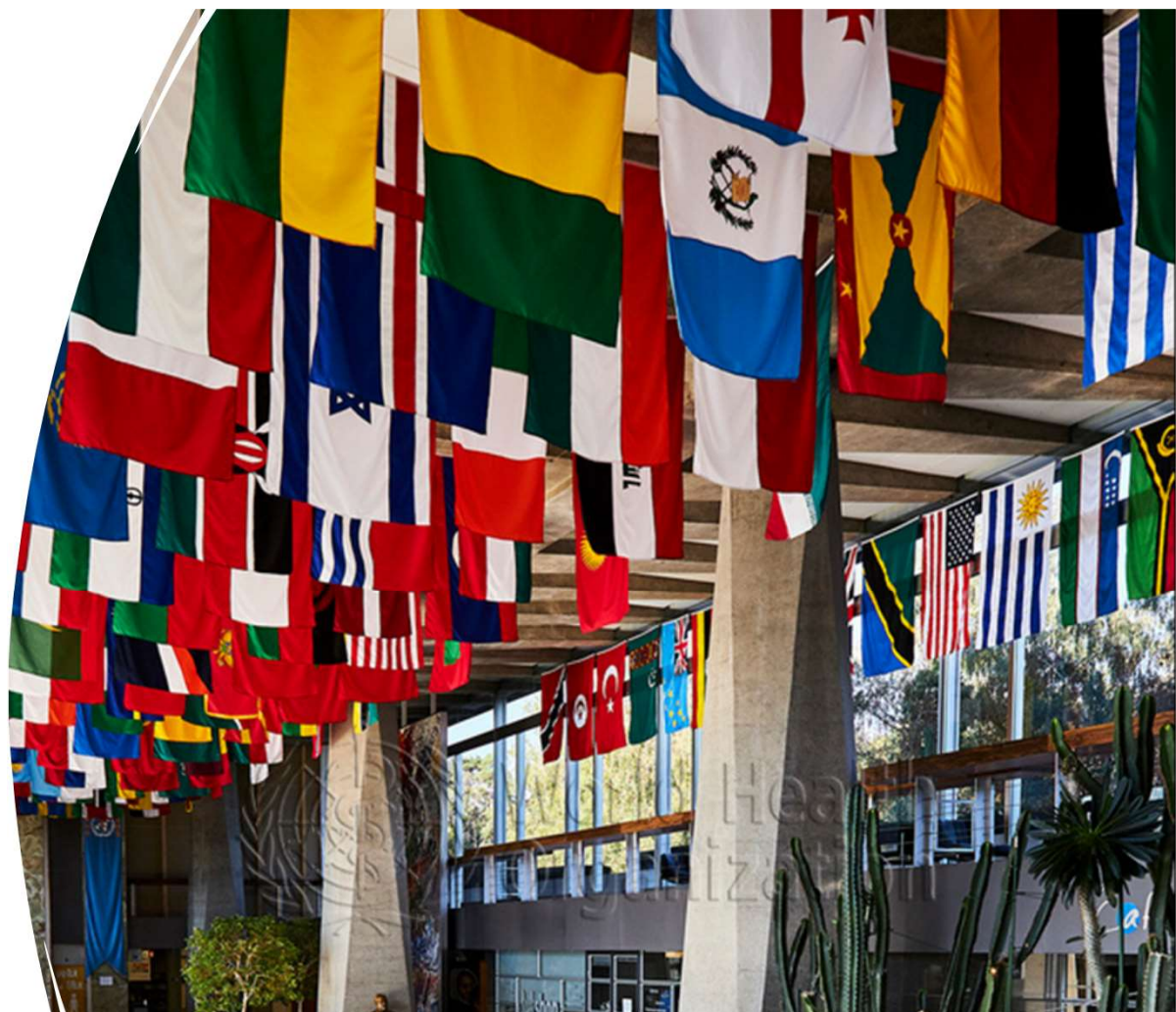


# Overview of Collaborative Registration Procedure: progress in implementation and identified challenges

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Department  
World Health Organization



**Workshop with Developing Countries Vaccine Manufacturers Network (DCVMN)  
on Collaborative Registration Procedure (CRP) for vaccines  
26 -27 September 2022**



## Access to medical products – global challenge

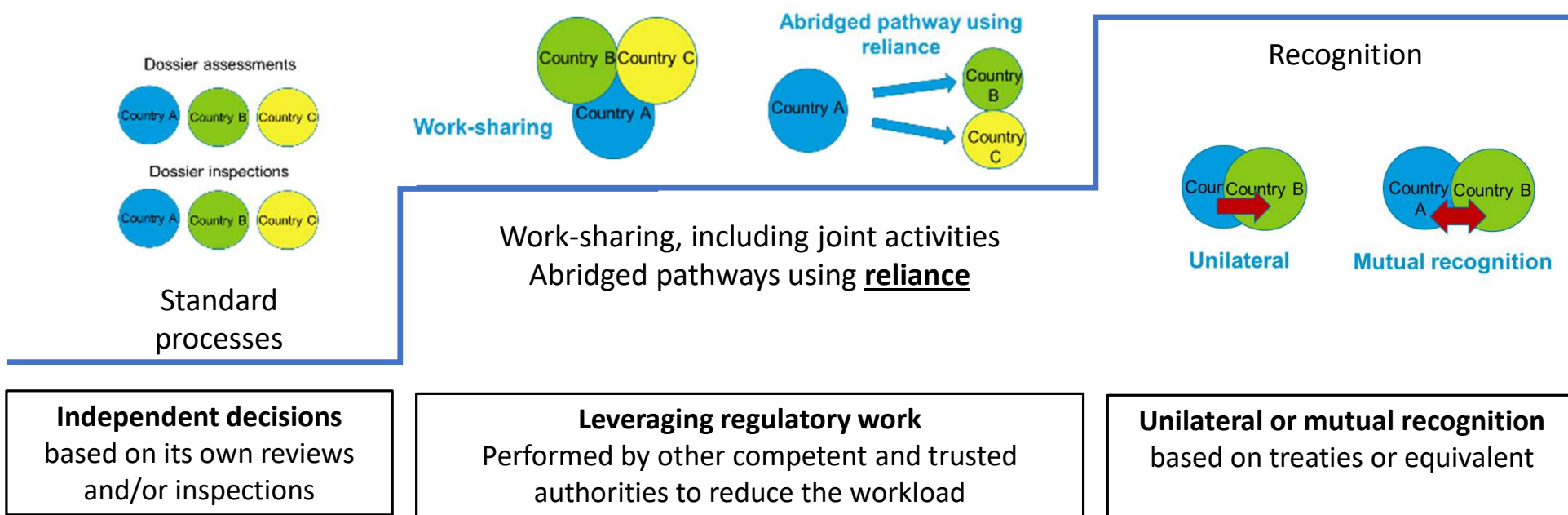
- Good health is impossible without access to medical products;
- An estimated **two billion people have no access or very limited access to essential medical products**;
- Reasons for limited/insufficient access are numerous – including insufficient/inadequate regulatory capacity and lack of collaboration and work sharing between countries in regulation of medical products.

# WHO efforts to facilitate good quality decisions – based on reliance



- Strong regulatory capacity is an essential component of a well-functioning healthcare system ([Resolution WHA 67.20, 2014](#))
- Globally, >70% of countries have weak national regulatory systems
  - Only 56 countries (29%) have regulatory systems at GBT **maturity level 3 or 4** (<https://www.who.int/initiatives/who-listed-authority-reg-authorities>)
- WHO regulatory systems strengthening programme responds to addressing this challenge
  - Benchmarking to document strengths and identify gaps
  - Capacity building, including training based on Global Competency Framework and Regulatory Curriculum
  - **Promoting smart regulation – good regulatory and reliance practices**

# Options to facilitate good quality regulatory decisions – reliance in the focus



# Promoting Good Regulatory and Reliance Practices



## Good regulatory practices

Set of principles and practices applied to the development, implementation and review of regulatory instruments in order to achieve a public health policy objectives in the most efficient way



Addressing responses to **common gaps in regulatory practices** identified during benchmarking of national regulatory systems



**Relevant to all regulators**, irrespective of resources, maturity or regulatory models (national, supranational and multiple institutions)

[Annex 11: Good regulatory practices in the regulation of medical products](#) (March 2021)



## Good reliance practices

The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision.



Importance of **international cooperation** to ensure the safety, quality and efficacy or performance of locally used medical products



**Make best use of available resources and expertise**, avoid duplication and concentrate regulatory efforts and resources where most needed

[Annex 10: Good reliance practices in the regulation of medical products](#) (March 2021)



# Reliance to support national regulatory decisions

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- Promoting a more efficient approach to regulatory oversight, thereby improving access to quality-assured, effective and safe medical products over their entire life-cycle;
- Relying authority remains **independent, responsible and accountable** regarding the decisions taken, even when it relies on the decisions, assessments and information of others.



## How to “transfer/translate” regulatory information from trusted sources to facilitate in-country approval of medical products?

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 decision making;
- How do we get the prequalified and “SRA”-approved product to the patients faster, and more efficiently?
- How do we ensure continued supply of quality-assured products post-registration?



# Facilitated Registration Pathways – key principles

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- 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.





# Reliance is “implanted” in facilitated regulatory pathways

WHO PQ  
collaborative  
registration  
procedure

- Vaccines: 2004
- Medicines: Started in 2012
- FDA-WHO joint pilot to accelerate access to HIV medicines (CRP-lite)
- Diagnostics: Pilot 2019
- Vector control: Pilot 2020

“SRA”  
collaborative  
registration  
procedure

- Initiated in 2015
- European Medicines Agency (EMA)
- UK Medicines and Healthcare Products Regulatory Agency (MHRA)
- 20 African NRAs

Regional  
regulatory  
harmonization  
initiatives and  
networks

African Medicines  
Regulatory  
Harmonization  
Initiative (AMRH)



ASEAN SIAHR Project



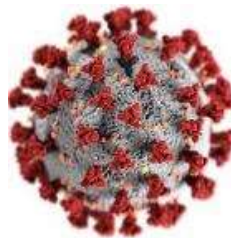
# Reliance supported national decision making during COVID-19 pandemic

## COVAX

With a fast-moving pandemic, no one is safe, unless everyone is safe

COVAX is co-led by CEPI, Gavi and WHO, alongside key delivery partner UNICEF. In the Americas, the PAHO Revolving Fund is the recognized procurement agent for COVAX.

CEPI



Expert Review of Clinical Pharmacology

<https://www.tandfonline.com/doi/full/10.1080/17512433.2022.2088503>

### Facilitation of EUL process

**31 December 2020, first WHO EUL for a COVID-19 vaccine** (BNT162b2 mRNA vaccine). Ten days after EMA scientific opinion.

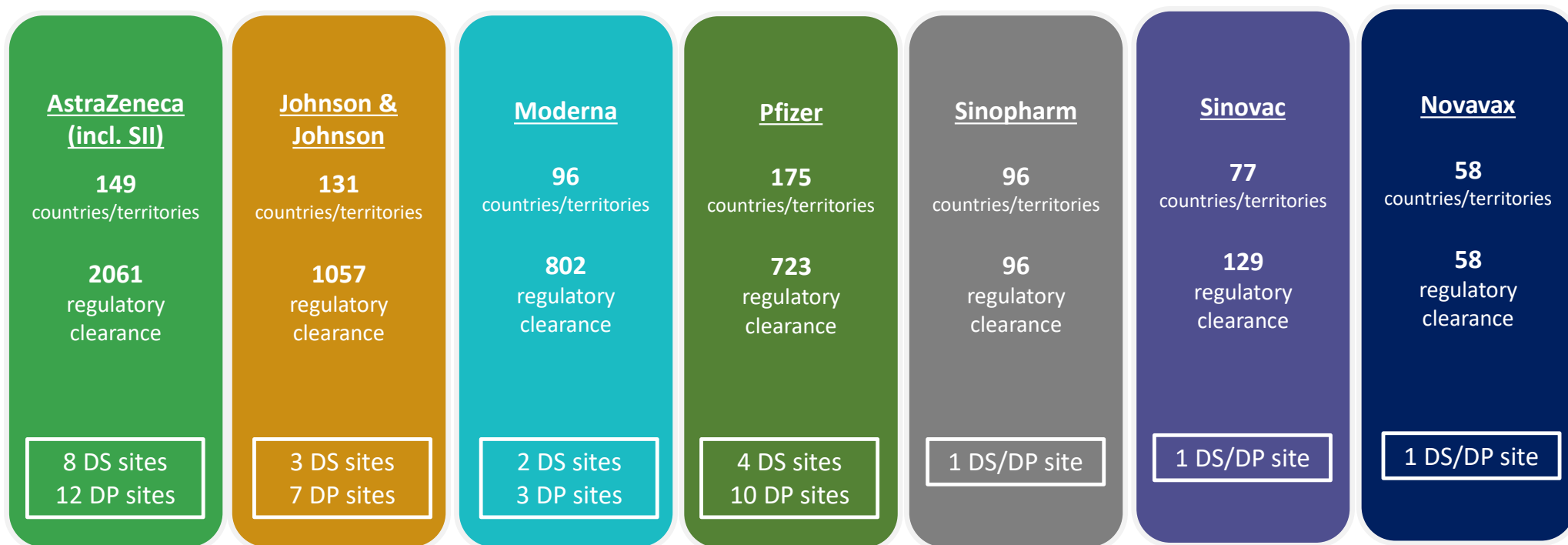
### In-country authorizations for use

**First roll-out in Feb-March 2021** ChAdOx1 vaccine  
**Approvals/import permits in 101 out of 145 countries (70%) within 15 days** of WHO EUL (15 February 2021)

Overall, over **2 billion vaccines doses** allocated in over **190 countries/territories** involving close to **5,000 regulatory approvals** as of August 2022

**Reliance in Lifecycle/all reg functions**  
Authorization,  
Pharmacovigilance,  
Batch release,  
Post authorisation

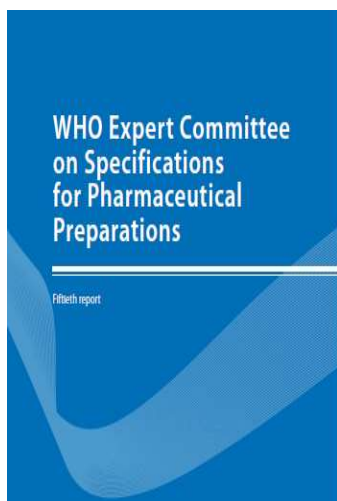
# Snapshot of donations/allocations (15 Aug 2022)



# Applicable guidelines for Collaborative Registration Procedures

For WHO prequalified medicines  
and vaccines

For medicines and vaccines  
approved by SRAs



|  |     |
|--|-----|
| <b>Annex 8</b>   |     |
| 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 |     |
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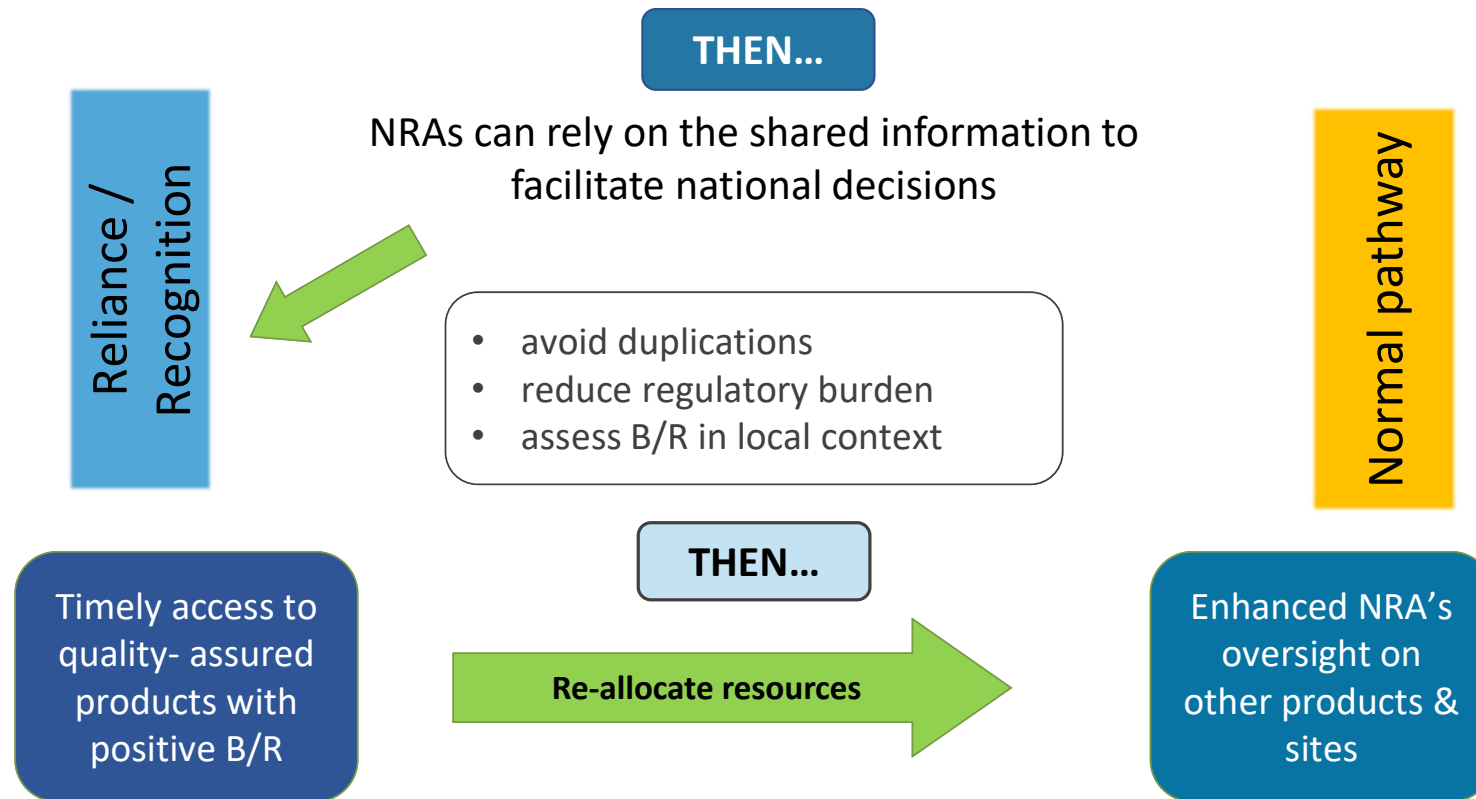
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<http://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1>

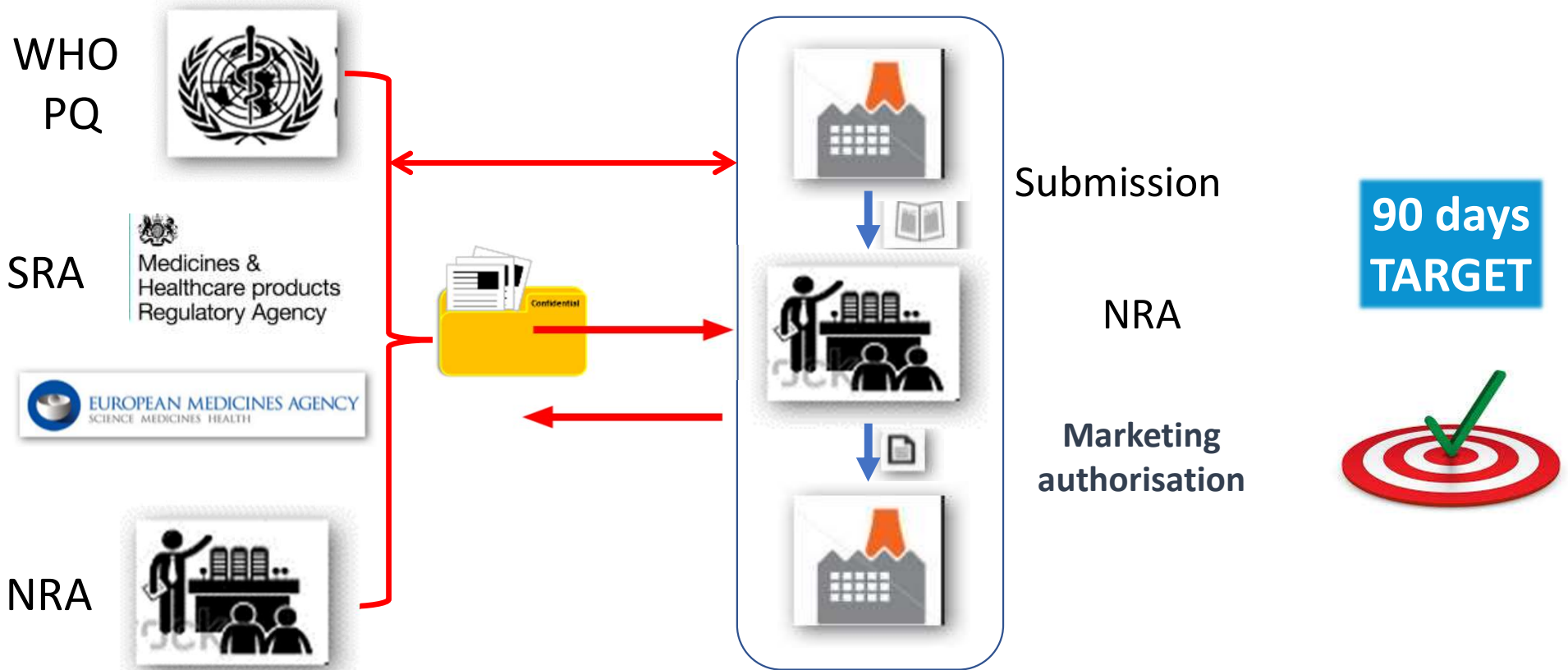
<https://extranet.who.int/pqweb/medicines/faster-registration-fpps-approved-sras>



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

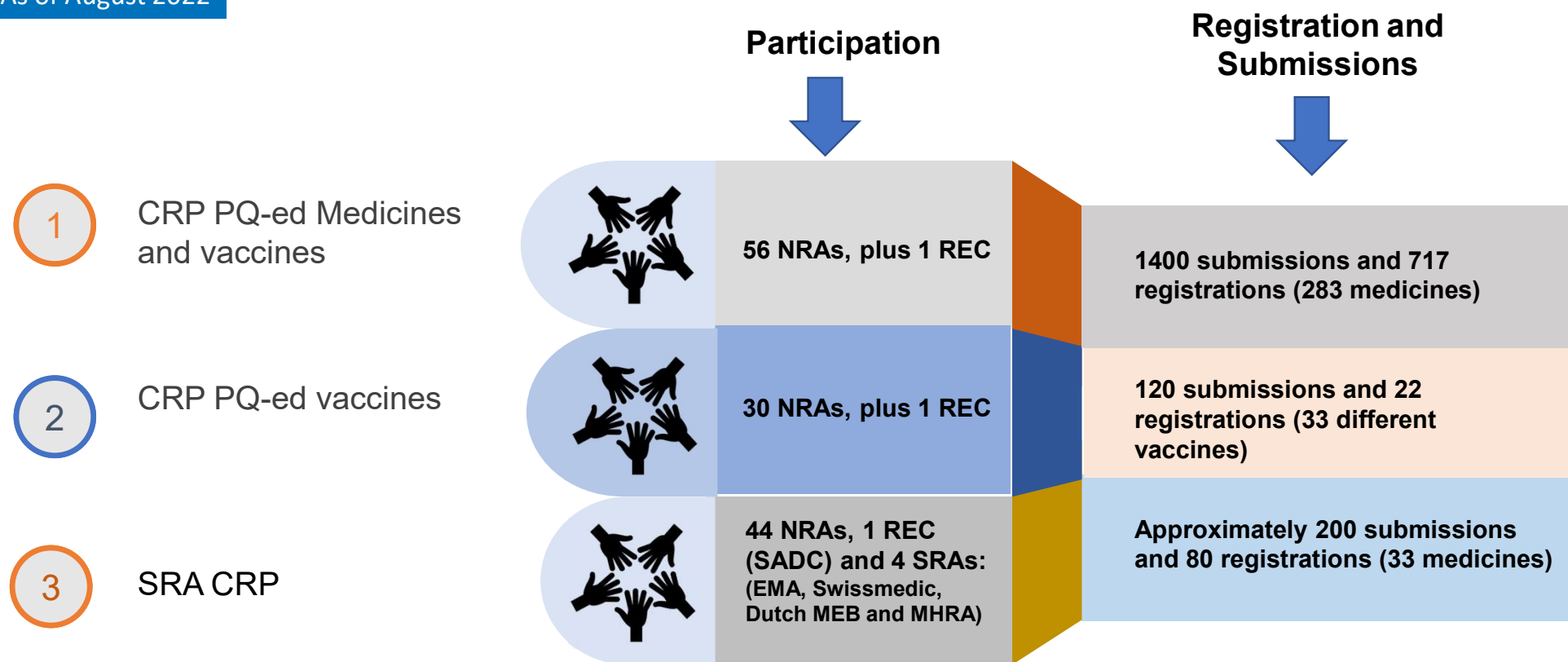


## How does the collaborative procedures work?



# CRP in facilitating in-country regulatory approval of medical products

As of August 2022



# WHO support to applicants on CRP

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- WHO individual meetings/trainings: Applicants – WHO;
- WHO Advocacy meetings/Workshops on CRP to applicants;
- Annual Meeting on CRP – open sessions to applicants;
- Regular interactions with applicants through different channels to support the applications;
- The first 1-3 products/submissions: WHO close follow-up with applicants and NRAs to provide necessary support.





# Collaborative Registration Procedure: “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.



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## Messages to bring forward:

- 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.

**[www.who.int/medicines](http://www.who.int/medicines)**

- Thank you for your attention!



## Back-up slides

- Questions from DCVMN and proposed answers from WHO;
- Suggestions from DCVMN for CRP Process Improvement;
- Expectations of DCVMN.



## Questions form DCVMN and proposed answers from WHO

1. Success rate of the process for vaccines is still indistinct; However, the process is quite successful and streamlined for Pharma (medicinal) products.

In terms of CRP procedure, the process for medicines and vaccines is basically the same and should work the same. In fact, the CRP procedure itself for prequalified vaccines has been started before medicines and showed to work and be successful as for prequalified medicines. The difference/challenge between the CRP for medicines and vaccines, is with availability of shareable clinical, CMC, inspection and testing reports for prequalified vaccines.

2. Manufacturers to be given restricted access to the exchange of information between the WHO-PQT and NRA (currently the access of web-portal for data exchange is between NRA and WHO only). Furthermore, a procedure tracking table/tool should be considered and implemented, for clarity and transparency in the process between applicant/WHO/NRA.

The existing MEDNET platform where documentation is shared with NRAs, is only accessible by NRAs to avoid any leakage of manufacturer's confidential information. The reasoning behind is to protect confidentiality of data received from applicants. However, we are moving now to a centralized platform where all stakeholders, including applicants, will be updated on real time on the progress and update of each CRP application. This new system called ePQS will ensure a more centralized coordination and communication between all stakeholders involved in a CRP application.

## Questions form DCVMN and proposed answers from WHO

3. Clarification needed on how the queries should be; from NRA's to the applicant/PQ holder keeping WHO in the loop or NRAs to WHO or WHO to the applicant/PQ holder.

Queries should be made from NRAs to applicant, as they have the contact of the applicant that made the administrative submission in the country, unless the request is about WHO PQ assessment reports. But in case we at WHO receive queries from the NRA to be addressed by the applicant we can facilitate the communication between the NRA and applicant.

4. Few countries are issuing certificate with validity. Rather, registration should be valid till product is on PQ list.

The decision on the validity of a product approval/registration is made by the NRA. This is based on their national requirements, policies and regulations. WHO cannot interfere here as it is a local administrative procedure and requirement. If a country only issues marketing authorizations with validity of 3 years, the company should make an application for a renewal of the authorization after the 3 years, if the product continues to be PQ-ed. WHO FPI can facilitate the communication between NRA and applicant on matters related to renewals, as requested, although this is outside the scope of CRP guidelines.

## Questions form DCVMN and proposed answers from WHO

5. As mentioned under Step 3, Appendix 3, Part B (Decision on acceptance by the NRA) is currently not received by the applicant/PQ holder.

This information is generally received by WHO via email, after we ask whether countries confirm acceptance of using CRP. In other words, as part our current procedure, when the company express interest in using CRP for a product, we contact the countries to ask whether they confirm acceptance of using CRP for the specific country. When the country replies to us confirming interest in using CRP (the equivalent to Appendix 3B), we provide it with access to the PQ assessment reports and we will inform you about the acceptance form country. This step is currently done manually by us, but it will be visible to all stakeholders when we move to ePQS, and applicants will have an update on all steps in real-time. At the moment this is only done manually via email by WHO and we only provide updates to applicants when we receive confirmation from countries.

6. List of vaccines registered through this process is not published on WHO webpage.

It is not available at the moment, but it will be when we fully move to ePQS. At the moment we are in a transition period to ePQS system and are not able to publish this data. We expect to fully launch ePQS by the end of the year, and this data will become automatically available on the website and will be updated in real time. In addition, the respective applicant of a CRP application, will have access to these registration updates in ePQS system itself.

## Questions form DCVMN and proposed answers from WHO

7. Variations management is still as per country specific requirement and the CRP PAC process is not followed.

In the CRP guidelines there are specific provisions to handle variations for CRP approved products. As for WHO FPI actions, we continuously promote the use of CRP and reliance for variations of CRP approved products in all our activities and trainings to countries. But in the end each country decides on their local requirements. Countries have been reporting back to us that they wish to use CRP for variations as well, their only issue is that applicants do not make the variation application to them (i.e., the administrative application, payment of fees, etc.).

When a variation application is made by the applicant to the country for a CRP approved product, the applicant notifies WHO and we ask PQ colleagues to share the assessment reports so we can make them available to countries. However, the problem seems to come sometimes from the applicant side too, as it seems that variations applications are not submitted to countries.



## Suggestions from DCVMN for CRP Process Improvement

A. List of vaccines approved through CRP procedure to be listed on WHO website along with the approving NRAs.  
*For FPI (as per 6 above)*

It is not available at the moment, but it will be when we fully move to ePQS. At the moment we are in a transition period to ePQS system and are not able to publish this data. We expect to fully launch ePQS by the end of the year, and this data will become automatically published in the website and will be updated and available in real time. In addition, the respective applicant of a CRP application, will have access to these registration updates in ePQS system itself.

B. The validity of the vaccine registration certificate licensed via CRP, should be harmonized with the WHO-PQ validity of the vaccine as the CRP relies on the WHO-PQ assessment.  
*For FPI (as per 4 above)*

The decision on the validity of a product approval/registration is made by the NRA. This is based on their national requirements, policies and regulations. WHO cannot interfere here as it is a local admin procedure and requirement. If a country only issues marketing authorizations with validity of 3 years, the company should make an application for a renewal of the authorization after the 3 years, if the product continues PQed. WHO FPI can facilitate the communication NRA-applicant on matters related to renewals, as requested, although this is outside the scope of CRP guidelines. FPI team will be happy to support on this as well as will continuously advocate for harmonization of guidelines/standards, but it is recommended to follow countries legal requirements too.

## Suggestions from DCVMN for CRP Process Improvement

C. Furthermore, a procedure tracking table/tool should be considered and implemented – For FPI

We are moving CRP to this new system/platform called ePQS, which will provide real time data/information to all stakeholders on the progress, status and updates on each CRP application procedure, allowing applicants to track and monitor their submissions. This will ensure a more centralized coordination and communication between all stakeholders involved in a CRP application.

D. NRAs are requesting applicants to submit country specific dossier (through CRP process) that delays the registration process; Therefore, in order to avoid delay, WHO shall emphasize on the acceptance of the agreed format (as per the WHO CTD guidance) to the NRAs. - For FPI

Countries should receive product dossier in ICH CTD format, as it is established in CRP guidelines. When a country signs the participation agreement, it concurs with this, therefore another dossier format should not be requested and we can support those companies that are requested to provide the dossier in a different format and facilitate communication with countries, providing any additional clarification. Nevertheless, countries may have additional local requirements which can be requested in addition to the product dossier provided in CTD format. It happens sometimes that countries have local legal requirements that will be requested in addition to the established requirements in CRP guidelines. This is foreseen and companies should be able to meet those requirements.

E. NRAs should accept the WHO's granted GMP status to avoid duplication. – For FPI:

Yes, indeed. We work and train countries to encourage them to use and apply reliance to the WHO GMP inspections. To promote the use of reliance and implementation of good reliance practices, it's part of our advocacy activities to countries. We can also facilitate communication with countries, when necessary, on this matter, companies only need to provide us this feedback and information on the CRP application. We also work to continuously promote reliance on WHO GMP inspections in our capacity building activities.

## Suggestions from DCVMN for CRP Process Improvement

F. There is no clear guidance regarding variation process through CRP. DCVMN suggest that the variation to such NRA's should be simplified and in harmonization with the WHO's guidance for reporting of variations to PQ'ed vaccines (July 2015).- Action for FPI (as per 7 above)

In the CRP guidelines there are specific provisions to handle variations for CRP approved products. As for WHO, we continuously promote the use of CRP and reliance for variations of CRP approved products in all our activities and trainings to countries. But in the end each country decides on their local requirements. Countries have been reporting back to us that they wish to use CRP for variations as well, their only issue is that applicants do not make the variation application to them (i.e., the administrative application, payment of fees, etc.). When a variation application is made by the applicant to the country for a CRP approved product, the applicant notifies WHO and we ask PQ colleagues to share the assessment reports so we can make them available to countries. However, the problem seems to come sometimes from the applicant side too, as it seems that variations applications are not submitted to countries.

G. As the local registration is based on the WHO PQ under CRP, the mock-ups, SmPC/ package insert, labelling component should be identical with the ones as approved during grant of prequalification by the WHO PQ.

Yes, indeed. We at FPI work and train countries on that direction, but sometimes countries may have additional local and legal requirements in some circumstances, which need to be respected.

## Expectations of DCVMN

1. Reliance on the functional (“semi-stringent”) NRA may expedite review and approval of new vaccines and post approval changes.
  - a. PQD\* - Submission to WHO submission in Parallel to NRA - \*Pre-Qualified Dossier.  
for PQ. It may not make much sense if the intend is to use PQ CRP, as countries will always need to wait for WHO prequalification reports, unless the product is SRA approved and, in that case, SRA CRP can be used, and submissions can be done in parallel (as it happens already with some products).
  - b. PAC - Submission to WHO in Parallel to NRA – for PQ. It is OK for FPI
  - c. Inspection - Relay on NRA on-site inspection report – for PQT.
2. Lifting the Functional NRAs to Stringent NRA.
  - a. Action: Roadmap to be designed between WHO and such NRAs and Action plan and timeline to be published and tracked. (For RSS to respond)
3. WHO-PQ/EUL team may consider to increase the numbers of vaccine reviewer’s/experts to incase the availability of PQ/EUL submission slot with overall strengthening of WHO assessment. (For PQT)
4. Several cost intensive guidelines having been issued by WHO which will have huge impact on both, the overall capacity as also the cost e.g.
  - a. Batch Specific Sterilization of Lyophilizers - It will reduce production capacity of the product by 25%. It will also impact on the over all working life of current Lyophilizers after batch specific sterilization; The practice of manual loading to Lyophilizers also criticized, which indirectly put pressure on manufacturers to shift to auto loader which is costly.
  - b. 0.2 µm filter implementation - The viral vaccines i.e., Measles, Rubella, Rabies, Rota will have impact on the yield and indirectly to meet the demand; manufacturer’s need to increase the capacities to compensate the losses during 0.2-micron filtration
  - c. Installation of RABS on filling line will call for temporary shutdown of facilities
  - d. Practice of manual loading being criticized that can indirectly put pressure on manufacturers to switch to auto loader which are very costly.

For PQT colleagues to respond