Product Registration 101

JUNE 2023

PEPFAR
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Maximizing Options to Advance Informed Choice for HIV Prevention

Overview

- **The Basics**
  - Word salad: acronyms & glossary
  - Steps to product registration
  - Components of a regulatory submission
- **Pathways for product registration**
  - National level
    - “Regular” review
    - Expedited review (when available)
  - WHO collaborative procedures
    - Pre-qualified (PQ) products
    - SRA-approved products
  - Regional harmonization
  - Temporary alternative to registration: special import permits/waivers
- **Key Takeaways**

Acronyms and Glossary

Acronym	Stands for…	Means…
CTD / eCTD	Common Technical Document / Electronic Common Technical Document	A set of specifications for a dossier that pharmaceutical companies must compile and submit to regulatory authorities when seeking approval for a new drug product. The CTD format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The use of the CTD format aims to simplify the application process and make it more consistent across different countries.
CRP	Collaborative Registration Procedure	Participating countries leverage an assessment previously conducted by WHO to evaluate & approve a pharmaceutical product that has received WHO Prequalification. The procedure is meant to lessen the burden on countries' National Medicines Regulatory Authorities, streamline the process for manufacturers, and accelerate product registration.
LTR	Local Technical Representative	A locally-registered entity that serves as a manufacturer's primary point of contact with the national health or regulatory authorities. The LTR submits the required documentation for product registration, responds to any queries or requests for additional information, and tracks the progress of the registration process. After the product is approved and launched, the LTR may be responsible for collecting and reporting data on its real-world use, including any adverse events or quality issues. They also ensure timely renewals of the product registration as required by local regulations.
MAH	Marketing authorization holder	The entity that has received approval from the regulatory authorities to market and sell a particular pharmaceutical product in a specific country or region. In many cases, this may be the manufacturer. Other times, it can be their LTR or a licensee.
NMRA	National Medicines Regulatory Authority	National governmental agencies that are responsible for the regulation of medicines and medical devices in their respective countries.
PQ	Prequalification	An assessment in which WHO applies unified standards of acceptable quality, safety and efficacy to evaluate of the quality, safety and efficacy of pharmaceutical products. Prequalification is based on information submitted by the manufacturers and inspection of the corresponding manufacturing and clinical sites.
SRA	Stringent Regulatory Authority	A subset of NMRAs
WHO	World Health Organization	A specialized agency of the United Nations responsible for international public health. It was established on April 7, 1948, with headquarters in Geneva, Switzerland.

What are the common Steps in Product Registration?

1. **Determine country-specific requirements**

Through 1) **online** research and 2) stakeholder engagement (**in person** when possible), determine country-specific registration requirements.

2. **Establish Marketing Authorization Holder**

Select and appoint a **Marketing Authorization Holder (MAH)**. Typically, this involves conducting diligence, entering into a contract with the selected MAH, and giving them Power of Attorney.

3. **Prepare and submit dossier**

Obtain required documents, typically including GMP certificate & Certificate of Pharmaceutical Product. Prepare modules 1-5 and submit dossier. (Dossiers can be 10s of thousands of pages!)

Submission

4. **Provide samples**

Determine number of samples and specific requirements; obtain import permit; coordinate shipment and delivery.

5. **Answer inquiries**

It is common for regulatory authorities to ask questions of the applicant upon review of their dossier. Applicants must answer within designated timeframes (usually with a short turnaround).

Approval

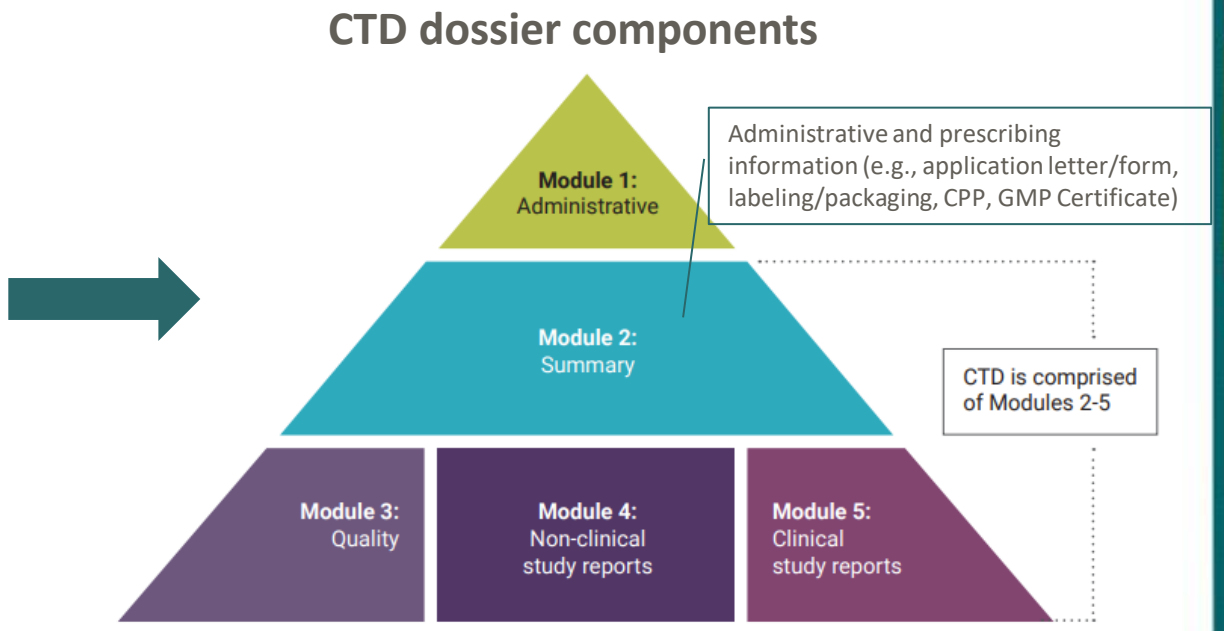
6. **Maintain & update**

Registration typically needs to be renewed on a regular basis. If any changes are made to the product, they need to be filed with (and sometimes approved by) the national regulatory authority.

Source: Robles, Wilberto, et al. *Product Registration Basics for Global Health Program Managers*, www.catalystglobal.org/wp-content/uploads/2022/01/EECO-Regulatory-Guide.pdf. Accessed 5 June 2023.

Typical components of a regulatory submission

- Product dossier
  - Many countries in Africa require the **Common Technical Document** (CTD) format, or the electronic version called the "**eCTD**"
  - WHO has also adopted the CTD format for the PQ process
- Product samples for testing and/or evaluating packaging
- Good Manufacturing Practices (**GMP**) audit of manufacturing facility
- Application fees



Source: Robles, Wilberto, et al. *Product Registration Basics for Global Health Program Managers*, www.catalystglobal.org/wp-content/uploads/2022/01/EECO-Regulatory-Guide.pdf. Accessed 5 June 2023.

Comparing pharmaceutical Product Registration Pathways

Procedure	Description	Timeline	Eligibility requirements
National registration procedure	Manufacturer applies directly (or via designated licensee or local technical representative) to the National Medicines Regulatory Authority (NMRA)	• **"Regular"** timeline unknown. Research/ consultation required to assess average timeline. • Some countries have **expedited** procedures: Research required to assess whether this timeline is adhered to in practice.	N/A (may be submitted by any entity that qualifies to be an applicant)
WHO Collaborative Registration Procedures			
Collaborative Registration Procedure for **PQ'd products**	Manufacturer submits a WHO Collaborative Procedure application to the participating NMRA as well as a dossier and samples. WHO provides the NMRA with its own assessment documentation, which the NMRA relies on to determine whether to grant authorization to the product.	Participating NMRAs commit to review within 90 days; however, real-world experience by FHI 360 with an SRH product showed an average of 128 days from submission to approval, with the range from 67 – 212 days.	Product must first be prequalified by WHO through "full" PQ procedure (not abbreviated process for SRA-approved products)
WHO Collaborative Registration Procedure for **SRA-approved products**	Manufacturer shares the full assessment and inspection reports from the SRA for the product with the participating NMRAs, as well as additional data documenting potential deviations from the product approved by the SRA.	Participating NMRAs commit to review within 90 days; data on actual timelines not available.	Product must first be approved by an SRA willing to collaborate with WHO & NMRAs (U.S. FDA has thus far declined to participate; to date, participating agencies have been EMA and MHRA).
Regional Harmonization Initiatives			
Regional harmonization initiatives, e.g., **ZAZIBONA, EAC, CARICOM**	Manufacturer still applies directly to each participating country (no centralized submission); however, requirements are the same for all countries except for limited number of country-specific requirements	Median time from submission to approval is 12 months for ZAZIBONA.	N/A (may be submitted by any entity that qualifies to be an applicant in each participating country as per national requirements)

Sources:

- Robles, Brett, et al. Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS) REGULATORY ASSESSMENT. 2018 Nov 29. Accessed at: https://www.hormonaliud.org/_files/ugd/fd8974_e99ca3d8295e4015a49d1214fd59f387.pdf 17 May 2023
- Sithole T, Mahlangu G, Walker S, Salek S. Regulatory Authority Evaluation of the Effectiveness and Efficiency of the ZaZiBoNa Collaborative Medicines Registration Initiative: The Way Forward. Front Med (Lausanne). 2022 Apr 25;9:898743. doi: 10.3389/fmed.2022.898743. PMID: 35547217; PMCID: PMC9082034. Accessed at: https://www.frontiersin.org/articles/10.3389/fmed.2022.898725/full on 17 May 2023

National Registration Procedures

Potential advantages

- May be cost-effective and flexible in application requirements.
- May be options for expedited review in some countries for an additional fee

Disadvantages

- Wide variation in country-specific requirements
- Submissions may be subject to extended delay outside of applicant's control

When to Consider

- You are only registering the product in one country in a region
- The product presentation will vary between countries
- The product does not have WHO PQ

Process

- Varies, but generally aligns with the general process on slide 5

Source: Robles, Brett, et al. Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS) REGULATORY ASSESSMENT. 2018 Nov 29. Accessed at: https://www.hormonaliud.org/_files/ugd/fd8974_e99ca3d8295e4015a49d1214fd59f387.pdf 17 May 2023

WHO Collaborative Registration Procedure (CRP) for Prequalified (PQ'd) Products

Potential advantages

- Excellent follow up and updates from WHO CRP team
- Easy to follow process with minimal paperwork
- Excellent experience with agencies that are committed to and familiar with process
- Advantage of having a dedicated CRP point person within NMRA
- Acceptance of harmonized module 2 – 5 and less queries from NMRA
- Often quicker than national variations which sometimes 'fall through the cracks'; and get parked or don't have a dedicated review process

Disadvantages

- Non-responsive NMRA's or NMRA's not sufficiently engaged (e.g., NMRA WHO CRP liaison person has left)
- NMRA not accepting dossiers due to internal issues
- NMRA only applying WHO CRP to certain therapeutic areas
- In some instances, NMRAs don't recognize inspections conducted by WHO (i.e., require own inspection)
- Time-lapse from submission to acknowledgement of submission and acceptance of WHO CRP
- Translations, legalization of documentation and requirement for a LTR are not solved by WHO CRP

When to Consider

- Product has WHO Prequalification
- Manufacturer intends to register in multiple countries participating in the CRP

Process

- Product must be first pre-qualified by WHO (which takes an average of 270 days)*
- In order for a product to receive a prequalification listing, it must first be included in WHO guidelines (clinical practice or public health policy recommendations made by the agency).
- Once the product is prequalified, the manufacturer announces to the relevant NMRAs that it intends to leverage the CRP for PQ'd products to register. If the NMRA accepts, then manufacturer applies directly to NMRA, and WHO shares assessment reports directly with NMRA.

Source: https://www.ghtcoalition.org/documents/pdf/Navigating-complexity-to-improve-global-access-supporting-a-more-efficient-and-effective-WHO-prequalification-program.pdf.

WHO Collaborative Registration Procedure (CRP) for SRA-approved Products

Potential advantages

- Similar advantages to WHO PQ collab procedure
- However, need to engage with SRAs in addition to NMRAs and WHO

Disadvantages

- Currently only 2 SRAs are participating: EMA and UK MHRA
- Newer procedure than PQ Collaborative procedure
- Countries increasingly value WHO PQ; if choosing this pathway b/c product isn't PQ'd, may need to explain why

When to Consider

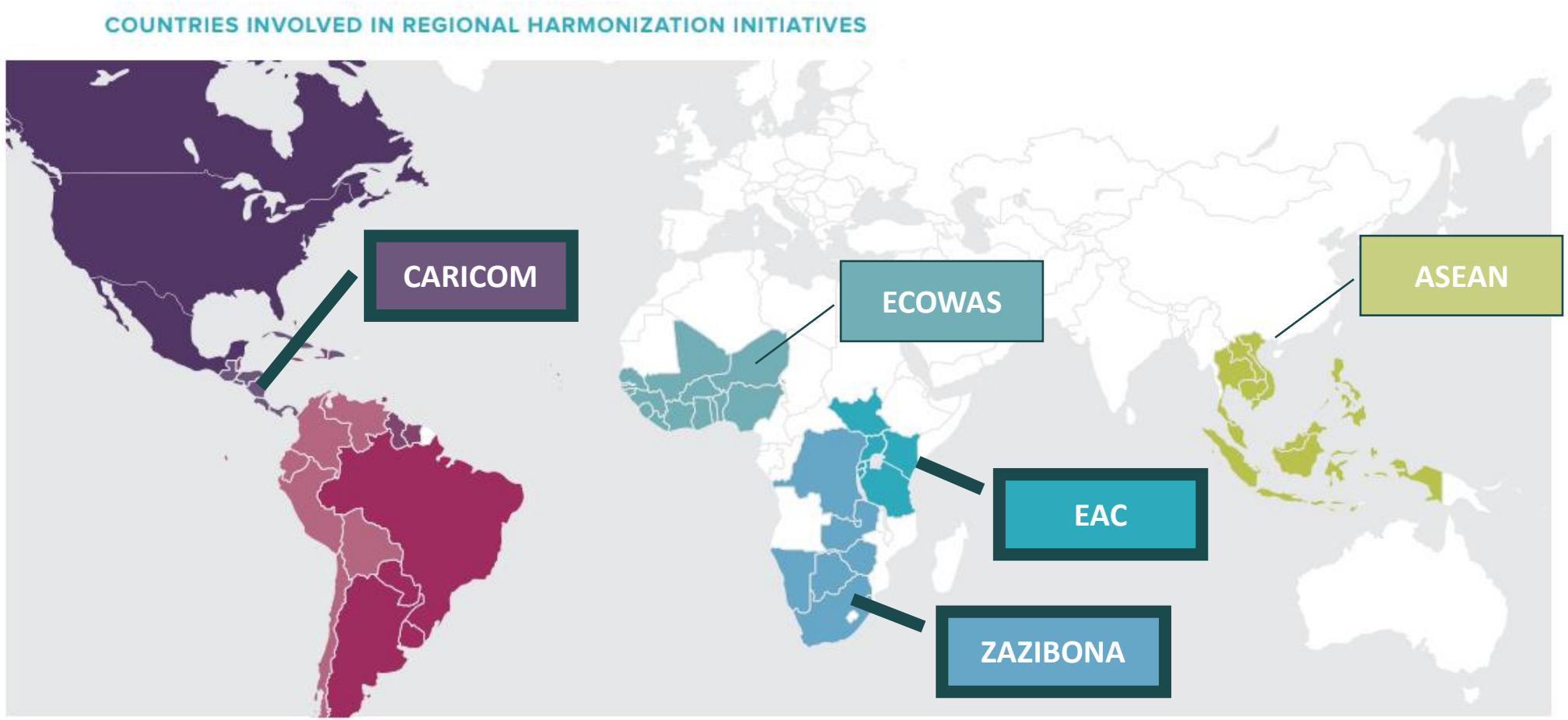
- When planning to register in multiple countries participating in the CRP
- The product does not have WHO Prequalification (or if PQ was obtained using the expedited process for SRA-approved products)
- The product has been approved by MHRA or EMA

Process

- Manufacturer shares the full assessment and inspection reports from the SRA for the product with the participating NMRAs, as well as additional data documenting potential deviations from the product approved by the SRA.

Source: Robles, Brett, et al. Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS) REGULATORY ASSESSMENT. 2018 Nov 29. Accessed at: https://www.hormonaliud.org/_files/ugd/fd8974_e99ca3d8295e4015a49d1214fd59f387.pdf 17 May 2023

Regional harmonization initiatives



Source: Robles, Wilberto, et al. *Product Registration Basics for Global Health Program Managers*, www.catalystglobal.org/wp-content/uploads/2022/01/EECO-Regulatory-Guide.pdf. Accessed 5 June 2023.

Regional Harmonization Initiatives

Potential advantages

- Three (EAC, ZAZIBONA, CARICOM) offer standardized guidelines and expedited review

Disadvantages

- None are yet operating at the level that an approval from a regional network would replace the application requirement at the national level

When to Consider

- When manufacturer intends to register the product in multiple countries within a region
- The product does not have WHO Prequalification
- The product is not approved by the EMA or MHRA

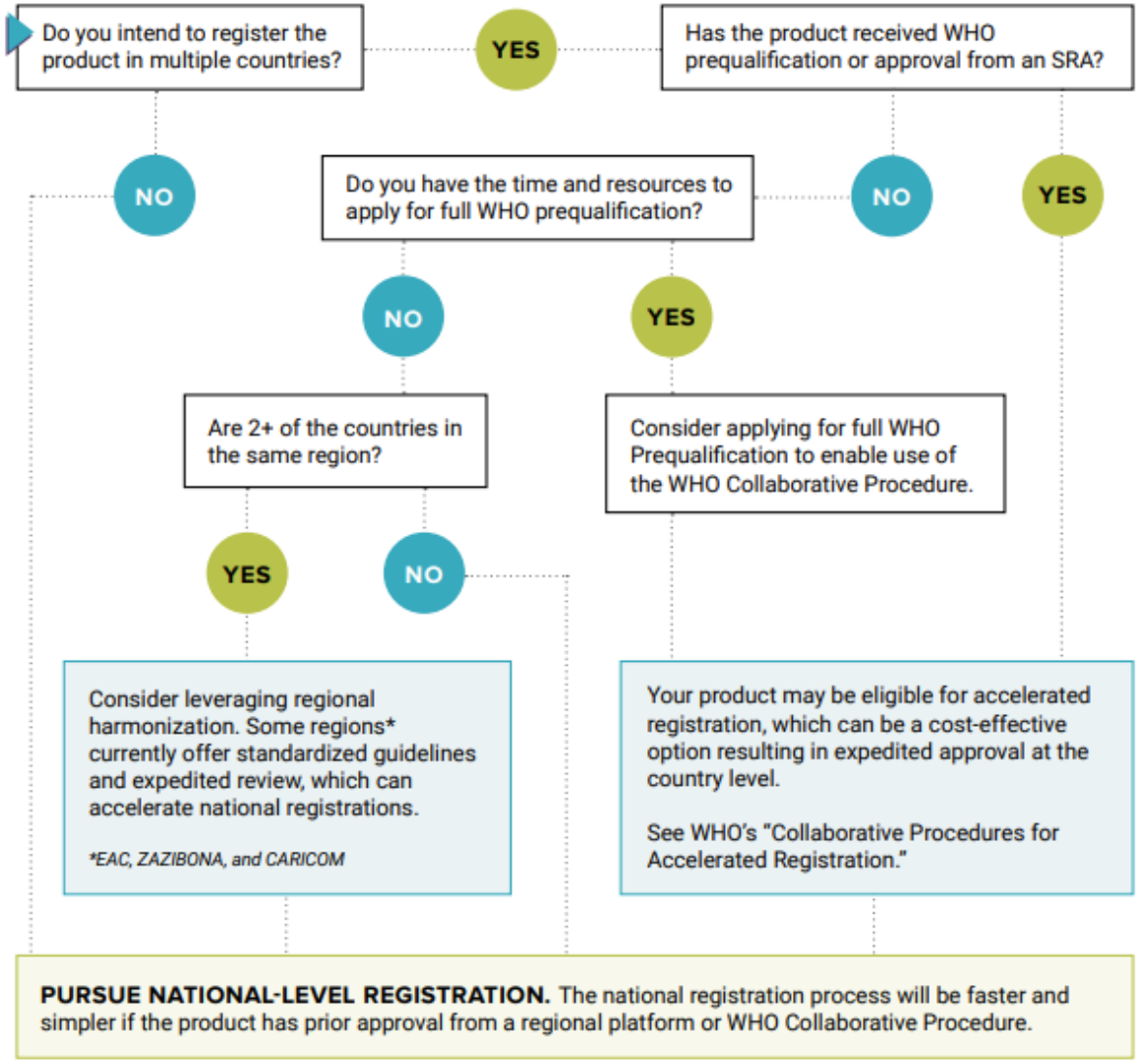
Process

- Lorem ipsum

Source: Robles, Brett, et al. Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS) REGULATORY ASSESSMENT. 2018 Nov 29. Accessed at: https://www.hormonaliud.org/_files/ugd/fd8974_e99ca3d8295e4015a49d1214fd59f387.pdf 17 May 2023

Regulatory Pathway Decision Tree

Instructions: Several potential regulatory pathways may be available to register your product. Use this decision tree to help identify which regulatory pathway would be most advantageous.



Source: Robles, Wilberto, et al. *Product Registration Basics for Global Health Program Managers*, www.catalystglobal.org/wp-content/uploads/2022/01/EECO-Regulatory-Guide.pdf. Accessed 5 June 2023.

Potential Short-Term Option: Waiver

- Many countries will allow a pharmaceutical product that is not yet registered to be imported through a waiver on an **exceptional basis**
  - Often granted for research
  - Must be granted by the Ministry of Health and/or national regulatory authority (in countries where this body does not sit under the MOH)
  - Some countries will only grant a waiver if the manufacturer has started the registration process and/or has made a commitment to registering the product in the country
  - Bilateral or multi-lateral organizations typically work with Ministries of Health to facilitate the waiver (e.g., for HIV/TB products, GF and PSM often work with MOH's to obtain the waiver)
- **Stakeholder engagement** would be needed to assess the feasibility of this pathway
- **Requirements** are country-specific but typically require supporting documents such as:
  - *Certificate of Pharmaceutical Product (CPP)* to help the importing country assess the quality of the pharmaceutical product
  - *Good Manufacturing Practice (GMP)* Certificate to attest that the product manufacturer is compliant with established guidelines, and
  - the applicable *Certificate of Analysis* to demonstrate the product quality

Timeline unknown; typically, several months

Key Takeaways

Regulatory processes and submissions are complex!

Historically, there was limited publicly available information about how to register products in many LMICs

There now exist some helpful resources that walk through the process at a high-level in non-technical terms.

Close partnership between manufacturer and local partners (e.g., to conduct landscape assessment, import samples, etc.) is essential.

The “best” choice of regulatory pathway depends on the country and product context

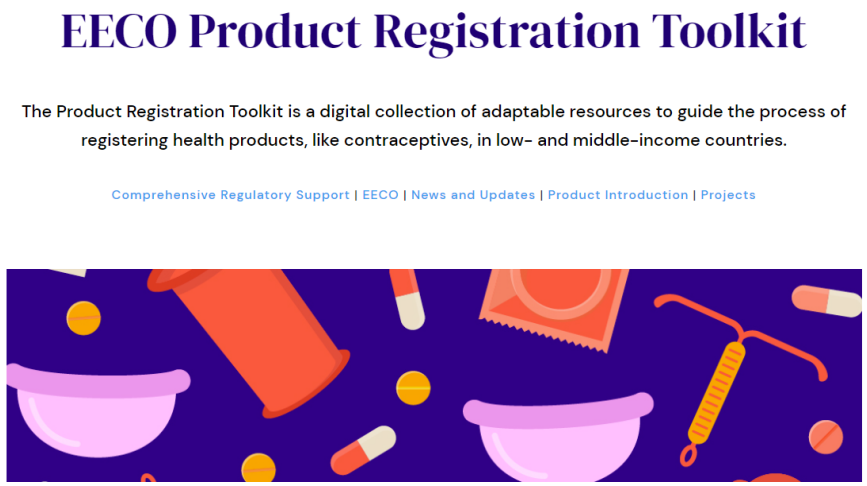
- None of the collaborative or harmonized procedures currently allow for “mutual recognition”/automatic approval by national regulatory body
- These procedures continue to evolve so it’s possible processes will continue to become more streamlined

Treat written timelines with caution; they are commonly exceeded in practice.

Acknowledgements

Much of the information in this presentation was adapted from the EECO Product Registration Toolkit. The toolkit it is a digital collection of adaptable resources to guide the process of registering health products, like contraceptives, in low- and middle-income countries. The resources include an **introductory video, a primer on product registration basics, and a selection of checklists, templates, and decision trees to help you navigate the product registration process from start to finish.**

Toolkit was developed by **Catalyst Global** with the support of the American people through the United States Agency for International Development (USAID), which funded the Expanding Effective Contraceptive Options (EECO) project (Cooperative Agreement Number: AID-OAA-A-13-00088).

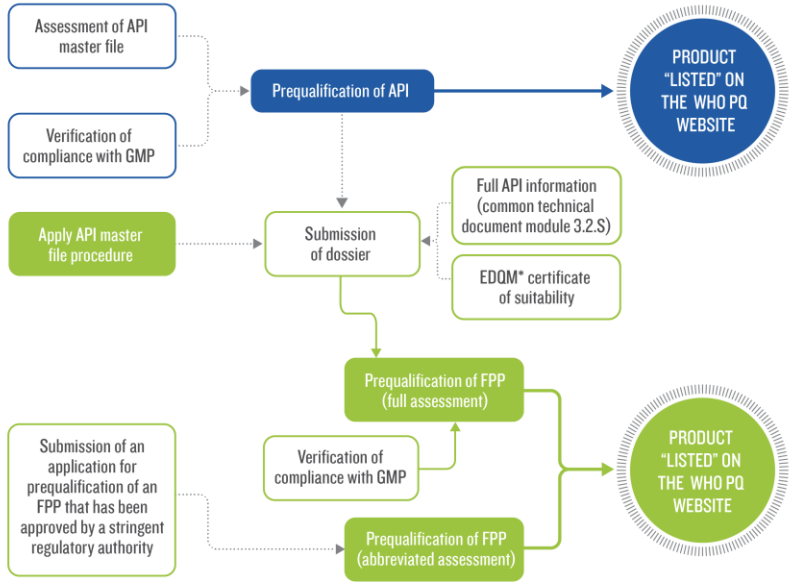


https://catalystglobal.org/2022/06/14/eeco-product-registration-toolkit/

APPENDIX

WHO Collaborative Procedure for PQ'd Products

Step 1: Get WHO Prequalified



Prequalification procedure for FPPs and APIs eligible for prequalification

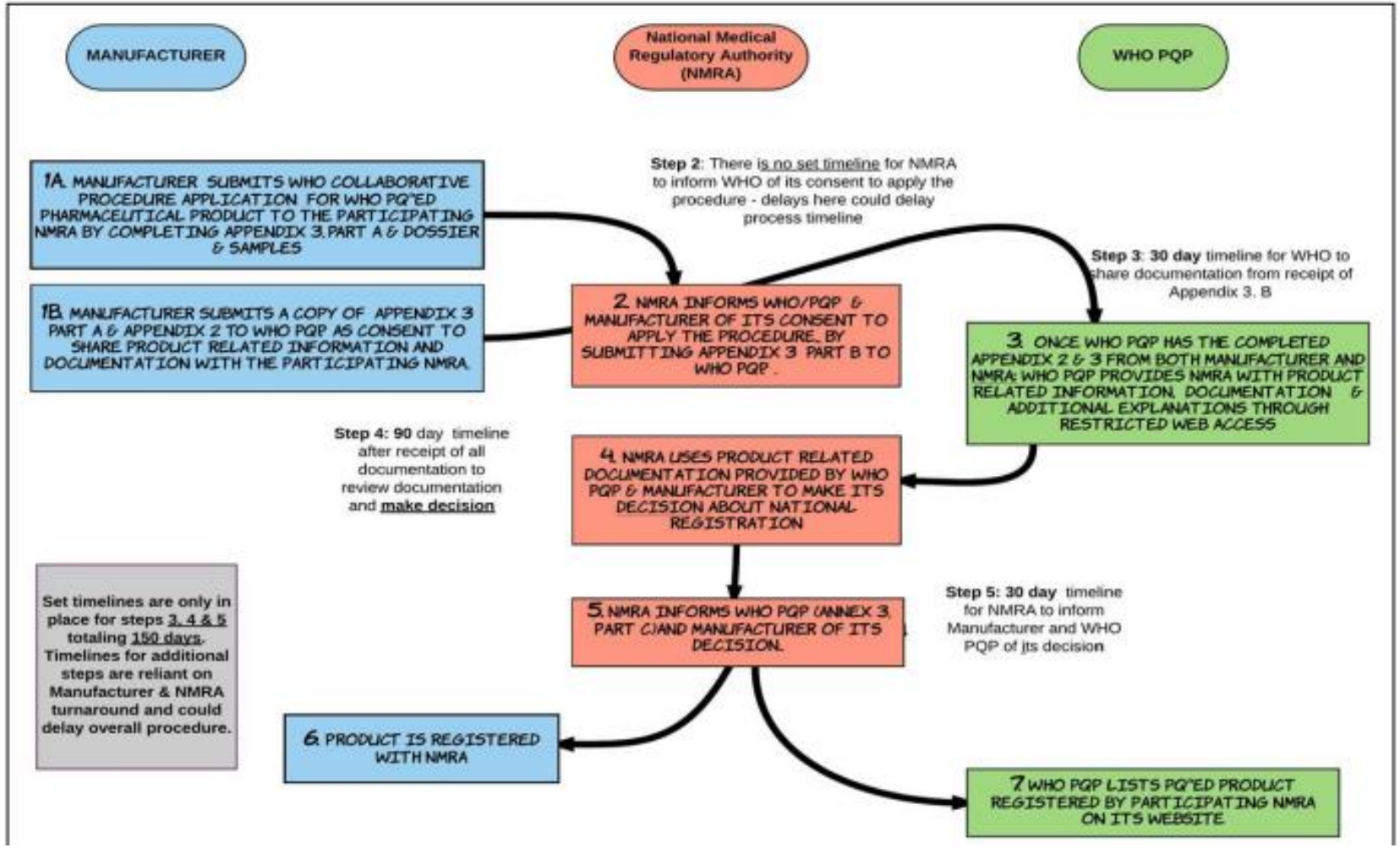
*EDQM: European Directorate for the Quality of Medicines and Healthcare

WHO Prequalification: medicines

Source: WHO. https://extranet.who.int/pqweb/medicines/prequalification-procedures-and-fees. Accessed on 6/5/2023

WHO Collaborative Procedure for PQ'd Products

Step 2: Leverage PQ to apply for national-level approvals (with help of WHO)



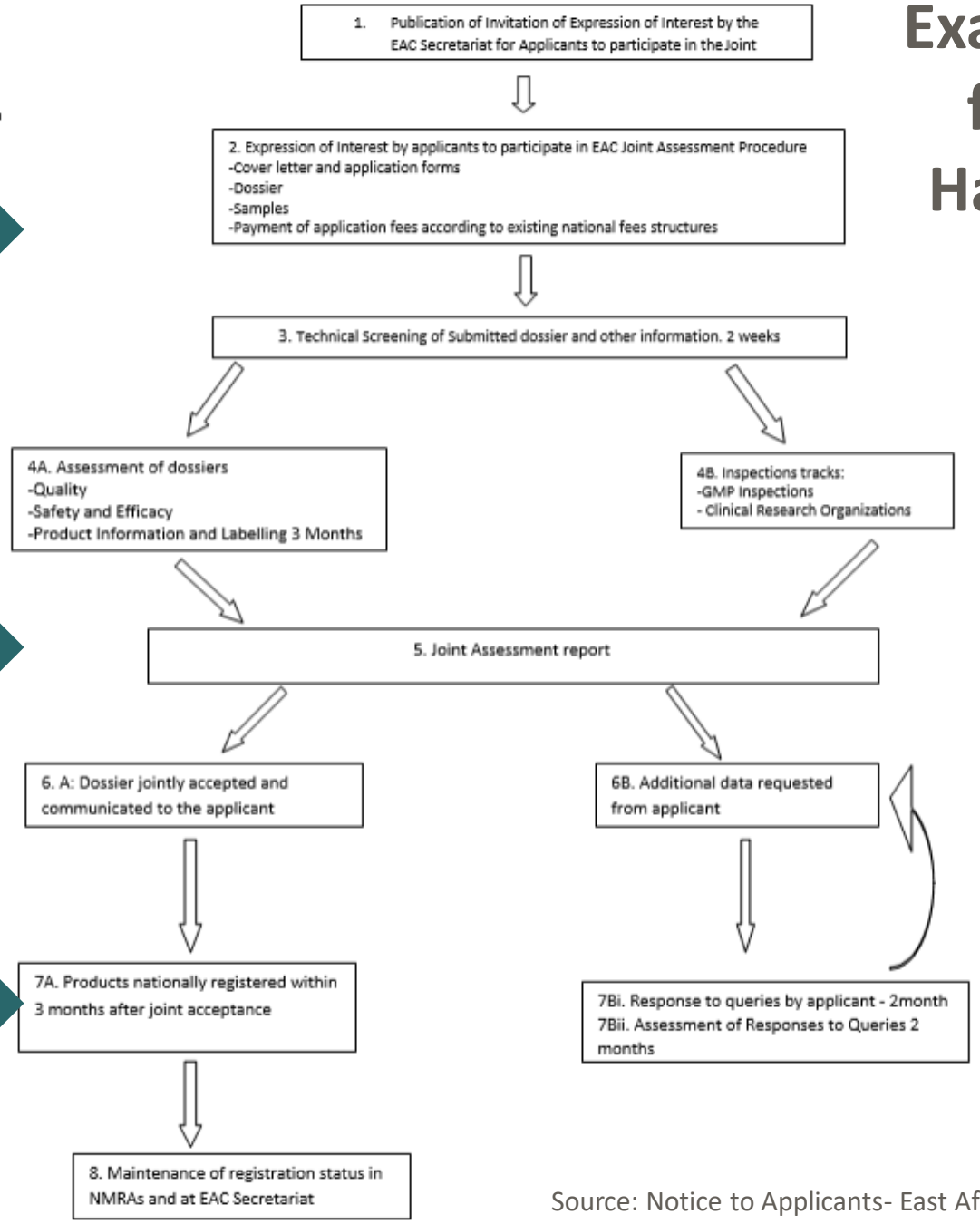
Source: Illustration created by T. Brett, 2018.

Example Process for Regional Harmonization (EAC)

Manufacturer submits application to regional body

Regional body makes a recommendation/assessment

Applicant applies to national bodies using regional assessment



Source: Notice to Applicants- East African Community's Procedure for Marketing Authorization of Medicinal Products, Effective January 2015