Collaborative Registration Procedure - overview of main principles

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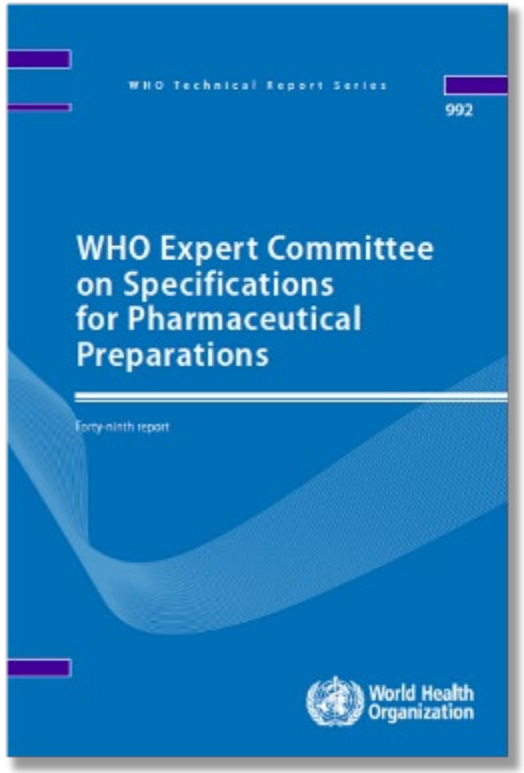
Access to medical products – global challenge

- WHO Constitution: "…the highest attainable standard of health is a fundamental right of every human being."
- Good health is impossible without access to medical products;
- Universal Health Coverage depends on the availability of quality-assured affordable health technologies in sufficient quantities;
- An estimated **two billion people have no access to essential medicines**, effectively shutting them off from the benefits of advances in modern science and medicine.
- Reasons for limited/insufficient access are numerous – including inadequate regulatory capacity and lack of collaboration and work sharing in medicines regulatory area between countries.

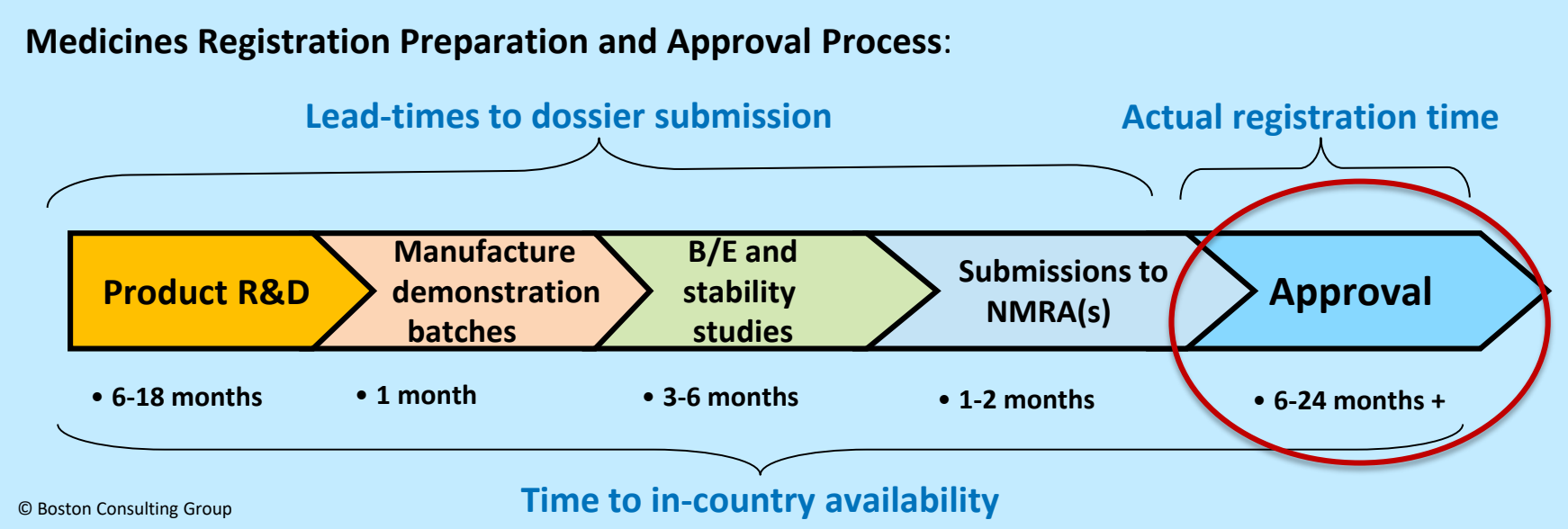
Globalization in medical products regulation (1)

- All medical products should be used in the countries **only after approval by the national or regional regulatory authority - in line with current international standards** (WHA Resolutions: WHA 67.20 (2014); WHA 67.21 (2014); WHA63.12 (2010)**;**
- There is no clear vision or policy about HOW to set up regulatory systems in times when it is unrealistic to manage all functions in one national setting for most regulators – due to **globalization of regulatory science**;
- New products are likely more complex and sophisticated – demanding advanced health systems and "quality use“.



Why focusing on national regulatory approval?

- To improve public health by increasing rapid access to safe and effective medicines of good quality for the treatment of priority diseases;
- Focus on in-country registration as one factor in the time it takes for beneficial therapies to reach patients in need.



How to “transfer/translate” the regulatory information from trusted sources to facilitate in-country approval?

The Sixty-seventh World Health Assembly resolution 67.20 recognized that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products

- WHO Prequalification and approval by “SRAs” provide good basis for informed national registration;
- How do we get the prequalified and “SRA”- approved product to the patients faster, and more efficient?
- How do we ensure continued supply of quality-assured products post-registration?

Regulatory information and knowledge could be transferred through facilitated pathways

MAIN PRINCIPLES:

- **Sharing information / expertise** (assessment, inspection and testing results or expertise) that serve as basis for authornational decisions – avoiding duplication.
- **Voluntary participation** – reference authorities, participating ities and manufacturers/sponsors

WHO PQ collaborative registration procedure

Vaccines: 2004

- Medicines: Started in 2012
- Diagnostics: Pilot 2019
- Vector control: Pilot 2020

**CRP-lite

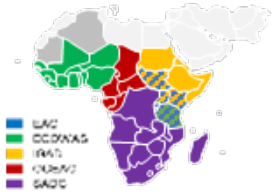
"SRA" collaborative registration procedure

Initiated in 2015

- European Medicines Agency (EMA)
- UK Medicines and Healthcare Products Regulatory Agency (MHRA)
- 20 African NRAs

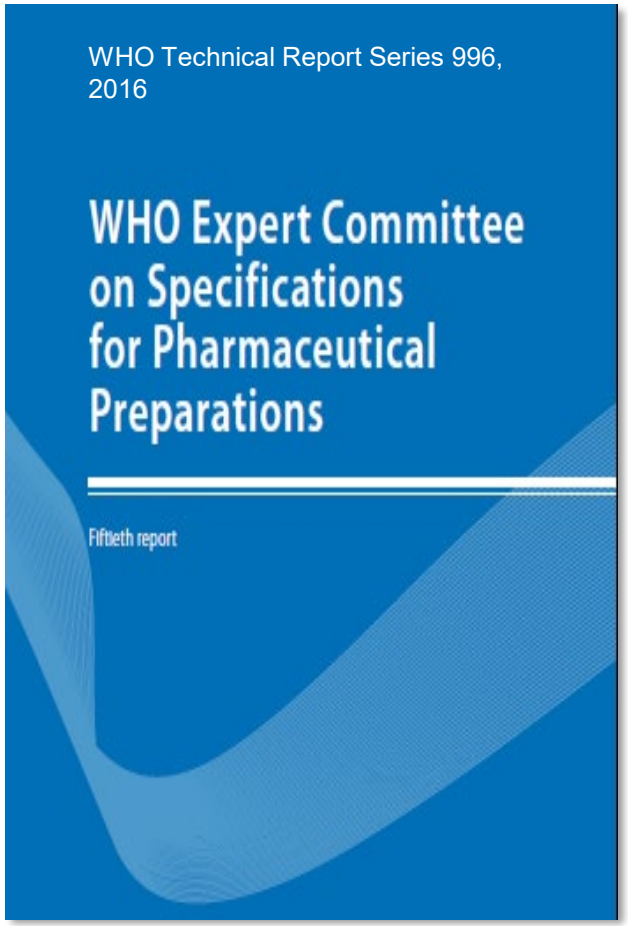
Regional networks

African Medicines Regulatory Harmonization Project (AMRH)



ASEAN SIAHR Project

Applicable guidelines for CRP



http://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1

Annex 8

Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

Facilitated registration based on reliance (1)

Regulators worldwide can benefit from already conducted scientific assessments and inspections to support the national registrations, if:

- Have access to regulatory expertise from trusted party (complete assessment and inspection reports);
- Have the same product;
- Have the same essential technical data;
- Understand validity of B/R for local environment;

Important to mention that:

- National legislation and sovereignty are not affected;
- Confidentiality of commercially sensitive information is respected;
- Regulatory follow-ups are properly managed.

If we share information (assessments, inspections, testing) for WHO PQ-ed or “SRA”-approved products

THEN…

NRAs can rely on the shared information to facilitate national decisions

Reliance / Recognition

- avoid duplications
- reduce regulatory burden
- assess B/R in local context

Normal pathway

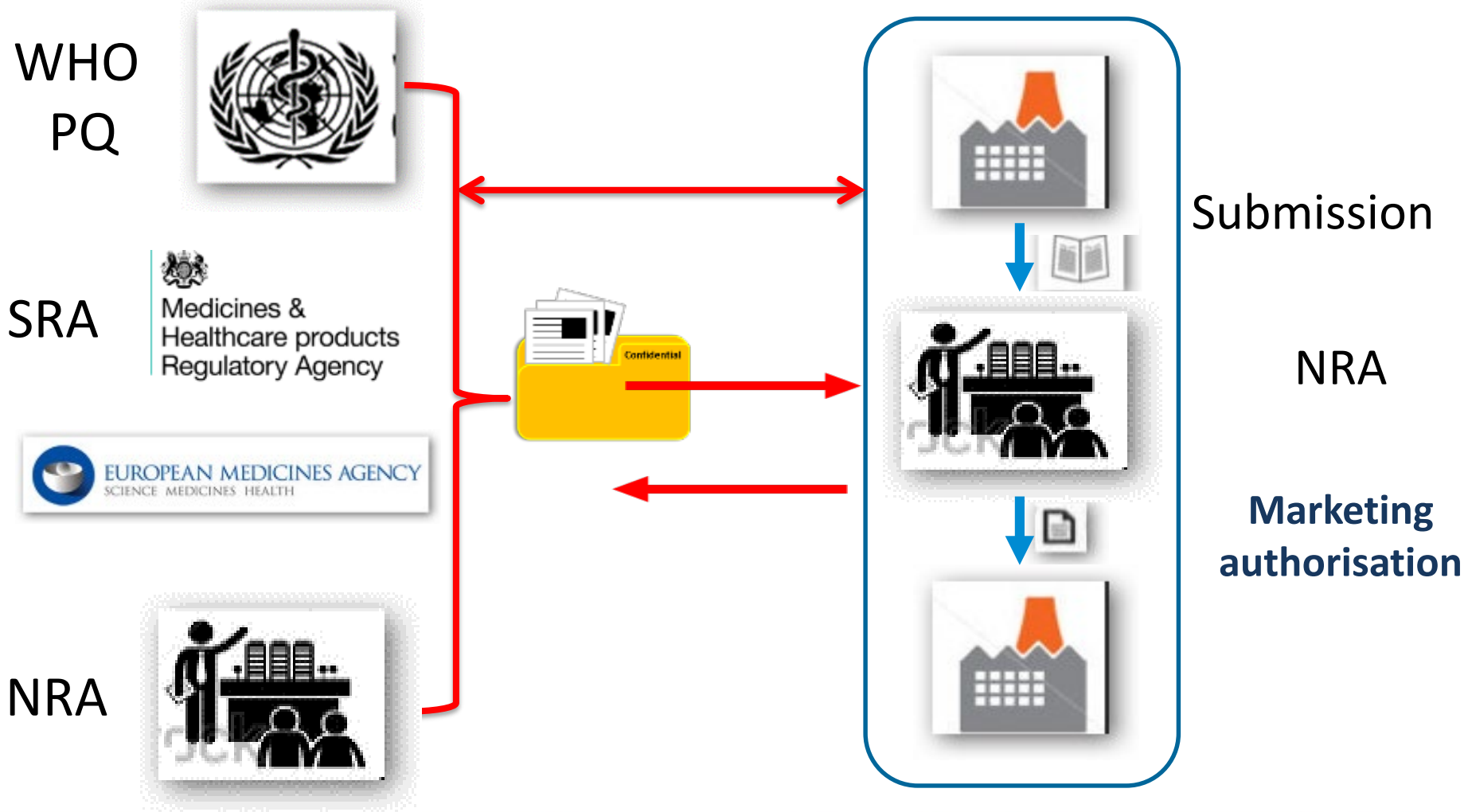
THEN…

Timely access to quality- assured products with positive B/R

Re-allocate resources

Enhanced NRA’s oversight on other products & sites

How does the collaborative procedures works?



Facilitated Registration Pathways – key principles

- Voluntary;
- Product and registration dossier in countries are “the same” as **prequalified by WHO or approved by “SRAs”;**
- Shared confidential information to support NRA decision making in **exchange for accelerated registration process;**
- “Harmonized product status” is monitored and maintained.

Win-win outcomes for all concerned stakeholders - patients in the focus

NRAs

- Having data well organized in line with PQ requirements;
- Availability of unredacted WHO assessment, inspection and performance evaluation outcomes to support national decisions and save internal capacities;
- Having assurance about registration of “the same” product as is prequalified;

WHO

- Prequalified products are faster available to patients;
- Feed-back on WHO prequalification outcomes;

Manufacturers

- Harmonized data for PQ and national registration;
- Facilitated interaction with NRAs in assessment, inspections, performance evaluations;
- Accelerated and more predictable registration;
- Easier post-registration maintenance;

Procurers

- Time, assurance, availability.

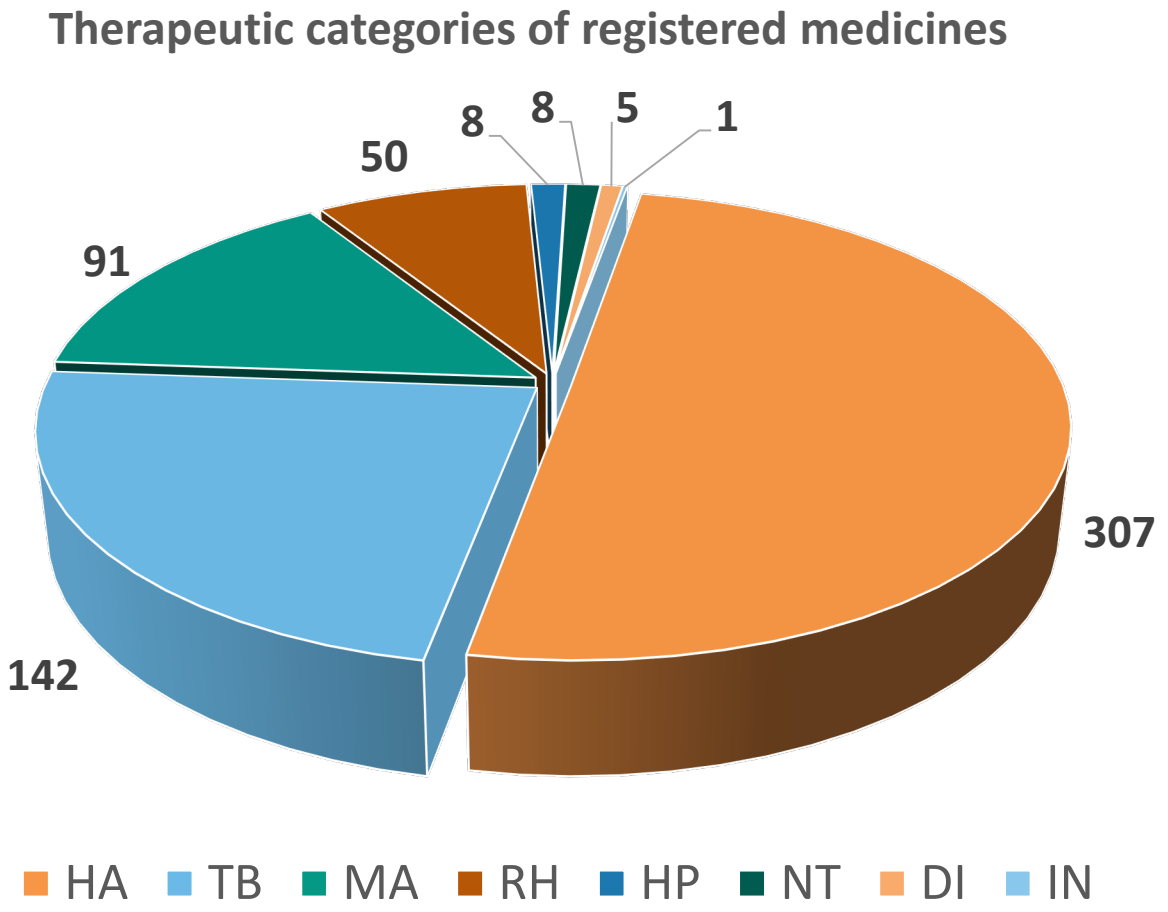
44 Participating NRAs, plus 1 REC - Medicines

As at 30 Nov 2020

Armenia
Azerbaijan
Belarus
Botswana
Burkina Faso
Bhutan
Burundi
Cameroon
*Caribbean Community (CARICOM)
Comoros
Cote d'Ivoire
Dem. Rep. Congo
Eritrea
Ethiopia
Georgia
Ghana
Kazakhstan
Kenya
Kyrgyzstan
Lao PDR
Madagascar
Malaysia
Malawi
Mali
Mauritania
Mozambique
Namibia
Nigeria
Pakistan
Philippines
Rwanda
Senegal
Sierra Leone
South Africa
Sri Lanka
Sudan
Tanzania
Thailand
Togo
Uganda
Ukraine
Uzbekistan
Zambia
Zanzibar
Zimbabwe

* CARICOM
Member States: Antigua and Barbuda, Bahamas, Belize, Dominica, Grenada, Haiti, Jamaica, Montserrat, Saint Lucia, St. Kitts and Nevis, St Vincent and the Grenadines, Suriname and Trinidad and Tobago
Associate Member States: Anguilla, Bermuda, British Virgin Islands, Cayman Islands and Turks and Caicos Islands

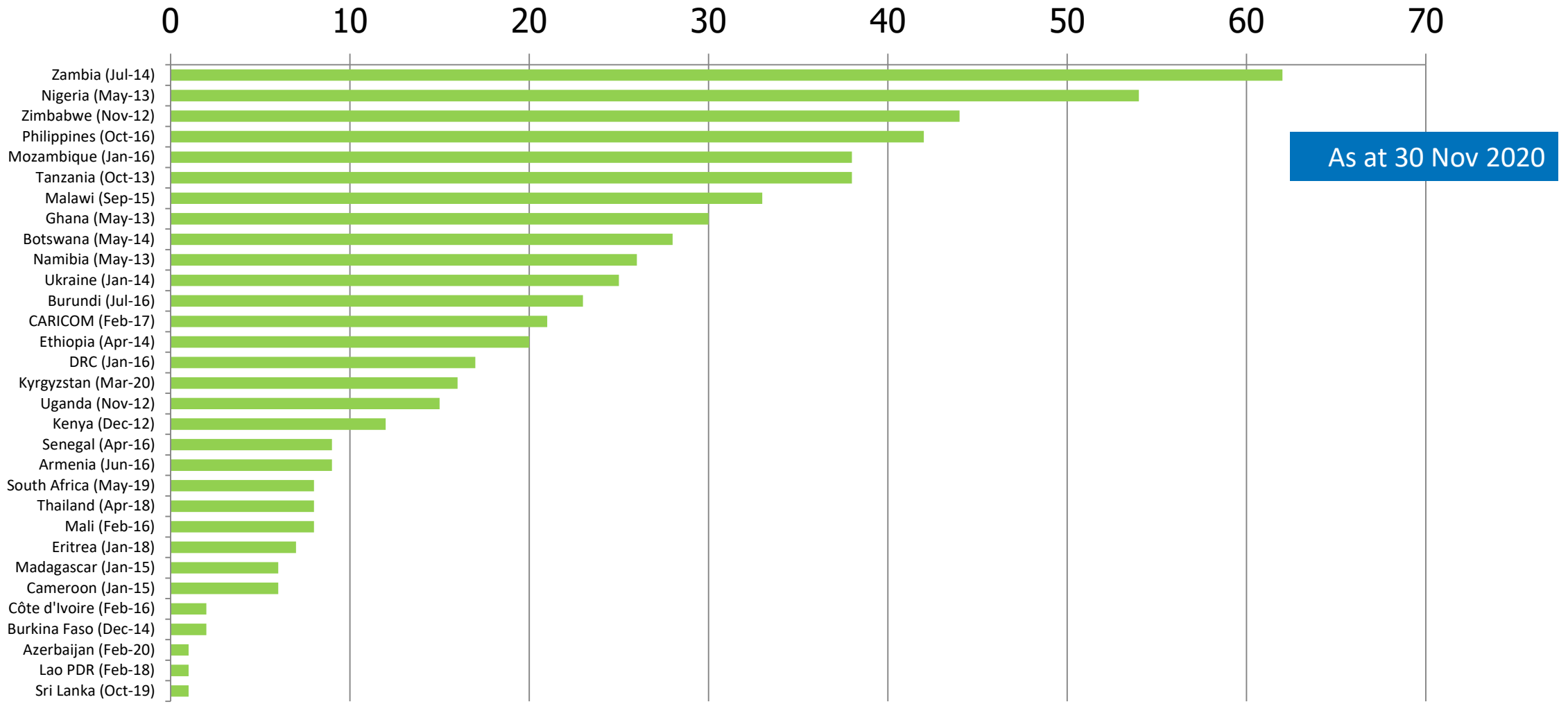
Registrations by therapeutic area



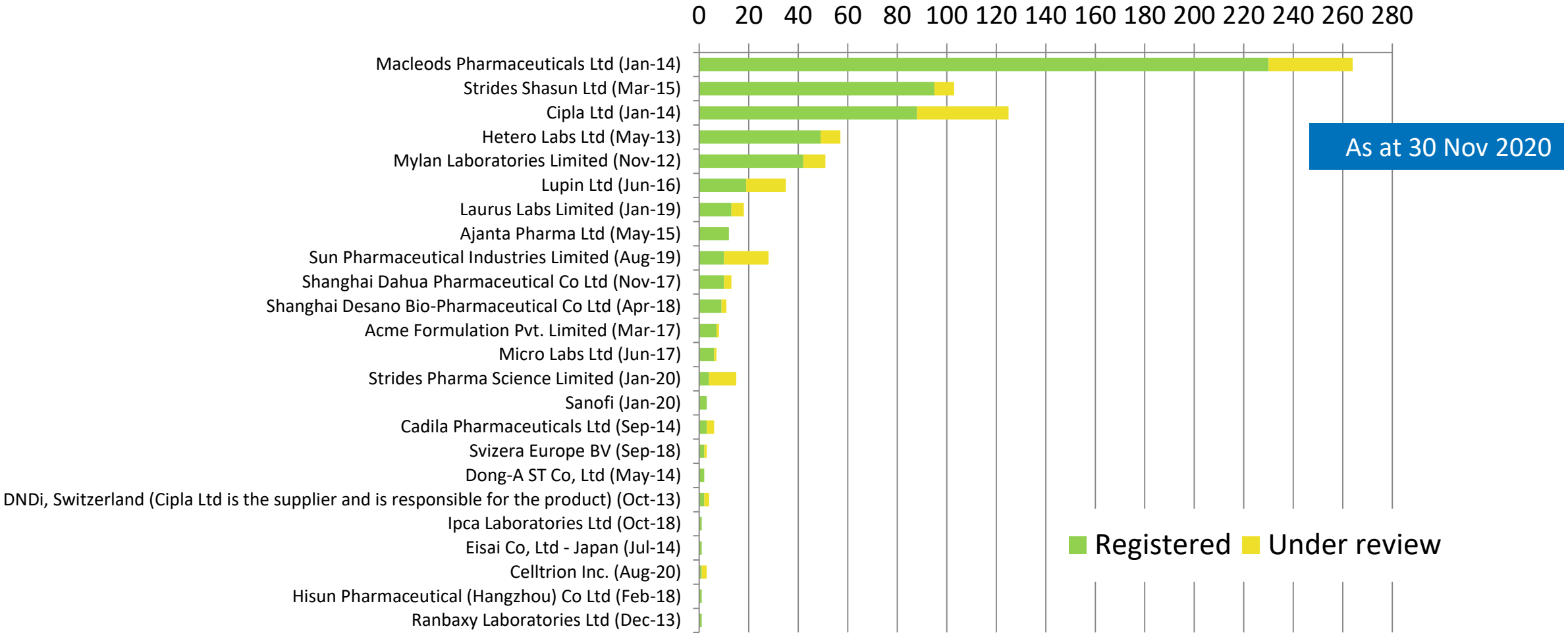
Total registrations: 612

As at 30 Nov 2020

Registrations by country



Registrations by manufacturer

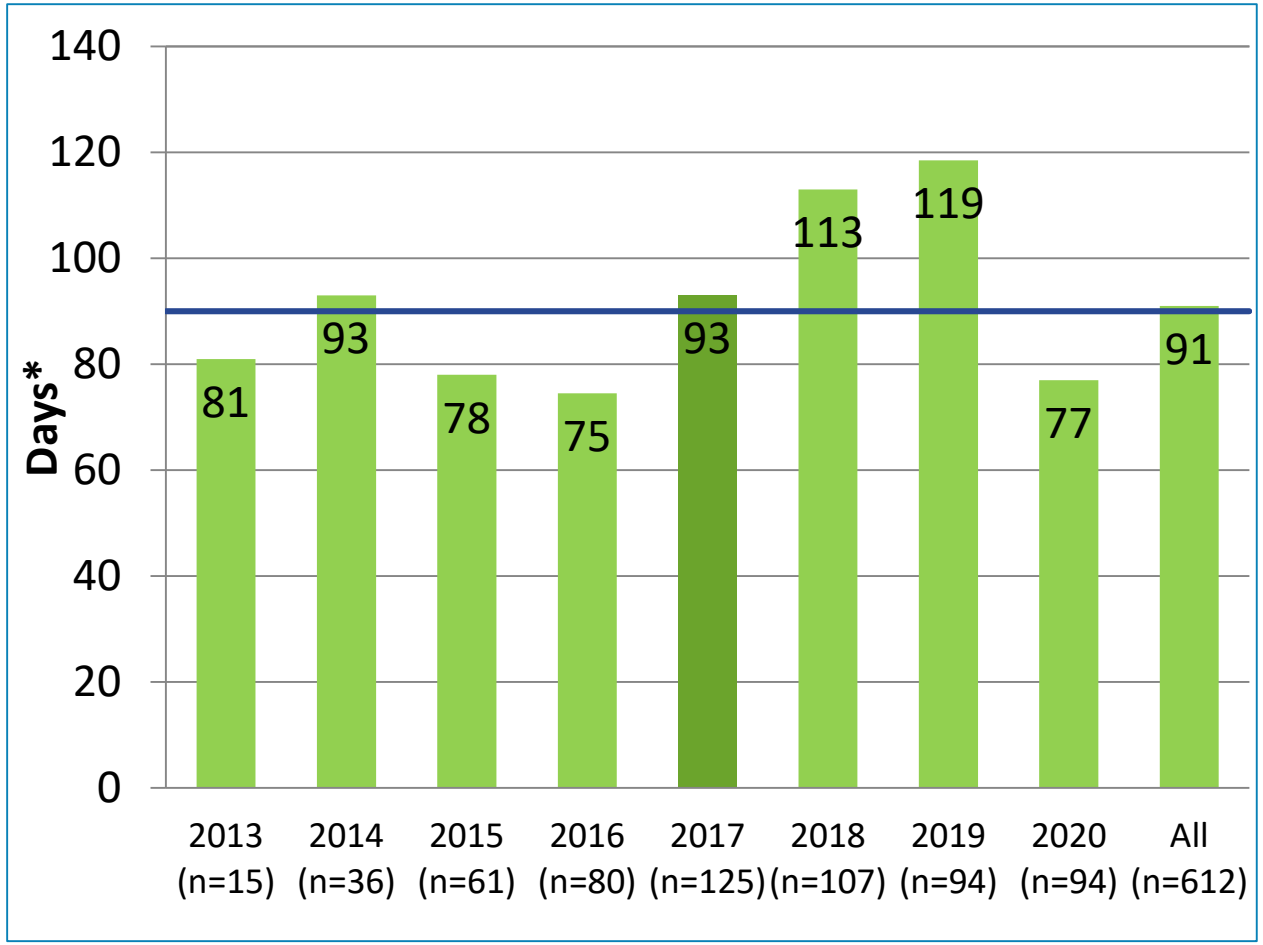


Median time to registration

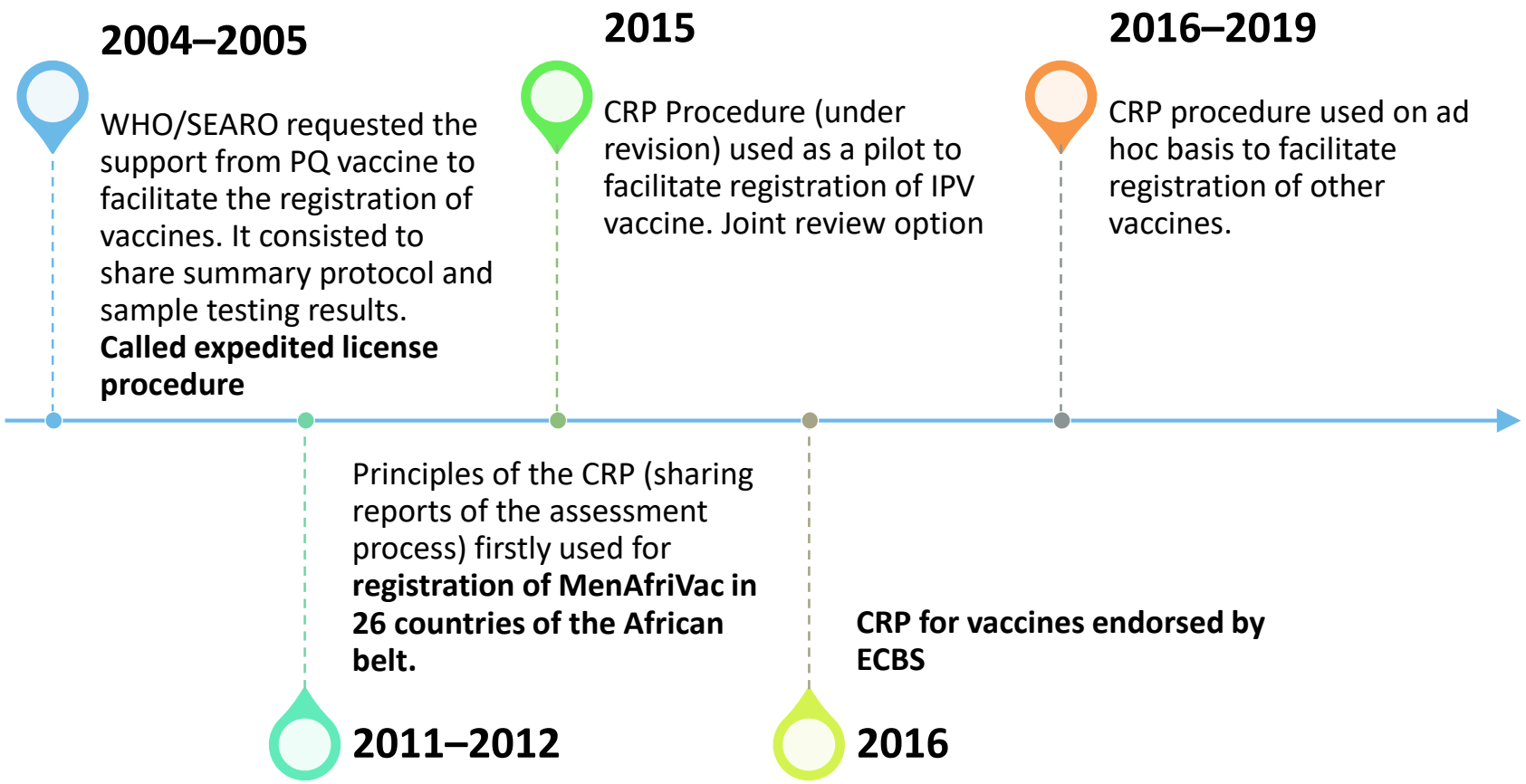
*Including regulatory time and applicant time

As at 30 Nov 2020

90 days TARGET



CRP for Vaccines: some history



44 Participating NRAs + 1 REC

2012	2013	2014	2015	2016	2017	2018	2019	2020
Botswana	Georgia	Armenia	Burundi	CARICOM**	Eritrea	Belarus	Azerbaijan	Malaysia
Ghana	Kyrgyzstan	Burkina Faso	Mali	Lao PDR#	Sri Lanka	Kazakhstan	Comoros	Rwanda
Kenya#	Madagascar	Cameroon#	Philippines	South Africa	Thailand	Pakistan	Uzbekistan	Mauritania
Namibia	Mozambique	Côte d'Ivoire#	Senegal#			Sudan	Bhutan	Togo
Nigeria	Ukraine	DRC						
Tanzania		Ethiopia#						
Uganda		Malawi						
Zambia		Sierra Leone						
Zanzibar*								
Zimbabwe								
10	5	8	3	3	3	4	4	4

#Confirmation and submission of updated CRP Agreements, inclusive of vaccines, is still pending.

** Regional Economic Community

Vaccine registrations

WHO PQ number	Product	Prequalification holder	Country of registration	Registration date	Registration number
87.40	Easyfive-TT 10 Vials	Panacea Biotec Ltd	Botswana	3/Jul/18	BOT1803403
304.10	Eupenta Carton of 1 dose [Dimensions 8.5x3.8x4.5 cm]	LG Chem Ltd	Ethiopia	20/Dec/17	3582/4794/NMR/2017
304.10	Eupenta Carton of 1 dose [Dimensions 8.5x3.8x4.5 cm]	LG Chem Ltd	DRC	23/Mar/18	MS1253/10/05/DGM/0162/ 2018
304.10	Eupenta Carton of 1 dose [Dimensions 8.5x3.8x4.5 cm]	LG Chem Ltd	Thailand	29/Dec/19	(blank)
305.10	Eupenta carton of 10 vials (100 doses) with dimensions 11.6 x 4.7 x 5.3 cm	LG Chem Ltd	Ethiopia	20/Dec/17	3582/4794/NMR/2017
305.10	Eupenta carton of 10 vials (100 doses) with dimensions 11.6 x 4.7 x 5.3 cm	LG Chem Ltd	DRC	23/Mar/18	MS1253/10/05/DGM/0161/ 2018
305.10	Eupenta carton of 10 vials (100 doses) with dimensions 11.6 x 4.7 x 5.3 cm	LG Chem Ltd	Thailand	29/Dec/19	(blank)
314.10	Rotavac 5 vials	Bharat Biotech International Limited	Nigeria	18/May/20	A6-0579
314.10	Rotavac 5 vials	Bharat Biotech International Limited	Zambia	20/Jul/20	233/005
318.10	Typbar-TCV 1 vial	Bharat Biotech International Limited	Zambia	20/Jul/20	233/007
336.10	Euvichol-Plus (Cholera) 50 dose	EuBiologics Co., Ltd.	CARICOM	12/Apr/18	CRS/112017/193/022
336.10	Euvichol-Plus (Cholera) 50 dose	EuBiologics Co., Ltd.	Nigeria	6/Jun/18	A6-0486
343.10	Rotavac 10 Vials	Bharat Biotech International Limited	Nigeria	18/May/20	A6-0579
343.10	Rotavac 10 Vials	Bharat Biotech International Limited	Zambia	20/Jul/20	233/006
347.10	Typbar-TCV 5 vials	Bharat Biotech International Limited	Zambia	20/Jul/20	233/008
374.10	Measles and Rubella 5 Vials + Ampoule	Biological E. Limited	Zambia	9/Jul/20	485/001
375.10	Measles and Rubella 10 Vials + Ampoule	Biological E. Limited	Zambia	9/Jul/20	485/002
384.10	Pneumosil 1 vial	Serum Institute of India Pvt. Ltd	Malaysia	9/Jul/20	MAL20076001AZ
385.10	Pneumosil 5 vials	Serum Institute of India Pvt. Ltd	Malaysia	9/Jul/20	MAL20076002AZ

Path forward for vaccines CRP

- Selection of vaccines;
  - Vaccines PQ-ed in the last 5 years:
  - Availability of shareable clinical, CMC, inspection and testing reports;
- Identification of priority countries based on:
  - WHO priorities - benchmarking/assessment and status of IDP implementation;
  - willingness of the manufacturers.
- Initiation of CRP in selected countries in several implementation waves;
- Follow-up, evaluation of the impact and expansion to other countries.

WHO PQ CRP Status update: In vitro Diagnostics

Pilot CRP for IVDs: April 2019 – Dec 2019

Objectives:

- Use the WHO-prequalification obtained for m-PIMA HIV-1/2 VL as a basis for country registrations.
- Assess feasibility of new WHO Collaborative Procedure including impact on registration timelines and requirements for additional country-specific studies.

Participating Countries:

Nigeria, Ivory Coast*, Tanzania, Ethiopia, Cameroon*. Upon Abbott request, Ghana was included in the pilot.

Results:

Three countries were able to register the products, Ivory Coast has not registered the product yet and *Cameroon did not participate*

Registration Status

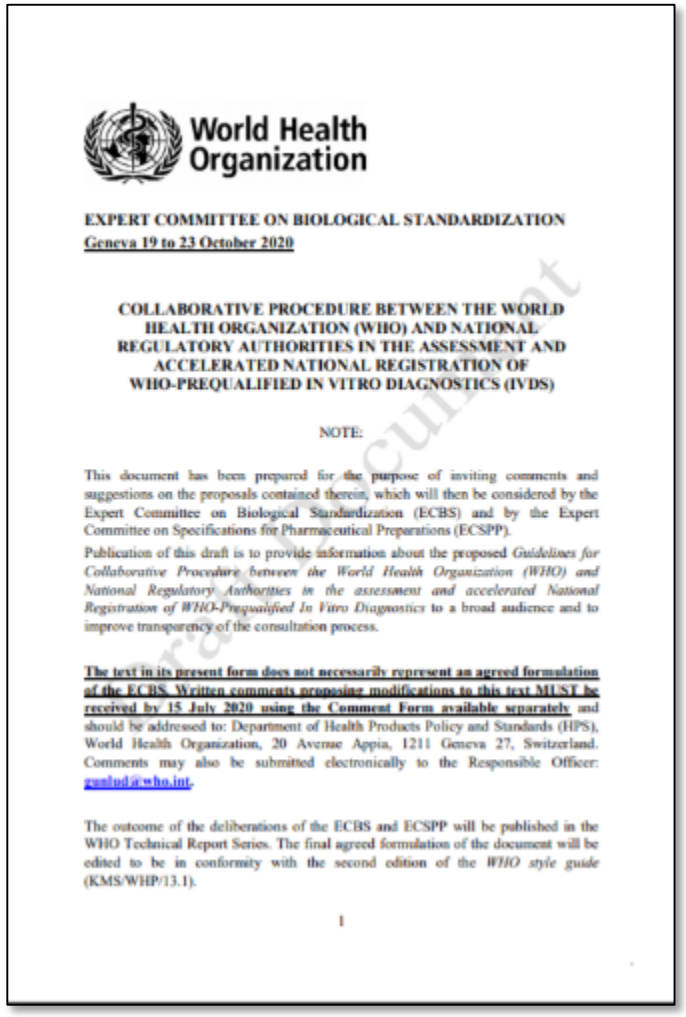
Product name	Applicant	Country of registration	Date of registration	Registration number
m-PIMA HIV-1/2 VL	Alere Technologies GmbH	Tanzania	29/Jul/19	H2013/CTD667/073
m-PIMA HIV-1/2 VL	Alere Technologies GmbH	Ethiopia	17/Oct/19	228/12
m-PIMA HIV-1/2 VL	Alere Technologies GmbH	Nigeria	24/Feb/20	03-7250.

Two of the three registrations completed within the 90 day-timeline

Lessons learned

- Proved to be a great innovative mechanism that can accelerate registration of diagnostics and facilitate timely availability of IVDs. Benefits exhibited include:
  - shorter regulatory approval times. IVDs can be registered within the accelerated **timeline of 90 days**.
  - reduced workload for NRA experts due to reduced need for in-country evaluations based on acceptance of WHO PQ reports.
- Factors which contributed to delays include:
  - In country registration requirements such as mandatory submission of samples and repetitive in country performance evaluation.
  - Inadequate communication between key participants.

Guideline endorsed by ECBS - October 2020



World Health Organization

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva 19 to 23 October 2020

COLLABORATIVE PROCEDURE BETWEEN THE WORLD HEALTH ORGANIZATION (WHO) AND NATIONAL REGULATORY AUTHORITIES IN THE ASSESSMENT AND ACCELERATED NATIONAL REGISTRATION OF WHO-PREQUALIFIED IN VITRO DIAGNOSTICS (IVDS)

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS) and by the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).

Publication of this draft is to provide information about the proposed *Guidelines for Collaborative Procedure between the World Health Organization (WHO) and National Regulatory Authorities in the assessment and accelerated National Registration of WHO-Prequalified In Vitro Diagnostics* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received by 15 July 2020 using the Comment Form available separately and should be addressed to: Department of Health Products Policy and Standards (HPS), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: gonlud@who.int.

The outcome of the deliberations of the ECBS and ECSPP will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the second edition of the *WHO style guide* (KMS/WHP/13.1).

1

Collaborative procedure between the World Health Organization (WHO) and National Regulatory Authorities in the assessment and accelerated national registration of WHO-prequalified In Vitro Diagnostics (IVDs)

Progress made

- WHO in collaboration with UNITAID have been conducting workshops with STAR Phase 3 countries for HIVST including Tanzania, Cameroon, Mozambique, Uganda, Indonesia and India with the objective of creating awareness on the benefits of the CRP in accelerating marketing authorization of new IVDs.
- Increased number of CRP applications for countries that participated successfully in the pilot project e.g. 3 new applications in Nigeria.
- Roll out of CRP for IVDs is planned next year after the Collaborative Registration Procedure guideline for in vitro diagnostics has been officially published.

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CRP – Recommendations

- Insufficient/lack of awareness among manufacturers/applicants – **continue advocacy and awareness activities;**
- Industry representatives confirmed their commitment to the CRP – **including for IVDs and VCP;**
- Challenges in accessing unredacted reports from reference agencies – **manufacturers to be proactive (give consent and share reports);**
- Performance on variations are not well monitored and reported – **manufacturers to proactively share the data on approvals and timelines with WHO;**
- PQ /SRA approved variations not submitted to NRAs – **manufacturer's responsibility to ensure variations are submitted timely to NRAs;**
- Progress so far with PQ-based CRP is remarkable – **for SRA-based there is a need of improvement.**

Conclusions:

- Timely access to medical products – never-ending challenge;
- Not a single regulator anymore can fulfil all regulatory work alone;
- To generate quality national decisions regulators globally MUST collaborate and MUST take into consideration the information available from other regulatory authorities;
- Not using the outputs and outcomes from other regulatory authorities means lost opportunity, duplication of efforts, increased regulatory burden and waste of scarce resources.

Questions to answer:

1. What worked well and what does not work well with CRP – regulators' and industry's perspective?
2. How to increase awareness of the CRP and its benefits among various stakeholders?
3. How to improve the procedure and its use for all products groups?

World Health Organization

www.who.int/medicines