Challenges for registration of vaccines in receiving countries

by Dr. Nora Dellepiane

Workshop: Global Registration and Vaccine Shortage

Taipei, Taiwan 6 to 10 March 2017

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Outline of the presentation

- WHO recommended regulatory functions
- Pathways to registration of vaccines
- Constraints for registration
- Potentially useful interventions
- Potential inputs from manufacturers

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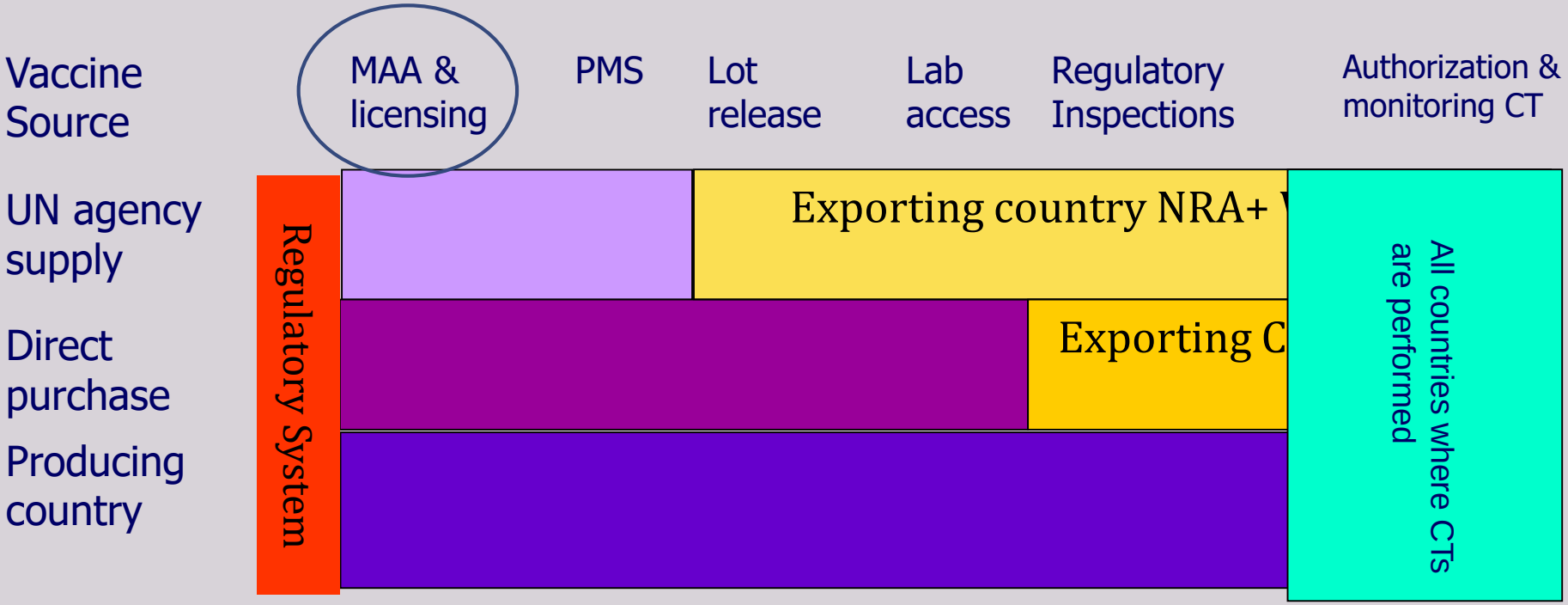
WHO approach to NRA strengthening efforts: Recommended functions according to vaccine source



WHO recommended approches to vaccine licensure

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VACCINE CATEGORY	PRODUCING COUNTRY	PROCURING COUNTRY	PROCURING THROUGH UN
INDIGENOUS	**Full CTD dossier review: required** **Ability to test: required** **Inspection of facilities: required** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: Ability to evaluate the product in full, including establishing testing capacity and performing regular inspections of facilities** **A performing post-marketing surveillance system is critical.**	**Not applicable**	**Not applicable**
IMPORTED NON-PREQUALIFIED	**Full CTD dossier review: may be needed or not depending on maturity of the NRA in producing country (if licensed there) and/or that of the NRAs in other countries where the vaccine may have already been licensed. Need to review clinical data to ensure relevance to indigenous population and programmatic needs.** **Ability to test: Not necessarily required. Based on release certificate by licensing authority, testing not needed. Access to a laboratory able to test a specific vaccine in case of problems** **Inspection of facilities: Not necessarily required. Access to GMP certification by licensing NRA, use of CPP or access to inspection reports from licensing or other NRAs should suffice.** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: Need for full CTD review depends on maturity of NRAs that have already licensed the product including that of the producing country if relevant. Testing and inspection should be avoided unless under special circumstances. A performing post-marketing surveillance system is critical.**		**Not applicable**
IMPORTED PREQUALIFIED	**Full CTD dossier review: Not required. Full review performed by NRA in country of origin plus WHO PQ,** **Ability to test: Not needed. Continued compliance with specs monitored by WHO PQ and NRA in country of origin. Data available on request** **Inspection of facilities: Not needed. GMP compliance monitored by NRA in country of origin and WHO PQ** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: Implement a facilitated and expedited procedure for registration of this category of vaccines. Focus resources in establishing and sustaining a performing post-marketing surveillance system-**		

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Ability to oversee clinical trials

Producing countries

- Ability to review CT protocols
- Ability to monitor CT
- Ability to review CT data

Countries targeted for CT

- Ability to review CT protocols
- Ability to monitor CT
- Ability to review CT data

or may opt to develop none or some of this capacity and outsource the expertise whenever a trial is planned in their country

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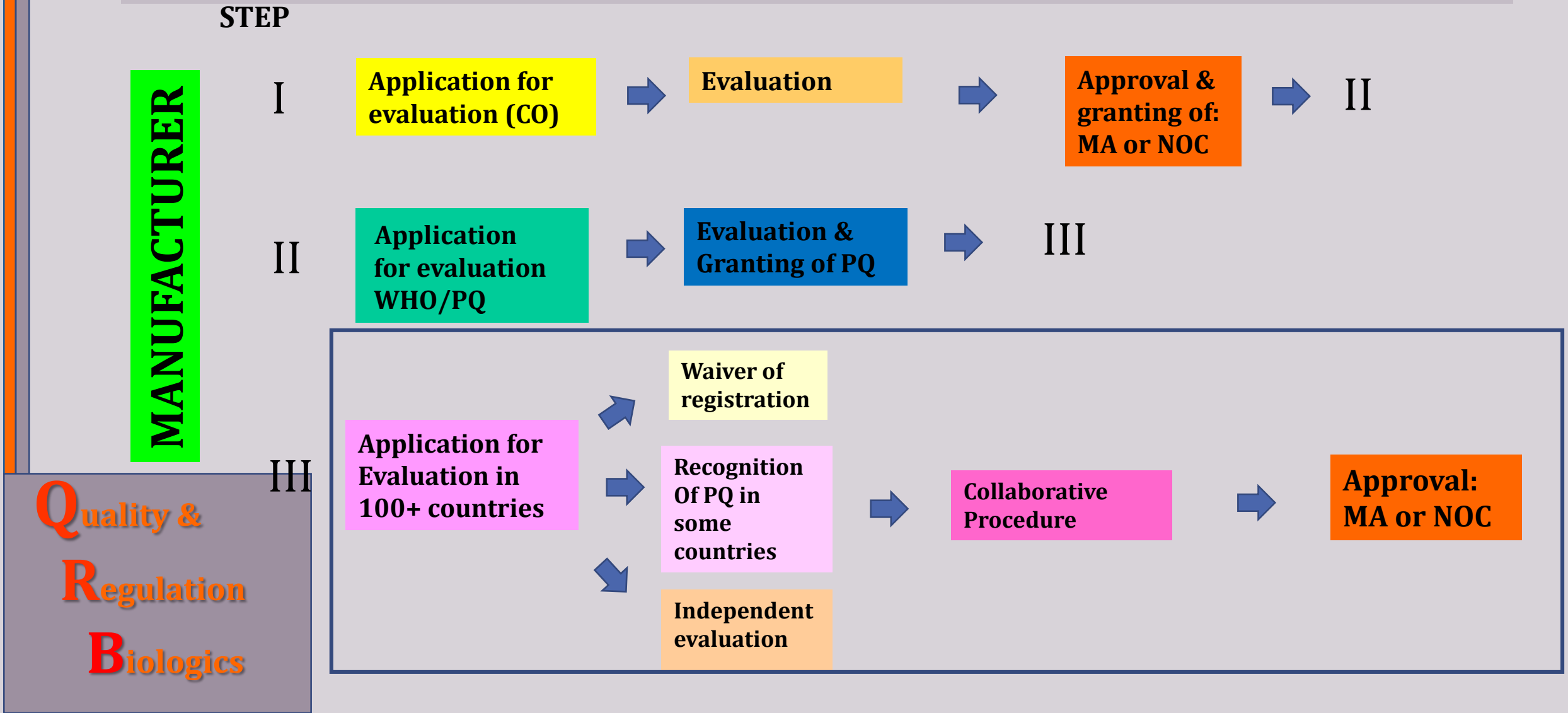
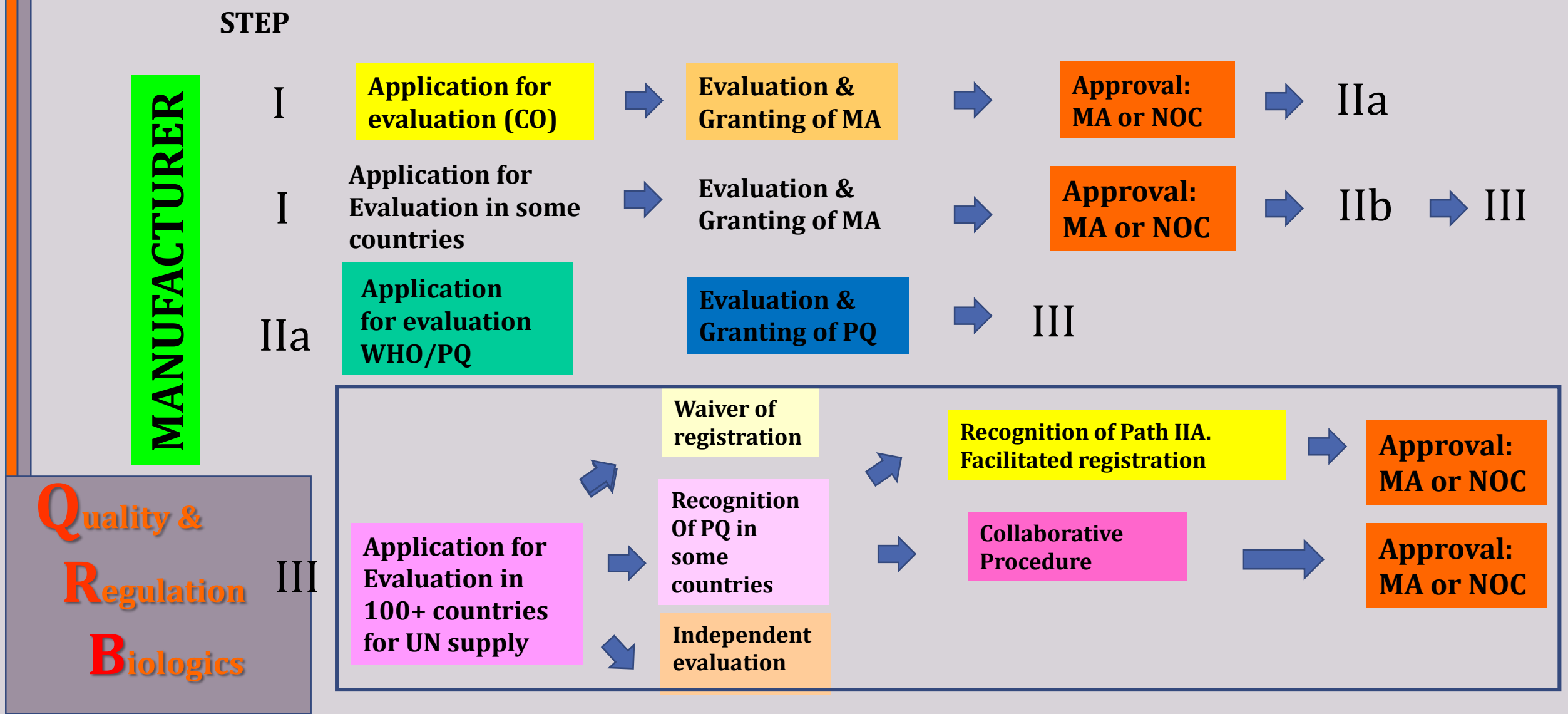
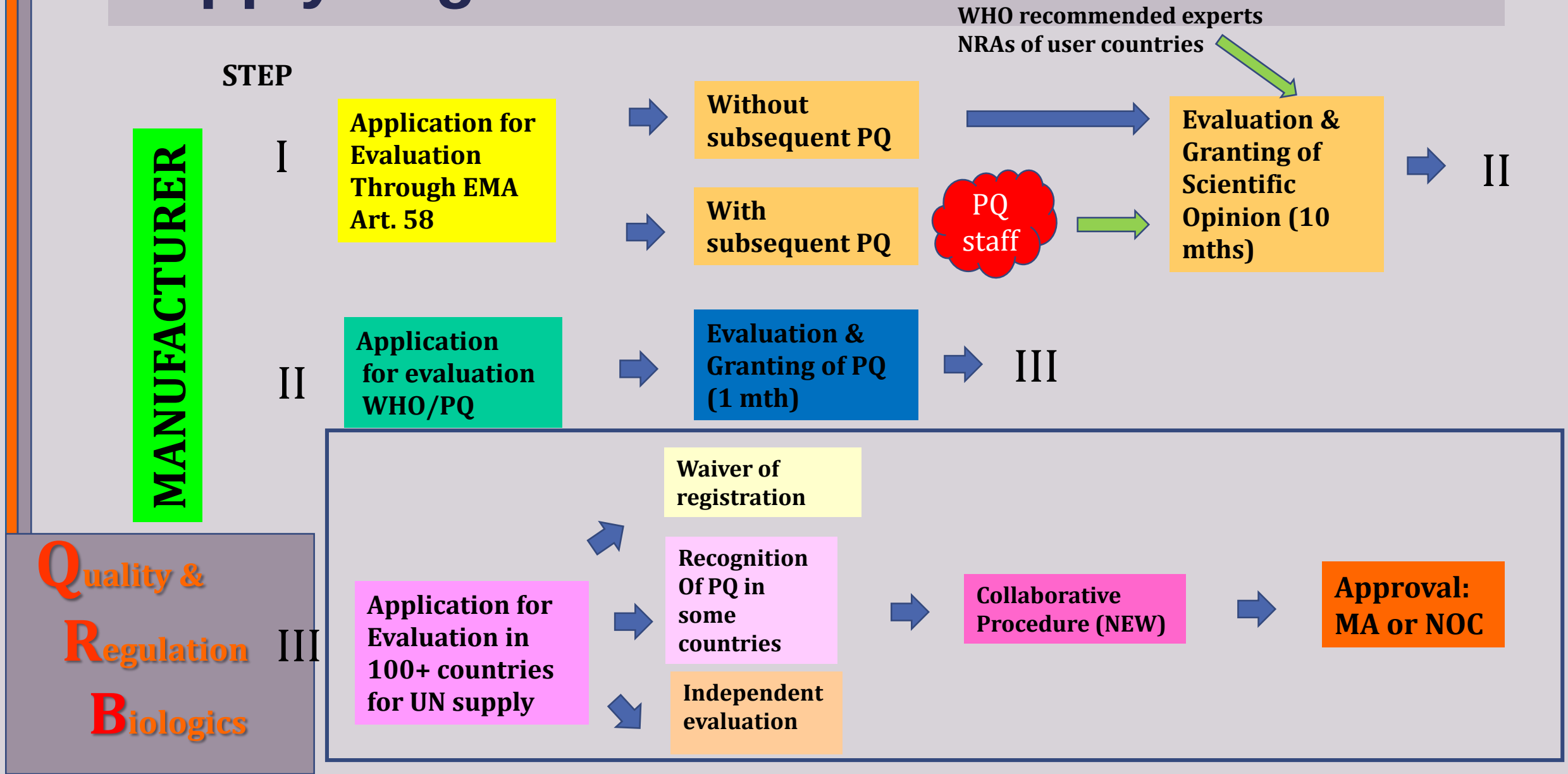
Pathway A to registration of vaccines for supply in global market



Pathway B to registration of vaccines for supply in global market



Pathway C to registration of vaccines for supply in global market



Constraints observed in some countries for registration: dossier

- Application form prior to submission, variety of formats
- Different dossier formats
- Differences in number and types of legal documents required
- Differences in format and contents of CTD (as discussed earlier)
- Different level of detail in dossier content requirements
- Different requirements regarding translations, legalization of documents, etc

LACK OF ALIGNMENT IN FORMAT AND CONTENTS OF DOSSIERS EVEN IF ONLY FOCUSING ON COMMON TECHNICAL DOCUMENT USED IN DIFFERENT REGIONS/COUNTRIES OF THE WORLD

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Constraints observed in some countries for registration

- Testing imposed as part of registration process
- Prior approval in a «reference country» in order for submission to be accepted
- Stability data for three consecutive lots, extensive real time stability data required
- Compliance with National Pharmacopoeias, which sometimes differ from international pharmacopoeias
- License of facilities prior to product registration
- Mandatory clinical trials at local level
- One site per license
- Redundant GMP inspections

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Registration in Sub-Saharan African countries

- ✓ The time between first regulatory authority submission for a given drug or vaccine to its registration in the last of 20 Sub-Saharan Africa countries was typically between 4 and 7 years.
- ✓ There are many factors responsible for this lengthy timeline:
  - Redundancy across steps since there was no leveraging of the technical reviews already performed by competent bodies,
  - Inefficiencies in the regulatory processes themselves,
  - and failure of manufacturers to meet the international standards required by WHO-PQ.

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Data source: Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries Ahonkhai, V. et al. PLOS ONE | DOI:10.1371/November 16, 2016

Summary of constraints

- Inadequate and/or rigid legislation that does not allow for flexibilities as required based on scientifically sound reasons (waiver of local clinical trials).
- Lack of provisions for reliance on work performed by other regulators or WHO including in cases where the products are needed for special circumstances (orphan products, compassionate use, donations, emergency use, etc)

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Summary of constraints (2)

- Technical or scientific limitations, where the necessary resources and expertise for an adequate evaluation may not exist or be insufficient,
- Imposition of irrelevant or excessive requirements in some cases.

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Summary of constraints (3)

- Cumbersome, inadequate or not fully defined procedures leading to inconsistent and lengthy registration processes
- Lack of transparency with respect to processes and procedures in place including route of the dossier, expert committees involved, timeframes for different steps, etc

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POTENTIALLY USEFUFUL INTERVENTIONS

- ✓ Availability of guidance documents. WHO is best suited for this. GRP guidelines under development. More implementation oriented guidelines are needed.
- ✓ 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, inputs from manufacturers and manufacturers associations, 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

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What could be potential inputs from manufacturers?

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Potential inputs from manufacturers

- ✓ Publication in a peer reviewed and open access journal the DCVMN concept paper highlighting the constraints faced for timely registration of vaccines in receiving countries
- ✓ DCVMN and IFPMA jointly approaching WHO to provide:
  - Comparative analysis of format and contents of CTD requirements by different authorities across the world (showing the lack of alignment even in the supposedly harmonized technical document
  - Review of gaps and overlaps in the most used guidelines published online providing advice on recommended processes and procedures for registration of medicines
  - A proposed common list of essential documents that could be used as a starting point for reaching some level of alignment in module 1 of the CTD and administrative requirements from authorities not using CTD format of dossier

  and to request WHO to follow up on each of the topics
- ✓ Approach regulatory networks (AVAREF and DCVRN) and partners to discuss the above mentioned inputs and advocate for follow up
- ✓ Other?

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References

- Good regulatory practices: guidelines for national regulatory authorities for medical products. Working document QAS/16.686 October 2016 Draft for comment Prepared by EMP/RSS
- Draft Concept Paper commissioned by DCVMN on “Registration of vaccines: Current challenges and opportunities”.
- Regulatory Pathways that facilitated timely registration of new group A meningococcal conjugate vaccine for Africa’s meningitis belt countries. N. Dellepiane et al Clin. Inf. Dis. (2015), 61(5): S428-S433
- Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. V. Ahonkhai et al PLOS ONE | DOI:10.1371/November 16, 2016

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Thank you
谢谢
Merci
Спасибо
شكراً
Gracias
Grazie
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Obrigado

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