World Health Organization

WHO's Approaches 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) and deployment of products in emergency settings
- Supporting convergence/harmonization and regulatory networks:

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

  WHO-IPRP survey

WHO's role in promoting reliance

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
- New Concept *WHO-listed authorities (WLA) – concept note out for consultation*

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
- These challenges are most acute 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
- But challenges to “operationalise”

WHO Survey on ‘reliance’

- WHO circulated a survey to IPRP* members – October 2018

Detailed responses originally from 8 members: ANVISA, US FDA, Health Canada, HSA, MHWL/PMDA, Swissmedic, TFDA (CT), TGA

Additional responses received from EU (EC/EMA), CECMED, COFEPRIS, MEDSAFE, Roszdravnadzor, TITCK

Wealth of information and suggestions from a total of 14 respondents, including one regional entity (EU):

- Clear and consistent messages – reinforced by new inputs
- Some novel ideas
- Multiple examples
- Serves to guide next steps

*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 – responses (1)

- Support for additional definitions, including equivalence, facilitated regulatory pathways (FRP) - including simplified/accelerated registration, work-sharing
- Number of terms/definitions currently in use or proposed
- Reliance: only information-sharing or include work-sharing (‘multi-lateral information sharing’)?
- Equivalence: pre-requisite to reliance/recognition; ensure coherence with SPS
- Implicit in various terms used to describe regulatory equivalence/alignment: ‘comparable’, ‘capable’, ‘similar’
- New term to consider: WLA

Definitions – responses (2)

- Facilitated *regulatory* (*versus registration*) pathways can be applied in broader sense, over product lifecycle; may or may not involve reliance
- Key terms/definitions essential for ensuring common understanding and interpreting guidance
- Common repository – helpful to describe various options/approaches that can favour efficiency of regulatory processes based on scientific evidence and GRP
- Support for WHO to undertake this work – Good Reliance Practices

Rationale for choice of reference agencies

- Underpinning all responses: principle of establishing that the referenced agency has ‘similar requirements’, robustness or ‘level of control’, or that where differences exist they are know and may be accounted for – i.e. *familiarity and trust*
- Criteria for selection of reference agency:
  - Longstanding ‘reputation‘ in international community
  - Established experience in working with the reference agency and WHO, including bilaterally, internationally
  - Availability of reports and experience gained through use of inspection and assessment reports
  - Direct assessment of requirements and system as part of MRA process; could include joint or observed work
  - Proximity and commonality of products

Rationale for choice of reference agencies

- Degree of effort undertaken in establishing equivalence also proportional to perceived level of risk (nature of products and area of reliance); may be greater where recognition (of decisions) involved
- Importance of knowing what stands behind/supports regulatory outputs and decisions, including good regulatory and review practices, etc.
- Challenges: time and effort in establishing similarity and differences, including report formats, level of detail (what reported versus what assessed), language, regulations, technical requirements, regulatory practices, standards for employees, etc.

Perceived benefits (1)

- Common and expected:
  - Regulatory efficiency (faster review, time to approval)
  - More effective use of resources (prioritizing of inspections)
  - Reduced duplication of effort
  - Quality of reviews/inspections/regulatory system
  - Strategy to address resources - insufficient resources to do everything in increasing globalized and complex world
  - Increased regulatory convergence and reduction of country-specific requirements
  - Potential for promoting greater collaboration

Perceived benefits (2)

- However, responses also reflect aspirations ('potential', 'possible', 'limited experience', 'still early to tell', 'complex', etc.)

…so are benefits fact or fiction, and how to objectively measure?

- Observation – probably a mix at this point
- Clear advantages and savings in some cases (for example, reduction in/prioritization of audits/inspections)
- For others, matter of gaining sufficient experience or refinement in approach, taking into account lessons learned
- Nonetheless, support for formalizing and making better use of reliance, in some instances following introduction of necessary enabling legal provisions and policy
- Number of agencies also expressed desire or plans to participate in work-sharing arrangements

Challenges and considerations (1)

While reliance holds great potential, a number of recurring challenges and considerations were identified:

- Existing differences in regulatory systems (see previous slide) and need for upfront (and continuing) investment to realize benefits
- Access to information, including unredacted assessment reports (particularly challenging for quality information) - promotes understanding of what reviewed and rationale for decisions; also promotes confidence and trust
- Ability to ask questions
- Raises issue of reference agency ‘regulatory community responsibility’ (next slide)

Challenges and considerations (2)

Buy-in from all key players, including:

- industry - who must see benefits and downsides and have clear guidance on its application (regulatory pathways defined)
- agency reviewers: need to change mind-set that reliance reduces autonomy, stringency and security – building trust a slow process

Enhanced by a framework for optimizing reliance:

- Review templates, assessor guides that clearly define approach, management support,
- Management and institutional support
- Training and face to face meetings/forum to build trust

Challenges and considerations (3)

- Importance of having a clearly defined framework within which a particular reliance practice is able to be used
- A clear understanding of the regulatory processes of agencies relied upon, especially how they differ – e.g., evaluator must first understand how pre-market assessment has been conducted
- Legal framework to support reliance extremely helpful, in particular to resolve divergent views
- Importance of building consensus and agreement progressively - critical investment for successful outcomes

Challenges and considerations (4)

- Successful reliance and cooperation require common approaches to regulatory activities. Many states, especially emerging economies experience need to harmonize regulatory activities, implement quality managements systems, adopt standard operating procedures for basic regulatory functions
- Differences in evidentiary requirements and ‘risk threshold’ for approval (surrogate endpoints, early phase data, risk tolerance)
- Need to maintain scientific capability and competence and clinical judgement in decision-making and labelling, bridging decisions in other countries to local benefit-harm context

Challenges and considerations (5)

- Related to the above, the consequences of reference agencies increasingly relying on other reference agencies and organizational efforts to understand and develop areas of expertise
- Implications of adaptive licensing/early approvals and challenges posed to other agencies who may wish to leverage
- Secure platform and procedures for the exchange and management of non-public information
- Differences in products and production sites, sponsors/legal manufacturers
- Confidence in reliability of review reports provided by applicants

Challenges and considerations (6)

- Metrics: how to measure and document success? Outcome difficult to measure objectively (however uptake of reliance pathways suggestive of impact)
- Reliance not an opportunity to reduce resources of participating NRAs, but rather ensure agencies avoid duplication and focus resources on key activities that bring value to the populations they serve
- Particularly useful for small market/small regulator to ensure we make the most out of limits resources, achieving the best outcomes, while retaining a high degree of regulatory stringency

Opportunities (1)

- Harmonize structure and format of inspection reports and include more discrete data fields/structured-format content to better leverage foreign inspections
- Similarly, provide product assessment reports in searchable electronic format
- Opportunity to consider convergence/harmonization of regulatory formats and guides to better leverage one another's reports? NB - ACSS and IPRP Quality WG have also undertaken work in this area
- Potential for further MRAs (inspection) – build on work done by ICMRA with PIC/S
- International workshop on reliance: experiences/best practices

Opportunities (2)

- Added emphasis on post-approval phase:
  - Proactive sharing of post-market safety data
  - Establish standards for timeliness and minimum information content for posting emergent safety issues or regulatory actions
  - Standardization of Good Vigilance Practices, including roles and responsibilities of industry in collecting foreign safety data
  - Support by reference agencies in relation to early approvals and post-market safety issues
  - Reliance/work-sharing in the area of PV, post-authorisation safety and efficacy monitoring

Opportunities (3)

- Discussions regarding how reference agencies provide assessment reports, 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?
- Broadening of existing reliance frameworks to include other therapeutic/health products and new technologies
- Substantial variations
- Wider acceptance and application of reliance and work-sharing worldwide: ***move from pilot stages to 'daily business'***

Opportunities (4)

- Important to ensure that the definitions of reliance wide enough to include regional regulatory systems such as that in the EU, but also those being developed in Africa, Caribbean, Gulf Council, Latin and South America, etc.
- (In addition to benchmarking) DRAs of ICH countries may create fora for emerging economies where the latter may become more familiar with advanced regulatory practices, approaches to assessment of new types of medicines which will contribute to wider use of reliance
- Opening of ICH…favours convergence
- Within the Americas: project on better use of CPP and PAHO project on regulatory convergence

Opportunities (5) – GBT and WLA

Assessment of NRAs with the Global Benchmarking Tool (GBT) of WHO/PAHO and the WHO-listed authorities' (WLAs) will provide evidences of NRA's performance and enable trust in decisions of NRAs….

….. active decision to 'regulate through reliance' is a positive attribute and not something that penalises or downgrades an authority being assessed…..

……WHO efforts on capacity building/maturity assessment became important tool for promotion of good regulatory practices and qualification of NRAs, helping to adjust national performance to common standards and thus 'increase the room for reliance and recognition'

World Health Organization

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

Emer Cooke
Director, Regulation of Medicines and other Health Technologies

Back up

Definitions

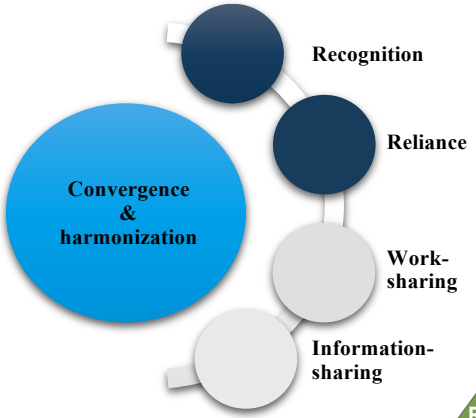
Reliance:

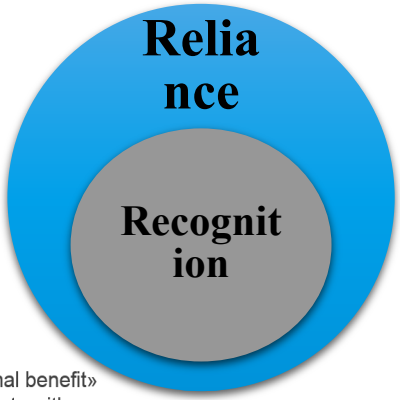
act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.

Recognition:

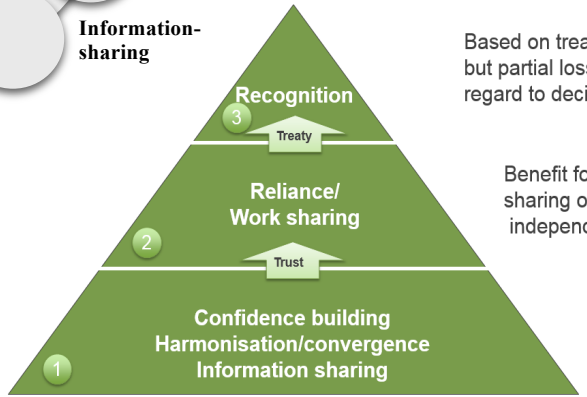
the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

Views on 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

«Foundation», Equivalence of requirements

Examples of reliance (1)

- Variety of pre-requisites, criteria, instruments and schemes
- Examples include (mutual) recognition and work-sharing
- Inspections: GMP, GCP, GLP
- Product assessments:
  - NCEs, biological products, generic drugs,
  - DMFs/ASMFs
  - Components of reviews
  - Complementary medicines/OTCs (planned)
- CTAs (fast track; noncompliance with review target)
- Guidelines

Examples (2)

- Special circumstances:
  - urgent public health need
  - access to internationally available drugs for unmet medical need (*planned* recognition pathway)
- “In post-market world, more about ‘timeliness’ and ‘accessibility’ of emergent safety information”

Examples (3)

- Facilitated registration of prequalified products
- New WHO/FDA Pilot on PEPFAR products (HIV)
- Impact of National Regulatory Authorities of Regional Reference (NRArr)
- Equivalence agreements for innovative medicines and devices (Mexico)
- Regulatory Technical Committees for transfer of Technologies (Cuba)
- Turkey: draft legislation on Recognition (Article 38) following self-benchmarking with WHO GBT

Examples (4) – Regional Examples

- European Union (EU) and Eurasian Economic Union (EAEU) – provides for single markets
- EU: long-established common legal framework for pharmaceuticals, underpinned by common legislation, scientific and regulatory standards, guidelines and procedures (including common application format)
- EEA: similar arrangements: Treaty and enabling legislation and common databases, allowing for combination of mutual recognition (MA), information-exchange and work-sharing (GMP inspections)
- New Gulf Health Council “centralised” approach
- Ultimate forms of reliance/recognition – possible elsewhere?

Examples (5)

- Article 58 procedure to promote access to medicines outside EU, taking into account local conditions of use, in collaboration with WHO and experts from target authorities*
- EMA-WHO pilot led to finalization of 'SRA' Collaborative registration Procedure in October 2018
- EU: real-time Information-sharing pilot under IGDRP - decentralized and centralized procedures – as discussed yesterday - lessons learned?

(* NB – similar 'special registration' frameworks in place in a number of other countries, most recently Switzerland)

WHO Listed Authority (WLA):

Working document QAS/19.808
May 2019
Draft document for comments

CONCEPT NOTE: A FRAMEWORK FOR EVALUATING AND PUBLICLY DESIGNATING REGULATORY AUTHORITIES AS WHO-LISTED AUTHORITIES

(May 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to nra_admin@who.int, with a copy to Ms Claire Vogel (vogelc@who.int) **by 17 July 2019**.

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under "Current projects". If you have not already received our draft working documents, please send your email address (to jonessi@who.int) and we will add you to our electronic mailing list.

https://www.who.int/medicines/areas/quality_safety/quality_assurance/qas19_808_WHO_listed_authorities.pdf?ua=1

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WLA: Concept note for public consultation

- Concept note outlines proposed framework for evaluating and publicly designating regulatory authorities as ‘WHO-Listed Authorities’ (WLA)
- Follows up on recommendations from the WHO ECSPP in October 2017 on replacement of the term stringent regulatory authority with WLA
- Note presents proposed definition for WHO-listed authority; procedures for designating a WLA; and the process for putting the framework into place

WLA: Timelines

- WHO intends to publish a draft WLA policy document shortly and draft operational guidance documents by end Q3 2019
- Given wide interest and implications, WHO will adopt a multi-pronged consultation process as outlined in this concept note
- Definition for WLA will also need to be reviewed by WHO Expert Committees in the context of its usage in place of stringent regulatory authority in existing WHO guidelines
- Introduction of the WLA framework will begin with a pilot phase in the first quarter of 2020

WLA: Definitions (1)

Maturity level 3 WHO listed authority (ML 3 WLA)

- *A regulatory authority which has been documented to comply with all of the indicators and requirements specified by WHO for maturity level 3 based on an established benchmarking process*
- Represents a stable, well-functioning and integrated regulatory system

Maturity level 4 WHO listed authority (ML 4 WLA)

- *A regulatory authority which has been documented to comply with all of the indicators and requirements specified by WHO for maturity level 4 and to consistently adhere to WHO and other internationally recognized standards based on an established benchmarking and enhanced performance evaluation process*
- Represents a regulatory system operating at advanced level of performance and continuous improvement (currently known as SRA)

WLA: Definitions (2)

Regional regulatory system

- *A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework.*
- *The common framework must ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies.*
- *The regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework.*
- *A regional regulatory system so described may be considered a single entity and therefore eligible for listing as a WLA.*