Collaborative Registration Procedure - overview of main principles

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World Health Organization
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.

**Medicines Registration Preparation and Approval Process:**

- **Product R&D:** 6-18 months
- **Manufacture demonstration batches:** 1 month
- **B/E and stability studies:** 3-6 months
- **Submissions to NMRA(s):** 1-2 months
- **Approval:** 6-24 months +

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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 author and national decisions – avoiding duplication.
- **Voluntary participation** – reference authorities, participating industries and manufacturers/sponsors

**WHO PQ collaborative registration procedure**

- Vaccines: 2004
- Medicines: Started in 2012
- 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 networks**

- African Medicines Regulatory Harmonization Project (AMRH)
- ASEAN SIAHR Project

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Virtual Joint Meeting | 30 November – 3 December 2020
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

1. Definitions
2. Background information
3. Principles of collaboration
4. Steps in the collaboration for national registration of a pharmaceutical product or a vaccine
5. Collaboration mechanisms for post-prequalification and/or post-registration variations
6. Withdrawals, suspensions or delistings of prequalified pharmaceutical products or vaccines and national deregistrations

References

Appendix 1 National regulatory authority participation agreement and undertaking for national regulatory authority focal points
Appendix 2 Consent of WHO prequalification holder for WHO to share information with the national regulatory authority confidentially under the Procedure
Appendix 3 Expression of interest to national regulatory authority (NRA) in the assessment and accelerated national registration, acceptance by NRA and notification of procedure outcomes
Appendix 4 Report on post-registration actions in respect of a product registered under the Procedure
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

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

THEN...

Re-allocate resources

Normal pathway

• Enhanced NRA’s oversight on other products & sites

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

Reliance / Recognition
How does the collaborative procedures work?

WHO
PQ

SRA
Medicines & Healthcare products Regulatory Agency

NRA

Submission
NRA
Marketing authorisation
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
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

Therapeutic categories of registered medicines

- HA: 307
- TB: 50
- MA: 91
- RH: 8
- HP: 8
- NT: 5
- DI: 1
- IN: 142

Total registrations: 612
As at 30 Nov 2020
Registrations by country

Zambia (Jul-14)
Nigeria (May-13)
Zimbabwe (Nov-12)
Philippines (Oct-16)
Mozambique (Jan-16)
Tanzania (Oct-13)
Malawi (Sep-15)
Ghana (May-13)
Botswana (May-14)
Namibia (May-13)
Ukraine (Jan-14)
Burundi (Jul-16)
CARICOM (Feb-17)
Ethiopia (Apr-14)
DRC (Jan-16)
Kyrgyzstan (Mar-20)
Uganda (Nov-12)
Kenya (Dec-12)
Senegal (Apr-16)
Armenia (Jun-16)
South Africa (May-19)
Thailand (Apr-18)
Mali (Feb-16)
Eritrea (Jan-18)
Madagascar (Jan-15)
Cameroon (Jan-15)
Côte d'Ivoire (Feb-16)
Burkina Faso (Dec-14)
Azerbaijan (Feb-20)
Lao PDR (Feb-18)
Sri Lanka (Oct-19)

As at 30 Nov 2020
Registrations by manufacturer

- Macleods Pharmaceuticals Ltd (Jan-14)
- Strides Shasun Ltd (Mar-15)
- Cipla Ltd (Jan-14)
- Hetero Labs Ltd (May-13)
- Mylan Laboratories Limited (Nov-12)
- Lupin Ltd (Jun-16)
- Laurus Labs Limited (Jan-19)
- Ajanta Pharma Ltd (May-15)
- Sun Pharmaceutical Industries Limited (Aug-19)
- Shanghai Dahua Pharmaceutical Co Ltd (Nov-17)
- Shanghai Desano Bio-Pharmaceutical Co Ltd (Apr-18)
- Acme Formulation Pvt. Limited (Mar-17)
- Micro Labs Ltd (Jun-17)
- Strides Pharma Science Limited (Jan-20)
- Sanofi (Jan-20)
- Cadila Pharmaceuticals Ltd (Sep-14)
- Svizera Europe BV (Sep-18)
- Dong-A ST Co, Ltd (May-14)
- DNDi, Switzerland (Cipla Ltd is the supplier and is responsible for the product) (Oct-13)
- Ipca Laboratories Ltd (Oct-18)
- Eisai Co, Ltd - Japan (Jul-14)
- Celltrion Inc. (Aug-20)
- Hisun Pharmaceutical (Hangzhou) Co Ltd (Feb-18)
- Ranbaxy Laboratories Ltd (Dec-13)

As at 30 Nov 2020
Median time to registration

*Including regulatory time and applicant time

As at 30 Nov 2020
CRP for Vaccines: some history

2004–2005
WHO/SEARO requested the support from PQ vaccine to facilitate the registration of vaccines. It consisted to share summary protocol and sample testing results. Called expedited license procedure.

2011–2012
Principles of the CRP (sharing reports of the assessment process) firstly used for registration of MenAfriVac in 26 countries of the African belt.

2015
CRP Procedure (under revision) used as a pilot to facilitate registration of IPV vaccine. Joint review option.

2016
CRP for vaccines endorsed by ECBS.

2016–2019
CRP procedure used on ad hoc basis to facilitate registration of other vaccines.
### 44 Participating NRAs + 1 REC

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

** Regional Economic Community
## Vaccine registrations

<table>
<thead>
<tr>
<th>WHO PQ number</th>
<th>Product</th>
<th>Prequalification holder</th>
<th>Country of registration</th>
<th>Registration date</th>
<th>Registration number</th>
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<td>87.40</td>
<td>Easyfive-TT 10 Vials</td>
<td>Panacea Biotec Ltd</td>
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<td>Eupenta Carton of 1 dose [Dimensions 8.5x3.8x4.5 cm]</td>
<td>LG Chem Ltd</td>
<td>Ethiopia</td>
<td>20/Dec/17</td>
<td>3582/4794/NMR/2017</td>
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<tr>
<td>304.10</td>
<td>Eupenta Carton of 1 dose [Dimensions 8.5x3.8x4.5 cm]</td>
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<td>DRC</td>
<td>23/Mar/18</td>
<td>MS1253/10/05/DGM/0162/2018</td>
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<td>Eupenta carton of 10 vials (100 doses) with dimensions 11.6 x 4.7 x 5.3 cm</td>
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<td>20/Dec/17</td>
<td>3582/4794/NMR/2017</td>
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<td>305.10</td>
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<td>LG Chem Ltd</td>
<td>DRC</td>
<td>23/Mar/18</td>
<td>MS1253/10/05/DGM/0161/2018</td>
</tr>
<tr>
<td>314.10</td>
<td>Rotavac 5 vials</td>
<td>Bharat Biotech International Limited</td>
<td>Nigeria</td>
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<td>336.10</td>
<td>Euvichol-Plus (Cholera) 50 dose</td>
<td>EuBiologics Co., Ltd.</td>
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<td>343.10</td>
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<td>385.10</td>
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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

<table>
<thead>
<tr>
<th>Product name</th>
<th>Applicant</th>
<th>Country of registration</th>
<th>Date of registration</th>
<th>Registration number</th>
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<td>Tanzania</td>
<td>29/Jul/19</td>
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<td>m-PIMA HIV-1/2 VL</td>
<td>Alere Technologies GmbH</td>
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<tr>
<td>m-PIMA HIV-1/2 VL</td>
<td>Alere Technologies GmbH</td>
<td>Nigeria</td>
<td>24/Feb/20</td>
<td>03-7250.</td>
</tr>
</tbody>
</table>

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

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.
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?
www.who.int/medicines