

Fostering global dialogue to improve access to vaccines through regulatory convergence

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Introduction

This presentation summarizes the contents of a concept paper developed by DCVMN members which describes from their perspective,

- ✓ *the current situation vis a vis the regulatory oversight of vaccines (in particular with regards to registration),*
- ✓ *the constraints observed which limit timely access to priority products, and the potential approaches that could be taken to overcome these limitations.*
- ✓ *It also proposes ways in which manufacturers could contribute to the work of other stakeholders to improve the current status.*

OUTLINE

- *Background*
- *WHO efforts to strengthen regulatory capacity*
- *Existing approaches to support appropriate regulatory oversight for vaccines*
- *Constraints*
- *DCVMN views on potential solutions*



Background



Objectives of regulatory oversight of medicines, including vaccines

- Facilitate access to needed medicines while ensuring their quality, safety and efficacy
- Exercise control over the medicines that are marketed in the country through registration, to prevent to the extent possible, the circulation of substandard or even counterfeit products
- Ensure that medicines circulating in their territories are of standard quality, safe and effective
- Monitor, investigate and address adverse reactions, including introduction of corrective measures if applicable
- Monitor the quality of products once they are introduced in the market and throughout their lifecycle



The Regulatory System

- Defines the responsible Institutions as well as their respective functions, roles and organizational structure
- Defines the scope of products covered
- The legislation, at different levels, (law, regulations, decrees) provide the legal framework on which the regulatory system is built.
- The highest level is represented by the law, which provides the overall and very general guidance. Regulations, decrees, procedures, etc provide increased level of detail as to the way in which the system works.



The Regulatory System (2)

- Every effort should be done to develop a «ROBUST» regulatory system that will take into account different situations and conditions of use of the vaccines
- Different provisions embedded in the regulatory framework are required to provide the necessary flexibility to achieve this
- Transparency, well defined and published processes and procedures applied in a consistent manner, are key elements of a robust system



WHO efforts to strengthen regulatory capacity



WHO recommended regulatory functions

**20+ years
helping countries
to develop
capacity to
regulate
vaccines**

- WHO focuses its capacity building efforts on development of a **regulatory system** and six **functions** considered important for the regulation of vaccines
- The aim is to exercise an effective and efficient regulatory oversight of the products while making the best use of existing resources and available knowledge about the product's quality, safety and efficacy.
- Prioritizes functions according to vaccine source
- Prioritizes countries on risk based considerations (producing countries highest vs UN procuring countries, lowest)

COMPLIANCE
REGULATION
BIOLOGICS

WHO recommended functions according to vaccine source

(prioritization strategy)

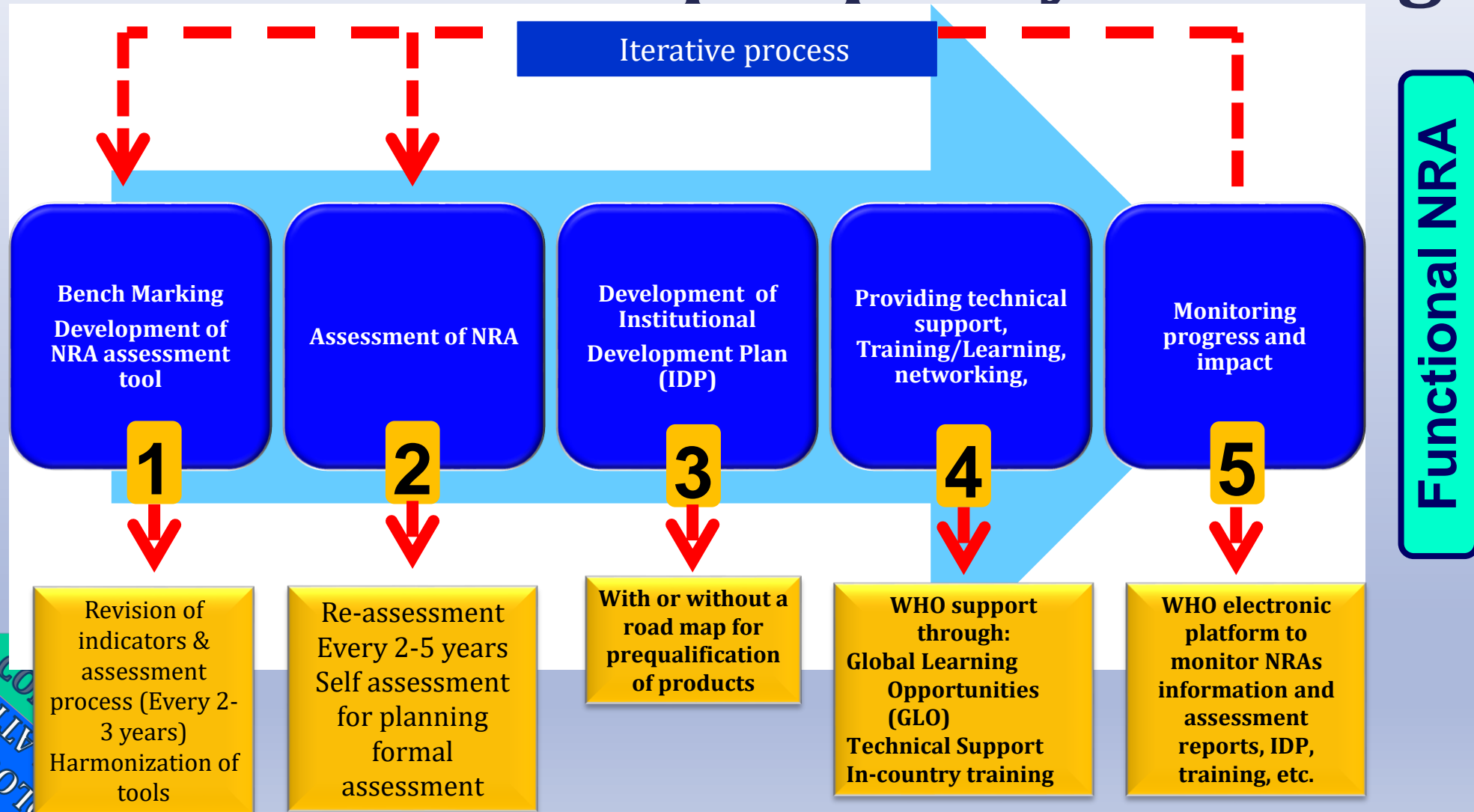
Vaccine Source	MAA & licensing	PMS	Lot release	Lab access	Regulatory Inspections	Authorization & monitoring CT
UN agency supply	Regulatory System		Exporting country NRA+ WHO-PQ			All countries where CTs are performed
Direct purchase			Exporting Country NRA			
Producing country						

WHO priorities for NRA strengthening activities

- Focus on development of a regulatory system in all countries
- Focus on development of the necessary functions according to vaccine source
- The necessary functions should not necessarily be fully developed by each and every NRA. **The concept of reliance comes into play**
- Regulators' Networks provide mutual support, and are likely to facilitate alignment of requirements, procedures and standards



WHO NRA 5 step capacity building



Existing approaches to support appropriate regulatory oversight for vaccines



Existing approaches to strengthen regulatory capacity

Guidance documents	WHO 5-steps capacity building	Networking opportunities	Scientific sessions and Joint Reviews	Other
WHO guidance published in TRS	Assessment by expert team against published indicators to identify strengths and gaps	Economic blocks within a region or sub-region, involve harmonization efforts (ASEAN, Mercosur, APEC, EAC, other)	Scientific sessions organized to discuss challenges faced for evaluation of novel products (rota, dengue)	Reliance mechanisms (Collaborative procedure between WHO and NRAs for PQd products)
ICH, FDA, EMA, APAC guidance among other	Preparation of an Institutional Development Plan (IDP)	WHO facilitated networks: DCVRN, AVAREF, Regional Alliance n WPRO, PANDRH, SEARO laboratory Network	Joint review by countries for evaluation and approval of CT protocols (Ebola)	Training courses and technical support by different stakeholders
PANDRH/PARF guidance documents	Technical support according to IDP Reassessment or FU	Harmonization initiatives: ICH, AMRH,	Joint review meetings to facilitate evaluation and registration of priority vaccines (Men A, IPV)	Emergency use assessment and Listing procedure (EUAL) for candidate vaccines in the context of Public Health Emergency
Different Pharmacopoeias	Assessments by other agencies (PAHO, EDQM, etc) + CB	ICDRA offers a forum to strengthen collaboration among regulators worldwide.		

Regulators worldwide are challenged

Due to factors such as complexity of new technology platforms and globalization of production among other ...

There is consensus among regulators globally, particularly from well developed regulatory agencies, that *not a single agency has the required resources to address all the relevant regulatory aspects for all product categories; and therefore collaboration, information sharing and worksharing including **RELIANCE** become essential.*

- ✓ *Avoidance of unnecessary testing is considered critical*
- ✓ *Avoidance of redundant inspections of manufacturing facilities is considered critical*
- ✓ *Trend is to focus on risk benefit equation, potential public health impact of the intervention vs necessary data and measures to monitor quality, safety and efficacy and to minimize risks*

Categories of vaccines

Three categories of products:

1. Vaccines required for emergencies (Ebola, pandemic flu, Zika virus)
2. Vaccines that are high priority for public health (Meningococcal A conjugate for Africa, IPV for polio eradication)
3. Novel vaccines aimed at reducing morbidity and mortality due to other vaccine preventable diseases (rotavirus, HPV, pneumococcal conjugate)



May require different regulatory approaches to enable timely introduction and use.

Approaches used to facilitate review and approval processes

1. For emergency use

- a) EUAL as a surrogate of PQ which may not be feasible under such conditions
- b) Joint reviews for evaluation and approval of clinical trial protocols
- c) Joint reviews to expedite registration

2. High priority for public health

- a) Collaborative procedure between the World Health Organization PQ and NRAs in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines
- b) Joint review meetings to expedite registration

3. Novel vaccines

- a) Scientific sessions to address regulatory challenges posed by novel products
- b) Discussion of regulatory challenges within networks
- c) Collaborative procedure
- d) Joint review meetings to expedite registration

Constraints



Lessons learned from JR meetings:

Positive aspects

- Participants appreciate greatly the opportunity, the technical and scientific information and the guidance received.
- Participation of manufacturers and NRAs from producing countries in some of these meetings eases communication and helps address GMP related and other questions that would normally take long to be addressed to the satisfaction of the NRAs.
- Joint reviews with African regulators for review and approval of CTs to be conducted in Ebola affected countries, resulted in a quicker approval of the trials
- Joint reviews organized to support evaluation and expediting licensure of vaccines under less extreme conditions (Men A, IPV) remained a training exercise that did not really impact the procedures followed in countries to register the products.



Lessons learned from JR meetings: Shortcomings

- Inefficient internal communication within NRAs (cascading from management to technical staff) about commitments taken by heads of agencies
- Failure by manufacturers to submit dossiers in timely manner
- Additional country specific requirements to be reviewed after the JR meeting
- Official submission and communication through national agents
- Commitment to using only report from joint review meeting not assured by all countries
- Timelines for registration unclear (unclear, non transparent process)
- Unclear if legal framework allowed for reliance on WHO PQ to facilitate registration
- Joint reviews are necessary but not sufficient to facilitate and accelerate approval and registration of vaccines in receiving countries

Examples of constraints in some countries as reported by manufacturers

- Application form prior to submission in a variety of formats
- High variability in country specific requirements
- Testing imposed as part of registration process
- Prior approval in a «reference country» in order for submission to be accepted, does not imply abbreviated review
- Stability data for three consecutive lots with requirement for extensive real time stability data
- License of facilities prior to product registration
- Local clinical trials are mandatory including for approval of variations
- Repetitive GMP inspections



Summary of constraints

- Inadequate and/or rigid legislation that does not allow for flexibilities as required based on scientifically sound reasons.
- Lack of provisions for reliance on work performed by others including in cases where the products are needed on an emergency basis.
- Technical or scientific limitations, where the necessary resources and expertise for an adequate evaluation may not exist or be insufficient,
- Cumbersome, inadequate or not fully defined procedures leading to inconsistent and lengthy registration processes
- Diversity of requirements, procedures and standards between individual countries, networks, blocks and harmonization initiatives



DCVMN views on potential solutions



POTENTIALLY USEFUL INTERVENTIONS

- ✓ Availability of additional guidance documents (model regulatory framework, model process for registration), WHO is best suited for this.
- ✓ Training provided to facilitate implementation of the guidance, WHO and other partners
- ✓ Further efforts towards alignment and harmonization of requirements, mostly through networks, economic blocks agreements, etc
- ✓ Collaboration between regulators (reliance and recognition including mutual recognition) through networking initiatives
- ✓ Technical/scientific expertise provided through joint review activities, twining between NRAs and other means
- ✓ Inputs from manufacturers networks and associations as a relevant stakeholder/ partner

Potential contribution from manufacturers

Collaborate with WHO in highlighting additional lower level guidance documents that may be needed to assist countries in achieving GRP implementation

Developing a common list of essential documents to address countries' specific requirements, aiming to address the diversity of requirements and advocate for some level of alignment.

Collaborate with WHO and other partners in mapping out existing guidelines globally and how can these be best used

Work with partners (WHO, UNICEF, GAVI and others) to jointly assist the simplification of registration procedures based on reliance principles and harmonization/ alignment of requirements



