What Program Managers Need to Know about Product Registration

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AGENDA

- Expanding Effective Contraceptive Options (EEO)
- Registration Overview
- Pathways to Registration
- Real-World Examples
  - Progesterone Vaginal Ring - Nigeria
  - Levoplant WHO Prequalification
- After Registration...
- Learning about Expanded Access and Potential of the LNG-IUS (LEAP LNG-IUS) Initiative
Exploring Effective Contraceptive Options (EECO)

- USAID-funded
- Contraceptive product introduction in FP2020 countries
- EECO portfolio addresses method-related reasons for non-use
Exploring Effective Contraceptive Options (EECO)

STAGE 1
Regulatory Assessment & Product Registration
- Perform regulatory landscape assessment
- Engage stakeholders and meet with regulatory authorities
- Support identification of a suitable market authorization holder
- Prepare the registration package, submit and support its lifecycle upon approval

STAGE 2
Consumer & Market Research
- Plan and conduct market research
- Complete market segmentation analysis
- Determine pricing and branding strategies

STAGE 3
Procurement & Quality Assurance
- Perform manufacturer audits
- Initiate pre-shipment inspection and testing of product
- Develop and initiate pharmacovigilance systems

STAGE 4
Marketing, Distribution & Service Delivery
- Launch product, with marketing and communications support
- Supply stock to commercial outlets and providers
- Deploy medical detailers to train and follow-up with providers

STAGE 5
Monitoring & Learning
- Monitor and course-correct
- Conduct baseline and endline evaluations
- Disseminate lessons learned
Why does registration matter?

Regulatory authorities protect public health by ensuring the safety, efficacy, and quality of drugs, medical devices, and other regulated products.
Who regulates?

**National Regulatory Authority (NRA)**
- Responsible for reviewing and granting or rejecting registration applications in the countries where they have the legal authority to do so.
- ZAMRA, NAFDAC, DPM

**Stringent Regulatory Authority (SRA)**
- Provide expertise and resources for the proper evaluation of regulated products.
- US FDA, Japan, Health Canada
Role of the World Health Organization (WHO)

- Supports access to essential medicines
- Sets norms, standards, develops guidelines
- Advises on issues related to quality assurance
- Assists in building national regulatory capacity
Common Technical Document (CTD)

Module 1: Administrative

Module 2: Summary

Module 3: Quality

Module 4: Non-clinical study reports

Module 5: Clinical study reports

CTD is comprised of Modules 2-5
WHO Prequalification Programme

Expression of interest calls for interested manufacturers to submit dossier based on WHO Guidelines

Assessment of dossier

WHO Public Assessment Report

Inspection of API, FPP & CRO sites

WHO Public Inspection Report

LIST OF WHO PREQUALIFIED PRODUCTS
**WHO Collaborative Procedure - Full PQ**

WHO shares assessments reports with NMRA

**Key Principles of WHO CRP**

- Product and registration dossier in countries are 'the same' as approved by WHO.
- Shared confidential information to support NRA decision making in exchange for accelerated registration process
- Harmonized product status' is monitored and maintained

MAH submits dossiers and samples to NMRA along with forms indicating that it wishes to follow the WHO CRP process

NMRA commits to a review in 90 days

NMRA informs MAH of marketing authorization
SRA Collaborative Procedure

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Key Principles of SRA CRP

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Harmonized product status' is monitored and maintained
Regional Harmonization Initiatives
Country-by-Country Registrations
Special Import Permits

• Short-term use
  • Research
  • Emergencies

• Application guidelines, and willingness to approve special import permits, are country-specific
So, which pathway to choose?

1. Do you intend to register the product in multiple countries?
   - Yes: Has the product received WHO PQ or approval from an SRA?
   - No: Do you have the time and resources to apply for full WHO PQ?

2. If No to 1, is there 2+ countries in the same region?
   - Yes: Consider applying for full WHO PQ to enable use of the WHO Collaborative Procedure.
   - No: Consider leveraging regional harmonization. Some regions* currently offer standardized guidelines and expedited review, which can accelerate national registrations.

   *EAC, ZAIBONA, and CARICOM as of 2018

3. If Yes to 1, has the product received WHO PQ or approval from an SRA?
   - Yes: Pursue national-level registration. The national registration process will be faster and simpler if the product has prior approval from a regional platform or WHO Collaborative Procedure.
   - No: Consider leveraging regional harmonization. Some regions* currently offer standardized guidelines and expedited review, which can accelerate national registrations.

   *EAC, ZAIBONA, and CARICOM as of 2018
QUIZ: Who can be a Marketing Authorization Holder?

- Local NGO
- Foreign Supplier
- Foreign Manufacturer
Real-World Example:

Registering the Progesterone Vaginal Ring in Nigeria
• A contraceptive developed by the Population Council for use by breastfeeding women for up to one year postpartum
• Manufactured by Grünenthal Chilena Ltda. as Progering®
• Registered in 10 countries in Latin America
• USAID-funded Delivering Contraceptive Vaginal Rings (DCVR) project

Photo Credit: Population Council
Real-World Example: PVR Registration in Nigeria

**STEPS IN THE PVR REGULATORY PROCESS IN NIGERIA**

1. Complete desktop and in-country Regulatory Landscape Assessment
2. Identify, evaluate and select MAH
3. Prepare and submit registration application to NAFDAC
4. Request from NAFDAC an import permit for samples
5. Send samples to NAFDAC for evaluation/analysis
6. Respond to queries, as necessary, during NAFDAC's review of the registration application
7. Receive Marketing Authorization from NAFDAC
Real-World Example:

Levoplant WHO Prequalification
Levoplant: DKT WomanCare’s Core Business

- DKT WC is responsible for regulatory, marketing, distribution and sales
- Leveraging DKT country offices and DKT WomanCare distribution network (100+ countries)
- Regulatory footprint for Levoplant in 20 Countries (approved) - additional 17 pending
Levoplant Prequalification

• Under BMGF grant FHI 360 provided technical and operational support to Shanghai Dahua Pharmaceutical Co, Ltd. on all international regulatory matters until 15 November 2018 including WHO Prequalification of Levoplant and regulatory submission in over 28 countries.

• DKT WomanCare who became exclusive distributor of Levoplant in February 2018 has continued to expand Levoplant regulatory footprint including leveraging WHO CRP.
Levoplant (RH028) Regulatory strategy post WHO PQ

3 pathways for Levoplant submissions to NMRAs for marketing authorization

- National Variation where the earlier version of the product was already registered (new API manufacturer, brand name change, improvements, duration of use from 4 years to 3 years)
- National Submissions
- National Submissions through the WHO Collaborative Regulatory Procedure
Levoplant submission June 2017-March 2019

37 SUBMISSIONS
(including CARICOM regional submission)

WHO COLLABORATIVE REGULATORY PROCEDURE (CRP)

NATIONAL VARIATIONS

NATIONAL SUBMISSIONS
Levoplant Regulatory Approval June 2017 - March 2019

**NATIONAL SUBMISSIONS**
- 197 Approvals
  - Average: 224 days
  - Range: (30 - 458 days)

**WHO CRP**
- 176 Approvals
  - Average: 176 days
  - Range: (67 days - 322 days)

**NATIONAL VARIATIONS**
- 224 Approvals
  - Average: 8 days
  - Range: (52 days - 456 days)

**20 Approvals including CARICOM (regional recommendation)**
RHO28 (Levoplant) WHO CRP experience to date

- 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 (Zimbabwe, Namibia, Tanzania, *CARICOM)
- Advantage of having a point person within NMRA
- Guidance from CARICOM and PAHO team on procurement options and engaging with local MOHs/Procurement agencies
- CARICOM approval is a gateway to a number of markets where there is limited information on national registrations.
- 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
RHO28 (Levoplant) WHO CRP experience to date:

**HOWEVER SOME CHALLENGES:**

- Non responsive NMRA’s or NMRA’s not sufficiently engaged
- NMRA not accepting dossiers due to internal issues
- NMRA only applying WHO CRP to certain therapeutic areas (i.e. not Reproductive Health)
- NMRA WHO CRP liaison person has left
- In some instances NMRAs don’t recognize inspections conducted by WHO (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 unfortunately not solved by WHO CRP
Levoplant regulatory footprint: March 2019

- REGISTRATION IN PROGRESS: Bangladesh, Brazil, Burundi, Bolivia, Cameroon, Cote D’Ivoire, Ecuador, Costa Rica, Guatemala, Mexico*, Mozambique, Niger, Nepal, Peru, Pakistan, Panama, Philippines, Vietnam
- REGIONAL APPROVAL THROUGH CARICOM*: Dominica, Trinidad, Guyana, Haiti
How 2018 Compares: Post WHO prequalification and aggressive regulatory strategy

Dahua Sales (excl. China & Indonesia)


* 2018 figures include all RFQs received through Oct. 1, 2018
Recommendation from Levoplant experience on WHO CRP

✓ ENGAGE early on with WHO CRP Team to discuss regulatory strategy and schedule annual/bi-annual meetings to discuss pending and in progress submissions.

✓ Ensure LOCAL TECHNICAL REPRESENTATIVE is aware of the procedure and highlights this during submission.

✓ MODULE 1 is still country specific and might required translations, notarization/legalization, local agents/local MAH and country specific samples. Be prepared for this!

✓ In most cases for countries familiar with the WHO CRP using the WHO CRP is a faster and more efficient pathway to marketing authorization.
After Registration...

- Marketing Authorization Approval
  - Renewals
- Post-Approval Changes or Variations
- Post-Approval Surveillance or Pharmacovigilance
  - Adverse Event Reporting
Learning about Expanded Access and Potential of the LNG-IUS (LEAP LNG-IUS) Initiative

- Funded by the Bill & Melinda Gates Foundation, and lead by FHI 360, in partnership with WCG Cares and PSI.
- Intended to help determine if and how expanded access to the LNG-IUS could increase contraceptive use and continuation rates in sub-Saharan Africa.
- Research among women and providers in Nigeria and Zambia as well as demand forecasting in Kenya, Nigeria and Zambia.
- A regulatory assessment was conducted in 2018 to identify potential strategies to expedite national registrations of LNG-IUS product(s) in FP2020 countries.
- An assessment of the national regulatory requirements in three countries which may be viewed as priorities for LNG-IUS registration and introduction: Ghana, Ethiopia, and Vietnam.
THANK YOU!

Questions?