Regulatory pathways available for vaccine registrations

DCVMN Webinar

11th March 2020

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Initiative 3
Support established efforts to advance regulatory convergence approaches (1)

A- Pre-marketing regulatory activities

DCVMN activities related to vaccine registration

Identified registration challenges in non-producing countries

→ Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Challenges for the registration of vaccines in emerging countries: Differences in dossier requirements, application and evaluation processes. N. Dellepiane, S. Pagliusi and Registration Experts Working Group. Vaccine 2018; 36(24): 3389-3396

↓

Made proposals for improvement: alignment of requirements and procedures

→ Dellepiane, N, Pagliusi, S, Regulatory Experts Working Group. Opportunities for improving access to vaccines in emerging countries through efficient and aligned registration procedures: An industry perspective. Vaccine 2019; 37: 2982-2989.

NOTE: Regulatory Experts Working Group in collaboration with representatives from IFPMA member companies.
Constituted mostly by Regulatory Affairs staff

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Initiative 3
Support established efforts to advance regulatory convergence approaches (2)

DCVMN activities related to vaccine registration

Main challenges

- Lack of alignment in dossier format and contents with country specific requirements
- Lack of alignment in registration procedures
- Unpredictable timelines
- Repetitive testing and inspections

Main Proposals for dossier alignment

- Standard model for M1with harmonized numbering system
- Country specific requirements to be added at the end, no alteration of numbering order
- Standard model for application form
- Adoption of EU CTD for all other modules

Main Proposals for procedural improvements

- Expert understanding and knowledge of regulatory pathways available and accessible to DCVMN manufacturers

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Support established efforts to advance regulatory convergence approaches (3)

DCVMN activities related to vaccine registration

- Standard model for M1with harmonized numbering system
- Country specific requirements to be added at the end, no alteration of numbering order
- Standard model for application form
- Adoption of EU CTD for all other modules

Implementation of proposed improvements by regulatory bodies depends on the work of all of us.

- When meeting regulators share the publications and the proposed forms
- Invite them to consider adoption
- Explain how simple it is, no regulation amendments are required
- Be active and proactive

Initiative 3

Support established efforts to advance regulatory convergence approaches (4)

DCVMN activities related to vaccine registration

Expert understanding and knowledge of regulatory pathways available and accessible to DCVMN manufacturers

THIS IS WHAT THIS WEBINAR IS ABOUT

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Regulatory Pathways
Outline of webinar

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- ✓ Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, commonly known as

  " the Prequalification procedure"
  - Standard
  - Streamlined
  - Fast track
  - Article 58 positive Scientific Opinion

- ✓ Emergency Use Assessment and Listing

- ✓ Collaborative Registration Procedure

The Prequalification Procedure

Did you know that the PQ procedure for vaccines is not a single procedure but **four procedures?**

1)Standard

2) Streamlined

3) Fast track

4) Art 58 Scientific Opinion

Do you know the differences between them and when each is applicable?

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Commonalities vs differences

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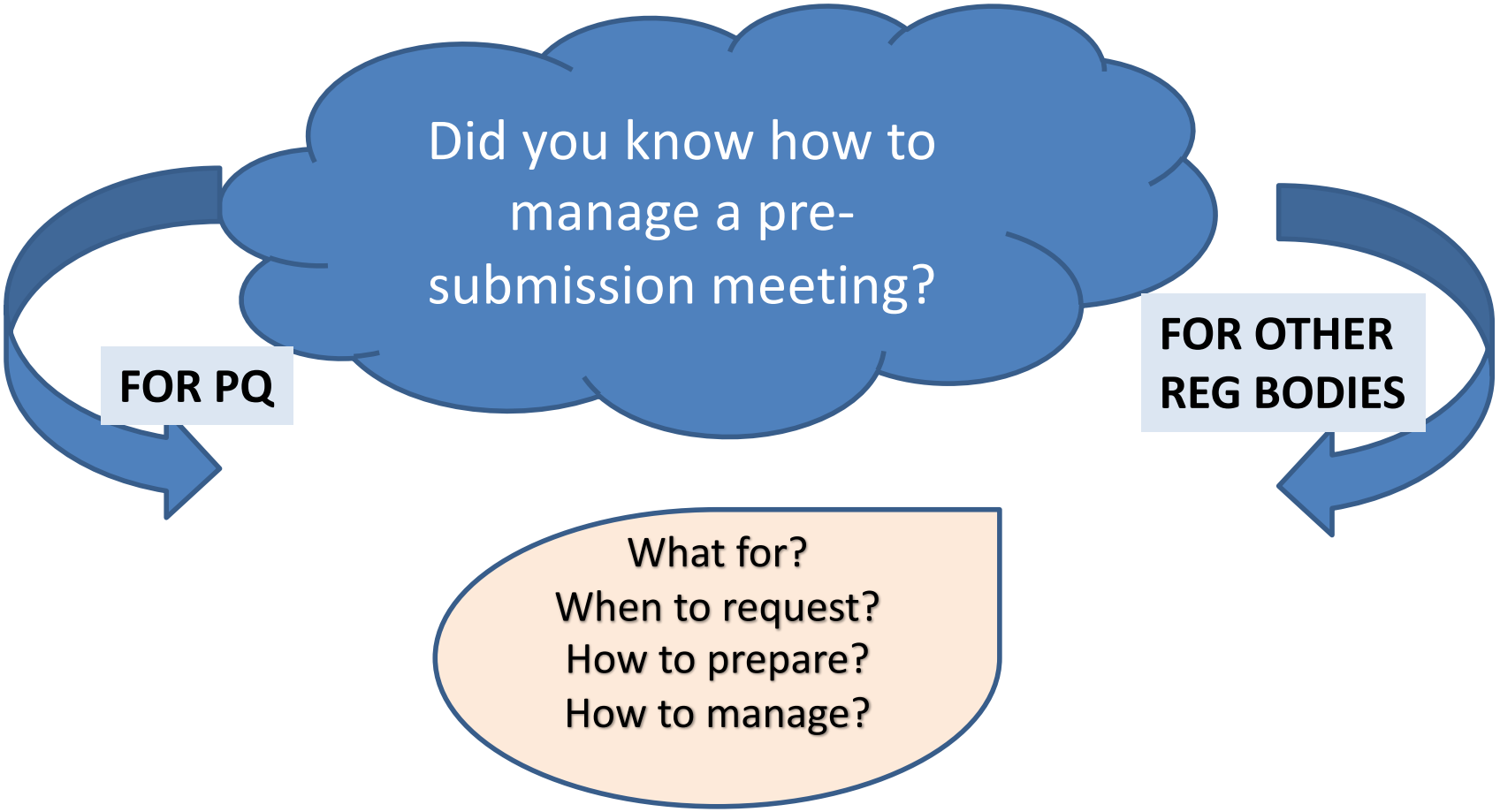
	Standard	Streamlined	Fast track	EMA Art. 58
Pre-submission meetings	Yes, all. Ideally as early as possible during vaccine development. For EMA: Scientific advice			
Functionality of NRA	Yes, all			
Status of NRA	Functional or WLA level 3	SRA or WLA level 4	Functional or WLA level 3	SRA or WLA level 4
Conditions	Normal submission	Normal submission	Special circumstances	Normal submission
MA available	Yes	Yes	Not necessarily	No (use intended outside EU) CHMP Scientific Opinion given
Leads to PQ	Yes	Yes	Yes	Not always

Pre-submission meetings



Would you need some guidance on this topic?

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Four different procedures leading to PQ

- ~~Standard~~ NOT DISCUSSED IN THIS WEBINAR
- Streamlined
- Fast track
- Article 58 positive Scientific Opinion

ADDRESSED IN THIS WEBINAR

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Streamlined prequalificatio procedure (1)

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Eligibility

- ✓ <u>For standard PQ procedure:</u> NRA responsible for product regulatory oversight (usually in country of origin) required to be functional, recently changed to meeting indicators and sub-indicators level 3 required in the WHO Global Benchmarking tool (GBT) for all vaccine related regulatory functions (WLA level 3)
- ✓ For streamlined PQ procedure: NRA responsible for product regulatory oversight (usually in country of origin) required to be considered “stringent or SRA”. Currently changing to meeting indicators and sub-indicators level 4 required in the WHO Global Benchmarking tool (GBT) for all vaccine related regulatory functions (WLA level 4)

Streamlined prequalificatio procedure (2)

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Assessment elements	Standard procedure	Streamlined procedure
Dossier review	Independently performed by WHO-PQ team	Based on review of reports from the responsible NRA
Samples testing	Independently performed by WHO-collaborating labs	Test results from NCL in country of origin are accepted
Inspection	Performed by WHO usually with representation of the NRA from country of origin	Based on the review of reports from the NRA in country of origin
Specifications	WHO review of UN related specifications including programmatic suitability characteristics	
Type of procedure	Regular	Alleged
Timelines	Estimated one year	Estimated 3-6 months

Fast track pathway to PQ (1)

Fast track eligibility criteria

✓ Acute shortage of a vaccine putting at risk the global supply of routine immunization programmes and/or an eradication effort;

✓ Emergency situation (i.e. an outbreak or epidemic of a disease for which no prequalified vaccine is available, or where availability is insufficient and an additional source of the same vaccine is required);

✓ Declaration of a pandemic of a disease for which production capacity needs to be established;

✓ Need for alternatives to existing vaccines to be used during an eradication effort.

NOTE: not applicable in the case of novel vaccines not yet introduced or recently introduced into routine immunization programmes.

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Fast track pathway to PQ (2)

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Fast track procedure

- ✓ Established submission deadlines for dossier are not applicable
- ✓ Inspection and testing in parallel without awaiting test results
- ✓ Inspection immediately after dossier review is completed
- ✓ Similarly to the streamlined procedure , WHO PQ can be based on review of reports from the CoO NRA

In Summary: Due to the urgency of the product need, maximum flexibility must be given to this process

Article 58 regulation

L 136/24 EN Official Journal of the European Union 30.4.2004

Article 58

1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with Articles 6 to 9. The provisions of Article 10 shall not apply.

2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 59

1. The Agency shall take care to ensure early identification of potential sources of conflict between its scientific opinions and those of other bodies established under Community law carrying out a similar task in relation to issues of common concern.

Article 61

1. Each Member State shall, after consultation of the Management Board, appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Medicinal Products for Human Use and one member and one alternate to the Committee for Medicinal Products for Veterinary Use.

The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62.

Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.

2. The committees may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

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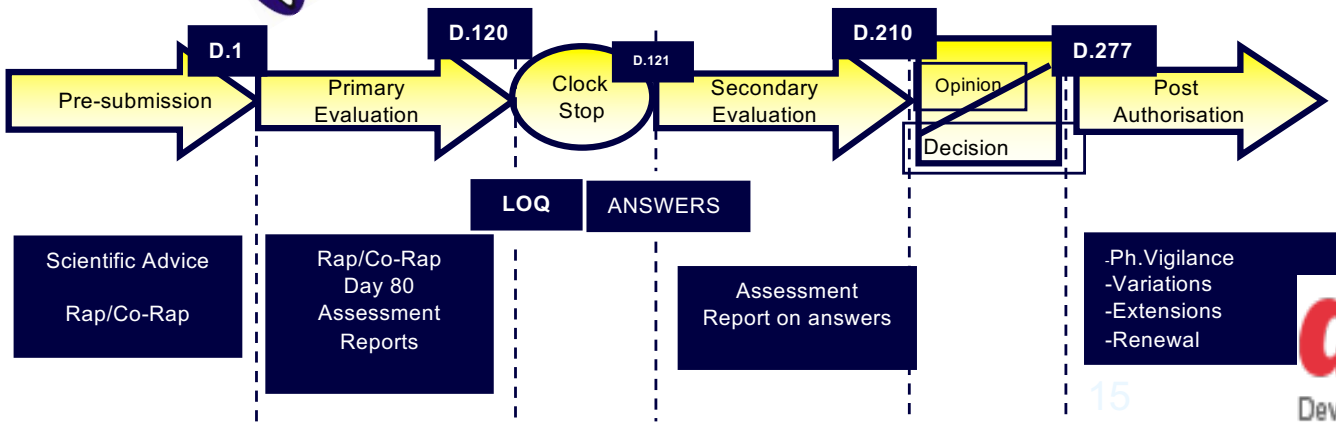
Centralised Procedure



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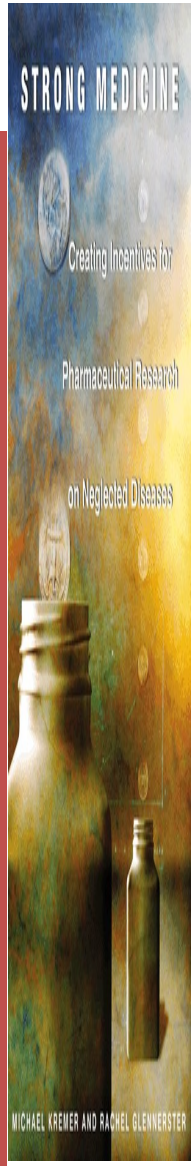
Article 58 CHMP Scientific Opinion

OBJECTIVE

- Prevent unavailability of medicinal products no longer marketed in place in EU for commercial reasons but still of use in countries outside the EU (i.e.combos containing wP, OPV)
- Access to medicines that are essential in countries outside the EU but are not relevant in the EU market (i.e. malaria)
- Responds to the need to protect public health and to give scientific assistance to non-member countries in the context of cooperation with WHO



ELIGIBILITY

- Vaccines used or of possible use in the WHO Expanded Programme On Immunization (EPI)
- Vaccines that are part of a WHO managed stock pile for emergency response
- Medicinal products for protection against WHO public health priority diseases *such as HIV/AIDS, malaria, meningitis, tuberculosis, lymphatic filariasis (elephantiasis), trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis (sleeping sickness), onchocerciasis (river blindness), dengue fever, Chagas disease, leprosy*

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Features (1)

TWO SCENARIOS

- ✓ It can be applied to products that will not be subsequently submitted for WHO prequalification
- ✓ It can be applied to products that will be subsequently submitted for WHO prequalification

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Features (2)

- ✓ Mimics the centralized procedure for granting marketing authorization: same process, timeframes and standard
- ✓ Takes into account specifics of the UN target population (i.e. clinical trials)
- ✓ Involves WHO designated experts in the evaluation process
- ✓ Involves representatives from NRAs of target countries as observers
- ✓ Involves WHO Prequalification staff if the vaccine will be subsequently prequalified

" ART. 58" Procedure without subsequent WHO-PQ submission

EMA

Joint scientific advice

ELIGIBILITY

PRE SUBMISSION

SUBMISSION VALIDATION

PRIMARY EVALUATION

CLOCK STOP

SECONDARY EVALUATION

"Art 58" Adoption of CHMP SCIENTIFIC OPINION

WHO/EMP

WHO/EMP

WHO EXPERTISE/ NRAs OBSERVERS

List of questions and assessment report

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" ART. 58" procedure with subsequent WHO-PQ submission

EMA

Joint scientific advice

ELIGIBILITY

PRE SUBMISSION

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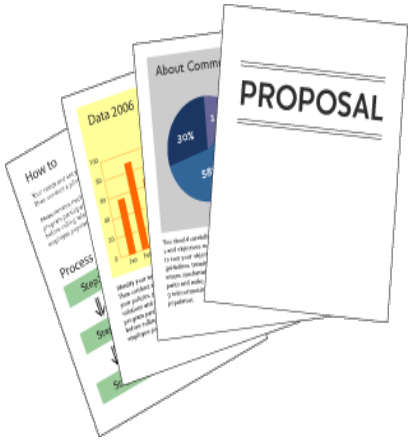

WHO EXPERTISE/ NRAs OBSERVERS

WHO/PQ team

+ consistency lots testing

+ UN tender specifications

+ inspection (if not done by EMA)

+ UN specifications

PQ

WHO

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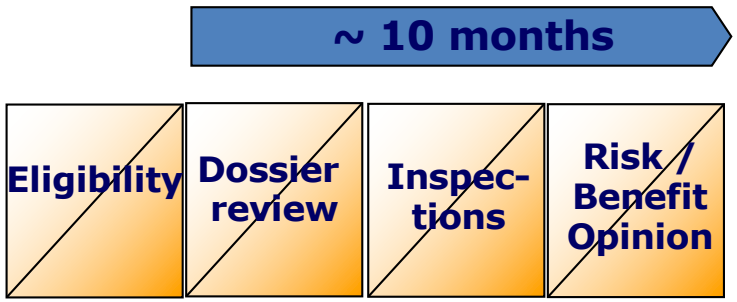
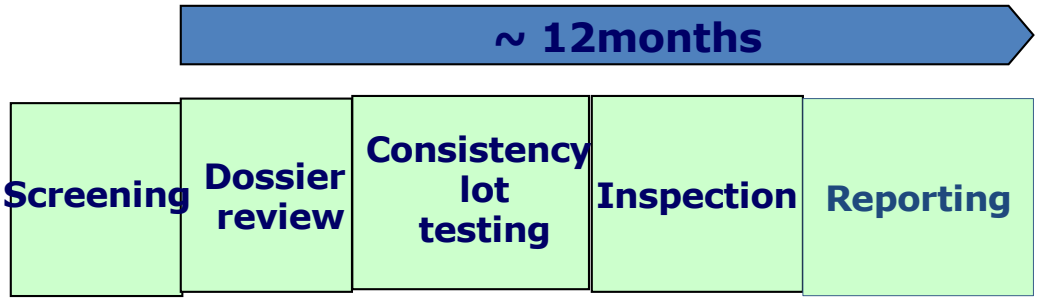
" ART. 58" & WHO vaccine prequalification independent timelines

EMA "Art. 58" process vaccines



Standard WHO PQ vaccines process



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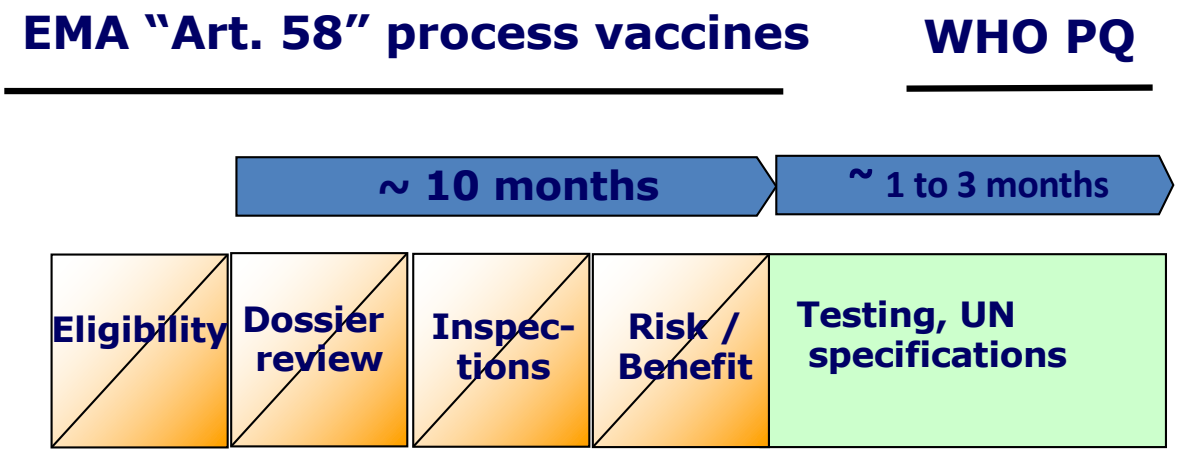
" ART. 58" & WHO vaccine prequalification combined timelines



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Article 58 CHMP Scientific Opinion(2)

Benefits

- ✓ Rigorous scientific assessment by European experts to the same high standards as for medicines intended for use in Europe;
- ✓ Involvement of experts from WHO and national regulatory authorities in target countries;
- ✓ Benefit-risk assessment tailored to intended non-EU population;
- ✓ A streamlined assessment under the WHO prequalification programme;
- ✓ Facilitated registration in target countries.

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Which are relevant to your companies?

STREAMLINED PROCEDURE: Depends on your NRA, not you

FAST TRACK PROCEDURE: Be aware of epidemiological and supply situation for its potential use

ARTICLE 58 SO: Discuss with colleagues and management feasibility of use in the context of your Company

Emergency use assessment and listing

What it is

- EUAL is a special procedure for vaccines in the case of a public health emergency established to expedite the availability of vaccines needed in such situations.
- Intended to assist interested UN procurement agencies and MS on the acceptability for use of a specific vaccine in the context of a PHE, based on a minimum set of available quality, safety, and efficacy data.
- Based on review of available quality, safety and efficacy data a on Risk/benefit analysis

What it is not

- It is not prequalification and should not be considered as such
- It is not a replacement of the PQ process

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Emergency Use Assessment and Listing (EUAL) (1)

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Eligibility

- ✓ The disease for which the vaccine is intended has been declared by the WHO Director- General to be a Public Health Emergency of International Concern (PHEIC). The Director-General may authorize use of this procedure for a public health emergency that does not meet the criteria of a PHEIC if s/he determines that this is in the best interest of public health.
- ✓ Depending on the specific public health emergency, a vaccine EUAL assessment applies when there is no licensed vaccine for the indication or for a critical subpopulation, or there is a specific vaccine shortage.
- ✓ The vaccine is subject to oversight by a NRA considered functional by WHO and willing to oversee batch release and post-EUAL product safety and quality.
- ✓ The vaccine is manufactured in compliance with current Good Manufacturing Practices (GMP).
- ✓ The vaccine applicant attests that it intends to complete the development of the product and apply for WHO prequalification.

Emergency Use Assessment and Listing (EUAL) (2)

Procedure

- ✓ Production and QC information
- ✓ Evidence of GMP compliance at manufacturing site
- ✓ Stability data demonstrating that vaccine maintains potency throughout its shelf life under the conditions of use
- ✓ Summary information on pre-clinical and clinical data
- ✓ Proposed labelling
- ✓ A plan to monitor quality, safety and efficacy in the field, and an undertaking to submit any new data to WHO as soon as these are available.
- ✓ A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

Collaborative registration procedure

Pathways to registration in user countries

MA in CoO

MA, enabler for PQ submission

PQ submission

Standard, streamlined, fast track or article 58 mechanisms

Product prequalification

CRP, enabler for country registration

User country registration

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CRP definition (2)

Procedure for collaboration between the World Health Organization (WHO) Prequalification Team (WHO/PQT) and interested national regulatory authorities (NRAs) in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines.

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CRP principles (3)

- ✓ The procedure is applicable to pharmaceutical products and vaccines that have been found to be acceptable in principle for supply through United Nations agencies
- ✓ Three major stakeholders: WHO/PQT, interested NRAs and those WHO PQ holders or applicants who agree that this Procedure is used for applications for national registration of their WHO-prequalified product submitted to an NRA.

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CRP procedure (3)

- ✓ WHO/PQT and participating authorities receive applications for the same pharmaceutical product or vaccine. The same pharmaceutical product or same vaccine is characterized by:
  - ✓ **The same product dossier**
  - ✓ **Same manufacturing chain, processes controls and batch release scheme**
  - ✓ **Same API and finished product specifications**
  - ✓ **Same product information, packaging presentation and labelling**
  - ✓ **WHO/PQT, with the agreement of the WHO PQ holder, shares the full outcome of prequalification assessments, inspections and, if relevant, also results of laboratory testing, including final assessment and inspection reports, with participating authorities, under appropriate obligations of confidentiality and restrictions on use**
  - ✓ **Participating authorities accept the product documentation and reports in the format in which they are routinely prepared by WHO**
  - ✓ **Fees to be paid by the applicants to participating authorities continue to follow standard national procedures.**
  - ✓ **Submission of samples for laboratory testing, continues to follow standard procedures as defined by NRAs.**
  - ✓ **Information and documentation should be treated as confidential**
  - ✓ **To issue its national regulatory decision on registration of a given prequalified product within 90 calendar days of regulatory time.**

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CRP features (3)

- ✓ These commitments are provided by each participating authority to WHO/PQT in writing by entering into the agreement for participation
- ✓ Each participating NRA nominates a maximum of three focal points and specifies their areas of responsibility for interaction with WHO and PQ holder
- ✓ The decision whether or not to register a given product in a particular country remains the prerogative and responsibility of each participating authority.
- ✓ Participation by WHO PQ holders/applicants is voluntary, through the submission to a participating NRA of the expression of interest
- ✓ The reporting of variations may not be the same between WHO and the country, leading to differences in the product being regulated. If such differences occur these should be communicated immediately to the counterpart.
- ✓ If products is withdrawn from the list by the PQ holder or delisted, this fact needs to be reported immediately. The same applies to NRAs

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DCVMN work related to CRP (4)

Background

- ✓ The CRP procedure applies both to WHO-prequalified pharmaceutical products and vaccines. It has been successfully implemented for pharmaceutical products. However, use of the procedure for vaccines remains low
- ✓ DCVMN in collaboration with IFPMA is engaged in finding options to assist countries to improve the efficiency of their registration procedures and alignment of requirements.
  - ✓ Registration based on reliance on PQ outcome is adopted only in few countries
  - ✓ CRP offers an informed reliance mechanism on the basis of the PQ assessment since it not just based on the outcome of the process but on the sharing of reports
  - ✓ DCVMN and IFPMA collaborate with WHO to foster implementation of CRP for vaccine products. WHO asked DCVMN to run a survey among manufacturers to identify five top priority countries and top products for CRP implementation

SURVEY FRAMEWORK

- Objective: Address WHO request to know the top five countries of interest from manufacturers perspective to be prioritized for CRP implementation in the 2020-2021 period
- Participants: DCVMN members with prequalified vaccines and other members planning to prequalify vaccines in the short term. In the context of the collaboration with IFPMA, their member companies, were also invited to participate
- Scope: Questions limited the scope to vaccines planned to be submitted for registration using the CRP within the two-years window
- Methodology: anonymized answers were pooled and analysed by an expert consultant and results summarized in the following slides

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SURVEY QUESTIONS

- The survey consisted of nine questions
- Companies were asked to list vaccine candidates that would be ready for registration within that timeframe and to specify whether the candidate vaccines were already prequalified or not
- Companies were asked to list the top five countries they would prioritize for registration of the listed vaccines
- Additional questions included volumes to be supplied to the listed countries, interest in engaging in CRP with those countries, whether they had a national agent or not, whether they planned and were prepared to submit the application in CTD

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Respondents to survey

Twelve (12) companies responded to the survey questions: 6/12 reported having vaccines already PQed and 6/12 are interested in registration of vaccines that are not yet prequalified and 5 may not be during the proposed period.

Top challenging countries

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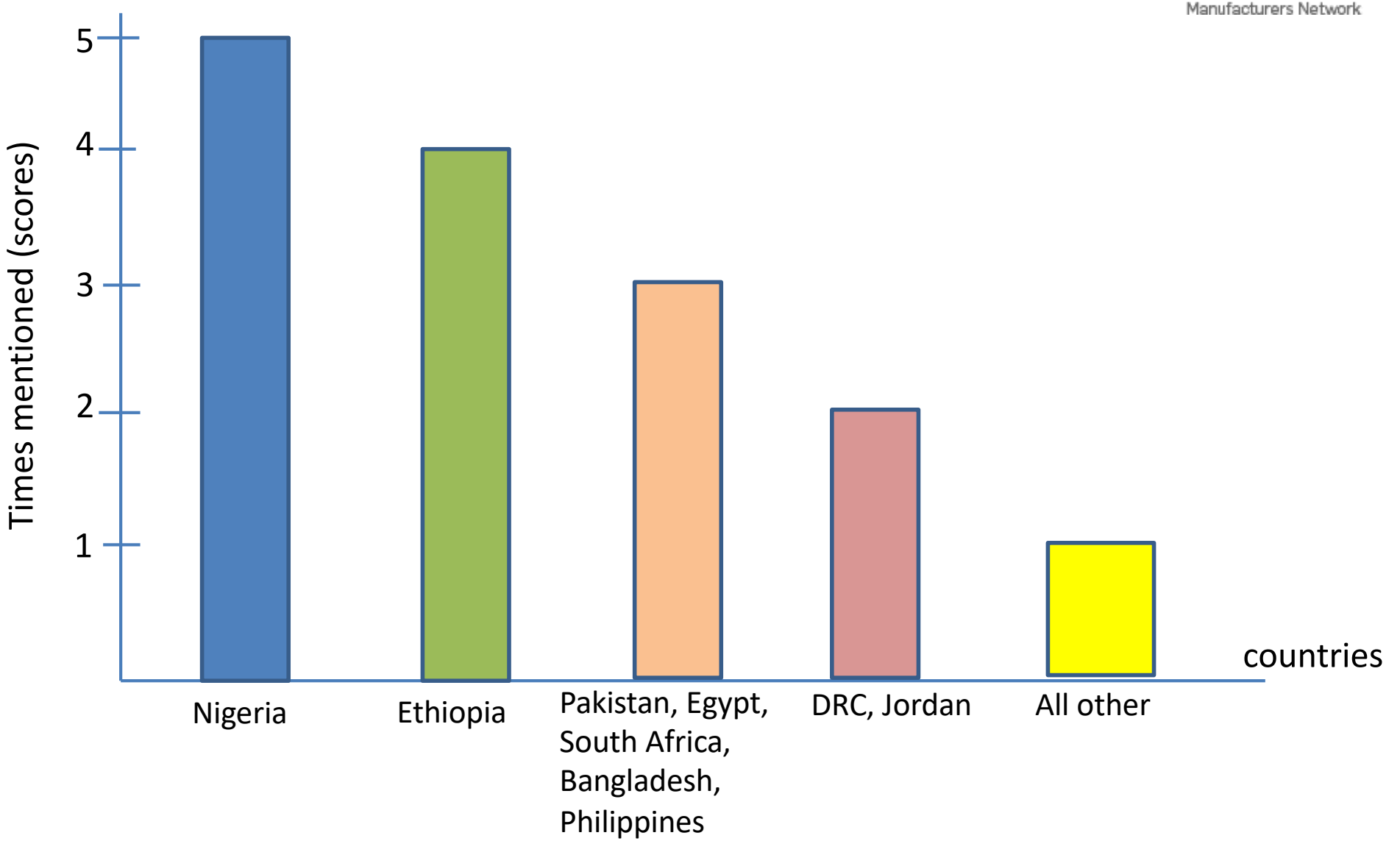

MATCHING PRIORITIZED COUNTRIES WITH POTENTIAL PRODUCTS FOR REGISTRATION

Vacs	Prioritized countries								
	Nigeria	Ethiopia	Pakistan	South Africa[1]	Bangla desh	DRC	Egypt	Phili ppine s	Jorda n[1]
Oral cholera		★			★	★			
Rotavirus	★	★ ★		★					★
PCV	★	★ ★							★ ★
JE (live)			★					★	
Penta	★		★	★			★		

[1] likely small supply. All other countries are high supply countries

Next steps

- WHO was satisfied with the information gathered through the survey
- WHO committed to work with relevant manufacturers bilaterally to implement the CRP in priority countries for the upcoming priority vaccines, rotavirus and PCV among other.

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References (2)

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THANK YOU

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