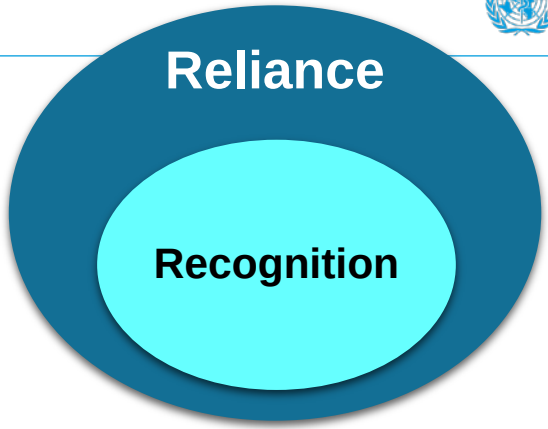
Reduction:
Streamline / reduce internal work

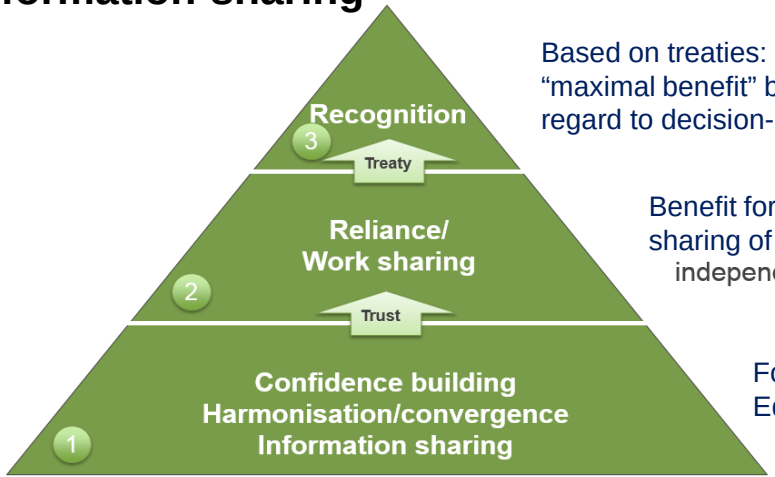
Replacement:
operationally, rely on decisions

- Both terms reflect concept of ‘relying on’ or ‘taking account of’ the output of other agencies
- May be unilateral or mutual
- May also be part of step-wise approach (confidence building) leading to recognition
- *Sovereignty maintained in both cases*

Reliance and Recognition







Based on treaties:
"maximal benefit" but partial loss of sovereignty with regard to decision-making

Benefit for regulators:
sharing of workload, but independent decisions
independent decisions

Foundation:
Equivalence of requirements

WHO's role in promoting reliance (1):

a multifaceted approach

- Development of international norms and standards – the cornerstone
- Support for convergence, harmonization and work-sharing through regulatory networks (technical requirements, joint work, capacity-building)
- Integral to the benchmarking of regulatory systems and institutional development plans
- Prequalification program and use of collaborative registration procedures to expedite national registrations – now extended to products approved by advanced regulatory authorities

WHO's role in promoting reliance (2):

a multifaceted approach

- Increasing body of guidance on reliance (good regulatory practices, desk-based inspections, strategies on the effective use of assessment reports)
- Secure platforms and process for exchange of non-public information (e.g., NCL Network for Biologicals)
- ICDRA and pre-ICDRA meetings: theme and recommendations from 14th, 17th and 18th meetings
  - Importance of reliance, transparency and trust
  - Taking account of one another's work to improve the efficiency of the global regulatory system
- On the horizon… *WHO-listed authorities (WLA)*

The message:

Regulatory systems should be science based, respect international standards and best practices, and adopt an approach that focuses on what cannot be done by others while leveraging the work of other trusted regulators and institutions for the rest

When can ‘reliance’ be used? (1)

Normal times:

- Resources insufficient to perform all required functions
- Resources may be sufficient but can be put to better use – reduce duplication

Emergencies:

- Timely access to therapies through use of evaluations performed by another regulator or other trusted institution to facilitate decision making

When can ‘reliance’ be used? (2)

Some elements of regulatory oversight can be shared:

- Evaluation of quality, efficacy and safety
- Inspections
- Lot release
- Pharmacovigilance (pre approval: clinical assessments (RMP); post approval: joint PV assessments, inspections)

Other elements of regulatory oversight must be local:

- Benefit/risk evaluation
- Licensing decision
- Local manufacturing oversight
- Pharmacovigilance (local reporting)
- Good distribution practices

WHO Survey on ‘reliance’

- WHO circulated a survey to IPRP* members – October 2018
- Detailed responses from 9 members:

  ANVISA, US FDA, EU, Health Canada, HSA, MHWL/PMDA, Swissmedic, TFDA (CT), TGA
- Wealth of information and suggestions:
  - Clear and consistent messages
  - Some novel ideas
  - Served to guide next steps

Of note: responses from predominantly high-income countries with mature regulatory systems – representative of low- and middle-income countries?

*IPRP: International Pharmaceutical Regulators Programme

Survey questionnaires:

1. *Does your agency practice reliance?*
2. *The WHO has developed definitions for reliance and recognition. Should other terms also be defined?*
3. *Please provide examples of reliance undertaken by your agency or by other agencies to your agency. Describe impact and outcomes.*
4. *Which authorities and institutions serve as a reference for reliance for your agency? Why were they chosen?*
5. *What are the key lessons learned to date in the use of regulatory reliance?*
6. *Why do you practice reliance? Has the use of reliance by your agency had the desired outcome?*
7. *What have been the main challenges and areas for improvement?*
8. *What do you see as the greatest future opportunities for reliance?*
9. *Do you have any further suggestions or comments on the subject of reliance?*

Definitions:

- Key terms/definitions essential for ensuring common understanding and interpreting guidance
- Reliance: only information-sharing or include work-sharing ?
- Equivalence: pre-requisite to reliance/recognition - implicit in terms used such as ‘comparable’, ‘capable’, ‘similar’

Rationale for choice of referenced agencies

- Establishing confidence that the referenced agency has ‘similar requirements’, or that where differences exist they are known and may be accounted for
- Criteria for selection of referenced agency:
  - Longstanding ‘reputation‘ in international community
  - Established experience in working with the reference agency
  - Availability of reports and experience gained through use of inspection and assessment reports
  - Direct assessment of requirements and system as part of MRA process

….all towards establishing trust and confidence

Perceived benefits

- Common and expected:
  - Regulatory efficiency (faster review, time to approval)
  - Regulatory effectiveness (prioritizing of inspections)
  - Regulatory capacity (insufficient resources to do everything)
  - Quality: of reviews/inspections/regulatory system
  - Regulatory convergence and reduction of country-specific requirements
  - Potential for promoting greater collaboration
- However, responses also reflect aspirations ('potential', 'limited experience', 'complex') ***…so are benefits fact or fiction, and how to objectively measure?***
- Probably a mix at this point, with some clear successes

Challenges

- Differences in report formats, level of detail (what reported versus what assessed), language, regulations, technical requirements, regulatory practices and ‘risk threshold’
- Buy-in: both industry and the technical community within authorities
- Need to maintain scientific competence and clinical judgement in decision-making and labelling, bridging decisions in other countries to local benefit-harm context
- Secure platform and procedures for the exchange and management of non-public information
- Metrics: how to measure and document success?

The increasing importance of transparency

- Transparency vital in building trust

  For example:

  - Unredacted reports shared with sponsor?
  - Information available on website?
  - Policy and procedures for sharing with other regulators?
  - Ability to interact with reference agencies?
- Also raised in relation to early approvals and post-market safety issues
- Emphasis placed on understanding what *stands behind/supports regulatory outputs and decisions*, including good regulatory and review practices

A new proposal aimed at promoting reliance:

WHO Listed Authority:

- Term ‘Stringent Regulatory Authority (SRA)’:
  - defined as original ICH member/observer,
  - developed to guide procurement decisions
- Widely used and recognized
- However growing concerns with term SRA:
  - with the fact that ICH doesn’t have remit or competence to assess regulatory capacity;
  - coupled with expanding membership
- WHO expert committee considered new WHO proposal in October 2017

Expert Committee recommendations:

- Term SRA be replaced by “WHO-Listed Authority” (WLA)
- Currently identified “SRAs” will be regarded as WHO-Listed
- Designation of additional NRAs be based on WHO Global Benchmarking Tool (GBT) + completion of ‘confidence-building process’
- Procedure for listing be developed through public consultation process
- *Status: concept note expected to be released shortly with 6-week comment period*

Considerations:

- Voluntary process – undertaken at request of country with the understanding that outcome to be made public
- WLA will include both ML 3 and ML 4 authorities. Listing will specify
- WLA ML 4 equivalent to SRA; however both WLA ML 3 and ML 4 expected to adhere to international standards and practices within the scope of designation
- Process must be transparent, robust and equitable to have intended effect
- Renewal process, including of former SRAs, to be developed taking into account existing assessments and evidence
- Must ensure continued supply of quality assured products for use by UN procurement agencies and countries
- WLA designation not intended to affect regional designations

Benefits of WLA:

- Provides pathway for regulatory authorities to be globally recognized and thereby help guide procurement decisions on medical products, including for products not eligible for prequalification
- Provides a robust framework to promote trust, confidence and reliance, enabling efficient use of regulatory resources
- Encourages investment in and continuous improvement of regulatory systems
- Expands the pool of regulatory authorities contributing to efficiency of Prequalification program through increased use of abridged procedure
- Creates an enabling regulatory environment for innovation and local production

WHO Good Regulatory Practices: background

14th International Conference of Drug Regulatory Authorities (ICDRA), 2010

- *Collect **best practices** of collaboration and cooperation between NRAs including information exchange, joint assessments and inspections and activities aimed at reducing duplication*

Regulatory framework (WHO NRA Forum, Bangkok, May 2011)

- Included themes on harmonization of regulatory initiatives and standards and sharing of information, as well as international and regional coordination and networking

Feedback from assessments of National Regulatory Authorities conducted by WHO between 1997-2014

- Request for guidance on how to develop legal frameworks, building transparency and have an efficient communication strategy

Development of **WHO Good Regulatory Practices:**
Guidelines for national regulatory authorities for medical products

Framework of Best Practices

for Regulation of Medical products

GRP Umbrella Statement

Global Regulatory Model

Good Regulatory Practices

Good Review Practices

Good Governance Practices

Regulatory Pathways: Good Registration Practices

Good Reliance Practices

Good Guidance Practices

Quality Management System for Regulatory Authorities

Performance Measurement

Models for Regulatory Systems

WHO GRP: Scope

- The guideline outlines internationally accepted principles of regulation of **medical products for human use**
- Is intended for NRAs and other related institutions responsible for the formulation of health policies, laws, regulations and guidelines
- Will assist WHO Member States in the implementation of GRP, both in **establishing new regulatory systems for medical products and in improving the existing ones**

WHO GRP: Outline of the Guideline

Part 1:

Principles of GRP

- Legality
- Consistency
- Impartiality
- Proportionality
- Flexibility
- Clarity
- Effectiveness
- Efficiency
- Transparency

Part 2:

Implementing GRP

- Policy-making process and regulatory impact analysis
- Drafting regulation to increase compliance
- Regulatory consultation
- Monitoring and Evaluation – Assisting effectiveness and efficiency

Appendices:

- Legal instruments and alternatives
- Iinternational regulatory cooperation
- The process of regulatory impact analysis

Benefit of the WHO GRP Guidelines

- Responds to requests from Member States *for guidance on how to develop legal frameworks*
- Foundational document that applies internationally accepted principles of GRP to the regulation of medical products
- Relevant to all regulators, irrespective of resources and system (centralized/decentralized/network)
- One in a series of "best practices" guidelines – an "umbrella guideline“;
- Will be followed by practical implementation tools (e.g., Good Reliance Practices, etc.).

A world where every child, man and woman has **access** to the quality essential medicines, vaccines and other health products they need to lead a healthy and productive life.

thank you for your attention

ご聴取　ありがとうございました。

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