LEAP LNG-IUS INITIATIVE

Learning about Expanded Access and Potential of the Levonorgestrel Intrauterine System (LEAP LNG-IUS)

REGULATORY ASSESSMENT

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List of Acronyms

ACTD	ASEAN Common Technical Document
ACTR	ASEAN Common Technical Requirement
AMRH	African Medicines Regulatory Harmonization
ASEAN	Association of Southeast Asian Nations
CARICOM	Caribbean Community
CGMP	Current Good Manufacturing Practices
CPP	Certificate of Pharmaceutical Product
CRP	Collaborative Registration Procedure
CRS	Caribbean Regulatory System
CTD	Common Technical Document
EAC	East African Community
ECOWAS	Economic Community of West African States
EECO	Expanding Effective Contraceptive Options
EMA	European Medicine Agency
FMHACA	Food, Medicines, and Health Care Administration and Control Authority
FP2020	Family Planning 2020
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IGAD	International Authority on Development
LARC	Long-Acting Reversible Contraception
LNG-IUS	Levonorgestrel Intrauterine System
MA	Marketing Authorization
MAGHP	Marketing Authorisation for Global Health Procedure
MAH	Marketing Authorization Holder
MRH	Medicines Regulatory Harmonization
NMRA	National Medicines Regulatory Authority
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PPWG	Pharmaceutical Product Working Group
PQP	Prequalification of Medicines Programme
QMS	Quality Management System
REC	Regional Economic Community
SADC	Southern African Development Community
SARPAM	Southern African Regional Program Access to Medicines and Diagnostics
SRA	Stringent Regulatory Authority
UEMOA	West African Economic and Monetary Union
WHO	World Health Organization

Executive Summary

With funding from the Bill & Melinda Gates Foundation, FHI 360 and partners Population Services International (PSI) and WCG Cares are implementing the **Learning about Expanded Access and Potential of the LNG-IUS (LEAP LNG-IUS) Initiative.** The project is intended to help determine if and how expanded access to the levonorgestrel intrauterine system (LNG-IUS) — a long-acting contraceptive — could increase contraceptive use and continuation rates in sub-Saharan Africa. Activities include research among women and providers in Nigeria and Zambia as well as demand forecasting in Kenya, Nigeria and Zambia. The findings from the project will help stakeholders better understand the potential demand for the LNG-IUS, experiences among users and providers, and continuation rates and cost-effectiveness of the LNG-IUS compared with other long-acting reversible contraceptive (LARC) methods.

In addition, under the LEAP LNG-IUS Initiative, **a regulatory assessment was conducted in 2018. The goal of the assessment was to identify potential strategies to expedite national registrations of LNG-IUS product(s) in Family Planning 2020 (FP2020) countries.** Results of the assessment are presented here.

This report is intended to provide both **strategic analysis and technical guidance** to donors, implementing organizations and LNG-IUS suppliers. The primary focus of the assessment was on LNG-IUS products that 1) currently have approval from a Stringent Regulatory Authority (SRA); and 2) are currently offered at an affordable public sector price in FP2020 markets. At this time, only Medicine360's LNG-IUS product, AVIBELA, meets these criteria, so this assessment will likely be most relevant for Medicines360 as well as donors, implementing partners and/or governments who are considering registering or introducing AVIBELA. However, the findings from this report may also be relevant for suppliers of other SRA-approved LNG-IUS products (e.g., Bayer Healthcare) and/or manufacturers of products that are not currently approved by an SRA (e.g., Pregna, HLL Lifecare, and Meril). In addition to commercial products, the International Contraceptive Access (ICA) Foundation provides donations of a free, unbranded LNG-IUS product in FP2020 countries. (See the **Overview of LNG-IUS Suppliers** section for more information.)

Several potential regulatory strategies to expedite country-level approvals of LNG-IUS product(s) are outlined in this document:

1. **Pursuing World Health Organization (WHO) prequalification either through:**
    a. Full WHO prequalification; or
    b. Abbreviated WHO prequalification for SRA-approved generic or innovator products
2. **Utilizing one of the WHO-supported collaborative procedures:**
    a. WHO Collaborative Procedure for fully WHO prequalified products; or
    b. Accelerated Collaborative Procedure for SRA-approved products
3. **Leveraging regional harmonization mechanisms**
4. **Applying for national registrations on a country-by-country basis**

A key finding from this work is that each potential pathway has advantages and disadvantages. For example, WHO prequalification or participation in a WHO-supported collaborative procedure could provide strategic value from a marketing perspective and/or be a quicker route to registration in FP2020 countries. However, there also are various challenges which should be carefully evaluated to determine whether following a WHO pathway would result in significant time or cost savings. Similarly, participation in regional harmonization initiatives may allow manufacturers to take advantage of harmonized guidelines and expedited approval timelines; however, these regional initiatives are at varying levels of maturity and implementation, and none of them currently allow for mutual recognition among countries.

Pursuing national registrations individually on a country-by-country basis would ensure that the applicant is compliant with local requirements, allow for the most flexibility, and could potentially offer a route for expedited review, yet there is wide variation in country-specific requirements and submissions may be subject to extended delay outside of the applicant's control. Thus, the benefits and limitations inherent in each of these registration pathways must be assessed in conjunction with the applicant's strategic objectives (time, cost, target number of registrations, and specific priority countries) to identify which pathway is most likely to yield the greatest benefit. Refer to the table below, also included in the Conclusions section, for a summary of the advantages and disadvantages of each pathway.

Pathway	Potential Advantages	Potential Disadvantages
WHO Prequalification & WHO-Supported Collaborative Procedures		
Full WHO Prequalification	Once prequalified through this mechanism, it would allow supplier to take advantage of the WHO Collaborative Procedure for a fully WHO prequalified product	More expensive and time-consuming than the Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products
Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products	Less expensive and faster than pursuing Full WHO Prequalification	Would not allow supplier to take advantage of the WHO Collaborative Procedure for a fully WHO prequalified product
WHO Collaborative Procedure for a fully WHO prequalified product	May be faster than filing country-by-country in FP2020 countries	Unclear if would result in substantial time or cost savings especially if target number of registrations is modest
Accelerated Collaborative Procedure for SRA approved products	This could be a cost-effective way to achieve registrations in FP2020 countries if supplier can use approval from the MHRA and EMA	The US FDA has not agreed to participate in this initiative due to data sharing concerns. As such, this pathway is only available to manufacturers who want to and are able to use an approval from the MHRA and EMA
Regional Harmonization Initiatives		
	Following regional guidelines may be a faster way to achieve registrations in multiple countries in a region once harmonization efforts are mature. Some regions (EAC, ZAZIBONA, CARICOM) offer standardized guidelines and expedited review	Mutual recognition has not yet reached maturity where a single regional application will be recognized by all countries in any given region. As such, manufacturers who want to register in multiple countries still have to follow country-specific guidelines and submission processes
National Registration Pathways		
	May be cost-effective and flexible in application requirements. May be options for expedited review in some countries	Wide variation in country-specific requirements and submissions may be subject to extended delay outside of applicant's control

In addition to strategic guidance about the advantages and disadvantages of the different overall regulatory pathways, this report also includes 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. These countries were selected for an in-depth assessment after consultation with stakeholders including donors and service delivery groups. However, it is important to note that a number of other countries were also considered as potential priorities, and inclusion in this assessment does not imply commitment from an LNG-IUS supplier or from donors to pursue registration in those three countries, nor does it imply that other countries are not viewed as a priority moving forward. The national regulatory assessments were conducted using online information from each country's National Regulatory Authority to identify country-specific requirements for pharmaceutical product registration. In-country stakeholders and regulatory teams were also consulted.

Finally, a summary Regulatory Assessment Matrix with information about each of the FP2020 countries is also included for use as a quick-reference document (see separate Excel file for the matrix). Summary information includes each country's participation in the WHO collaborative procedure, the level of maturity of its applicable regional harmonization initiative (if any), an assessment of the ease of its local registration processes, information about LARC (implant and IUD) use and expansion rates, and a note about whether the country was considered to be a current priority for LNG-IUS registration by stakeholders that were interviewed as part of this process. Information in this matrix is subject to change and includes subjective assessments, based on our team's knowledge and experience.

Additional Background about LEAP LNG-IUS team: Members of the LEAP LNG-IUS Initiative team have extensive expertise registering drug products and devices worldwide. Under the USAID-funded Expanding Effective Contraceptive Options (EECO) project, WCG Cares (WCG) supported registration applications for Medicines360's LNG-IUS, AVIBELA, in Madagascar (2016), Zambia (2017) and Nigeria (2018). Since 2013, FHI 360 has consulted with Medicines360 on their LNG-IUS global introduction and regulatory strategy including sharing lessons learned from the Gates-funded Sino-implant (II) Initiative. Through that project, FHI 360 is supporting national registrations of Levoplant/Sino-implant (II) – another long-acting contraceptive containing levonorgestrel – in over thirty countries, with sixteen approvals to date (three through the WHO Collaborative Procedure and one using the CARICOM harmonization initiative). FHI 360 led a regulatory assessment for Medicines360's LNG-IUS in India (2015) and a preliminary regulatory assessment in Nigeria (2016). In addition, the Consortium members bring an understanding of current regulatory harmonization initiatives and have strong relationships with the WHO prequalification and collaborative procedure teams.

Methodology

The assessment included the following components:

Assessment of WHO Prequalification & the WHO-Supported Collaborative Procedures

To help inform decisions about whether an SRA-approved LNG-IUS supplier should consider pursuing WHO Prequalification, we documented the steps involved with two potential pathways to achieve Prequalification: 1) pursuing full WHO Prequalification and 2) pursuing the Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products. We also documented the steps involved with the two WHO-supported Collaborative Procedures: 1) the WHO Collaborative Procedure for a fully WHO prequalified product and 2) the Accelerated Collaborative Procedure for SRA-approved products. Information was downloaded from the WHO website and staff at WHO were contacted to ask clarifying questions, when needed. The team also applied lessons learned from the recent Sino-implant (II) initiate including with the Collaborative Procedure for fully prequalified products. For each pathway, we assessed and documented the key advantages and disadvantages of each.

Assessment of Regional Harmonization Mechanisms

To evaluate the potential pathways for utilizing a regional harmonization mechanism, we considered regional harmonization initiatives with harmonized guidelines available. We evaluated the current mechanisms applicable to the FP2020 countries to submit a centralized registration, and whether there is mutual recognition for registration activities. Lastly, we assessed whether there were any advantages to receiving approval from regional harmonization initiatives to expedite national registration activities.

National Regulatory Assessments

National regulatory assessments were conducted for Ghana, Ethiopia, and Vietnam. To select these countries, we solicited input from a range of stakeholders on priority countries (including donors and service delivery groups) and considered a number of other factors including local level registration difficulty (**Appendix 1**), availability of information from online sources, current prevalence and recent growth of LARC use, and past track record of acceptance of the WHO Collaborative Procedure. To conduct the national regulatory assessments, a list of general and technical questions were identified by regulatory experts at WCG and FHI 360. Using these questions as a guide, assessments were conducted using each country's online National Regulatory Authority (NRA) portal and relevant country guidelines. For both Ghana and Ethiopia, the online portals were available in English. In Vietnam, the portal was only available in Vietnamese, and therefore documents were downloaded and translated. Using the online systems, guidelines applicable to pharmaceutical product registration were identified. Country-specific guidelines were evaluated to identify requirements for pharmaceutical product registration. If country-specific guidelines were not available, WHO guidelines were used as a supplementary resource. In-country stakeholders and/or regulatory teams within countries were also consulted.

WHO Prequalification & WHO-Supported Collaborative Procedures for the LNG-IUS

As described above, the overall goal of the regulatory assessment was to identify potential strategies to expedite country-level approvals of the LNG-IUS in FP2020 countries. One potential pathway that an SRA-approved LNG-IUS supplier could consider is seeking **WHO Prequalification** and/or using one of the WHO-supported **collaborative procedures** for accelerated registration at the national level. The following section describes 1) the rationale for potentially seeking WHO Prequalification; 2) eligibility of the LNG-IUS for WHO Prequalification; 3) potential pathways for an SRA-approved product to pursue Prequalification; and 4) the two collaborative procedure pathways supported by WHO that potentially allow for accelerated national registrations. The Marketing Authorisation for Global Health Procedure (MAGHP) offered through Swissmedic is also described below. A summary of conclusions and recommendations about these pathways is also included below.

1. Rationale for potentially pursuing WHO Prequalification for the LNG-IUS

Potential advantages of an LNG-IUS supplier such as Medicines360 pursuing WHO Prequalification include the following:

- ***Strategic/reputational value –*** Ministries of Health and other global and in-country stakeholders often view WHO Prequalification favorably. Prequalification could provide a competitive advantage (e.g., when responding to country-level tenders).
- ***Potential to participate in the WHO Collaborative Procedure for Accelerated Registration –*** Depending on the pathway taken, the WHO Collaborative Procedure can be faster than filing country-by-country in FP2020 countries for products that have been WHO Prequalified. It is important to note that even if an SRA-approved product has not gone through WHO Prequalification, a manufacturer can still participate in the WHO-supported Accelerated Collaborative Procedure for SRA approved products. However, there are challenges with utilizing this process for products that have been approved by the US Food and Drug Administration (FDA). See below for more information.

For additional potential advantages, see here. It is important to note that, in practice, the advantages of WHO Prequalification are greater in some markets than in others and there are challenges associated with pursuing WHO Prequalification. See below for additional details and discussion.

2. Eligibility for WHO Prequalification

Products that have been included in an Expression of Interest (EOI) issued by WHO are eligible for Prequalification. The LNG-IUS was included in WHO 8th EOI. For more information, see here.

3. Pathways to Achieve WHO Prequalification

There are two potential pathways for a LNG-IUS supplier to pursue WHO Prequalification. These are outlined in sections 3.1 and 3.2.

A pre-submission meeting is compulsory for all new applicants to the WHO Prequalification process and can be done face-to-face or virtually. See here for the pre-submission meeting request form. During the

meeting, WHO is able to advise on all aspects of a submission format, as well as contents of the dossier. Guidance on pre-submission processes can be found here.

3.1 Full WHO Prequalification process

The full WHO Prequalification pathway would require a company to submit a dossier and pay WHO's full fees. See **Table 1** below and here for estimated fees for both full WHO Prequalification process and abbreviated process. A supplier such as Medicines360 would be required to submit an application to WHO in accordance with the WHO Prequalification procedure. Timelines to achieve Prequalification via this pathway vary by supplier and product type; however, the process takes substantially longer than the Abbreviated pathway described in section 3.2 below. Key requirements of this procedure are available on the WHO Technical Report Series here and summarized in **Appendix 2**.

3.2 Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products:

This is a faster pathway to achieve WHO Prequalification for SRA-approved products; it applies to a product that has already been approved by a Stringent Regulatory Authority (SRA) (**Figure 1**). A supplier such as Medicines360 would be required to share relevant information with WHO such as the SRA assessment and inspection reports. WHO bases its decision to prequalify on the basis of this information. In such cases, the time to prequalification is generally much less (typically less than six months) than the time to prequalification of a product that undergoes full assessment, and with significantly lower fees (**Table 1**). Requirements are summarized in **Appendix 3**.

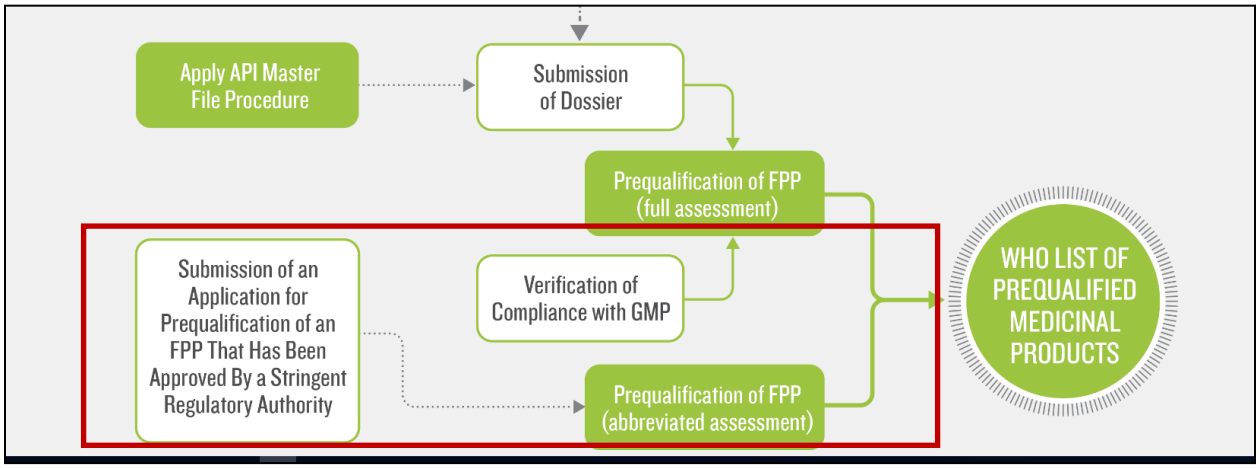
FHI 360 has confirmed with WHO that a product approved by US FDA can go through this procedure. However, if any product has gone through this abbreviated pathway, it is **not eligible** to go through the WHO Collaborative Procedure for a fully WHO prequalified product (described in section 4.1 below).

Table 1: Estimated fees for full WHO Prequalification process and abbreviated process

	Single registration fee per product	Annual fee per product	Post-Prequalification changes
	Application Fee	Annual Fee	Major variation
FPP – Full Assessment	$25,000	$20,000	$3000
API – Full Assessment	$20,000	$8,000	
FPP – Abridged Assessment	$6,000	$5,000	N/A
API – Abridged Assessment	$10,000	$4,000	
API Master File			$3000

Source: World Health Organization

Figure 1: *Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products*



Source: World Health Organization

4. Collaborative procedures for accelerated registration at the national level

There are two collaborative procedure pathways supported by WHO that potentially allow for accelerated national registrations:

- The collaborative procedure to facilitate the assessment and accelerated national registration of a product that has gone through **full WHO Prequalification** (described in section 4.1 below).
    - *In this case, WHO has made a determination about the product and the National Medical Regulatory Authority (NMRA) utilizes the WHO assessment.*
- The collaborative procedure to accelerate registration of a **SRA-approved** product (described in section 4.2. below).
    - *In this case, the SRA has made the determination about the product and the NMRA utilizes the SRA assessment. In this case, WHO only plays a role as facilitator between the SRA and the NMRA.*

4.1 WHO Collaborative Registration Procedure for a fully WHO prequalified product

Once a manufacturer has achieved WHO Prequalification, the key steps to use the WHO Collaborative Registration Procedure (CRP) would include:

- Manufacturer submits a WHO Collaborative Procedure application (provided by WHO) for the WHO Prequalified product to the participating NMRA as well as a dossier and samples. The dossier is normally in common technical document (CTD) format with Module 1 meeting country-specific requirements.
- In addition, the manufacturer submits a copy of the application to the WHO Prequalification of Medicines Program (PQP) as consent to share the product related information and documentation with the NMRA.
- The NMRA then reviews and gives permission to WHO PQP and the manufacturer to apply the WHO Collaborative procedure.
- Once WHO PQP has the completed forms from both the manufacturer and NMRA, WHO shares the product-related documentation and additional explanations through restricted web access to the NMRA.
- The NMRA then uses the product-related documentation provided by WHO PQP and the manufacturer to make an independent decision about the national registration.
- NMRA informs WHO PQP and the manufacturer of its decision

See **Appendix 4** for additional details. According to WHO, **NMRAs who are actively engaged in the WHO CRP process commit to making a decision within 90 days.** However, in FHI 360's recent experience with Levoplant in Zimbabwe, Tanzania, Namibia, and with CARICOM, the average length was 128 days with a range of 67-212 days (from submission of dossier to approval time). See **Table 2**. In contrast, national approvals of Levoplant that have not utilized the CRP process have averaged 247 days with a range of 30-431 days. Another point of comparison for national approvals is the recent approval of Medicine360's AVIBELA product in Zambia which took 181 days from submission to approval.

The full list of NRAS participating in the WHO Collaborative Procedure is available here. *(Note: Ukraine has limited the use of the WHO CRP to specific therapeutic areas and is not accepting RH dossiers. Botswana and South Africa are currently not accepting any dossiers due to internal changes in their NMRAs, and Burundi is not accepting dossiers to deal with current backlog.)*

For detailed information, refer to WHO Technical Report Series which can be found here.

Table 2: Assessment of Advantages and Challenges of WHO Collaborative Registration Procedure (CRP) Based on Recent Experience with Levoplant (which is a 2-rod contraceptive implant that was WHO Prequalified in 2017) as of October 2018

Summary of 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 (e.g. Zimbabwe, Namibia, Tanzania, CARICOM) • Advantage of having a dedicated CRP 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 process
Summary of Challenges: • 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 (e.g., not reproductive health) • 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 unfortunately not solved by WHO CRP
Source: Presentation made by T. Brett at the 18th International Conference of Drug Regulatory Authorities, Ireland, September 2018.

4.2 Accelerated Collaborative Procedure for SRA approved products

Any LNG-IUS product which has SRA approval, regardless of whether it has been WHO Prequalified, could potentially utilize the accelerated procedure for SRA-approved products described below. However a major limitation is that as of September 2018, the US FDA has not agreed to participate due to data sharing concerns (see below for more information).

The key steps in this process include:

- Manufacturer can submit a product for national registration that is the same (as defined by the procedure – see Box 1 below) as the SRA-approved product, to participating NMRA(s). In the case of deviations from the SRA-approved product, these must be specified. The product dossier will normally be organized in the CTD format that was approved by the SRA and adapted for the purpose of the procedure.
- In the case of innovator medicines, the applicant will be advised to provide a "bridging report" that contains additional discussion of data relevant to the countries to which the application is being submitted, if the SRA assessment report does not cover these elements sufficiently.
- The manufacturer — with the agreement of the relevant participating SRA — will then share 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. In organizing the sharing of the reports, the applicant will help to minimize any administrative burden on participating SRAs. The role of the SRA will be limited to data authentication, and, when specifically agreed with individual SRAs, provision of additional explanation of their decisions, should either or both be requested by the NMRAs.
- Participating NMRAs will use the data submitted to support their decision-making regarding registration. They will seek to issue an "accelerated" decision regarding registration within 90 days of their acceptance of the submission. The procedure will not interfere with their national, regulatory decision-making processes, or with national legislation, or with levying of regulatory fees. Similarly, it will be the NMRAs' responsibility to reach agreement with applicants regarding specific risk-management plans and pharmacovigilance follow-up.

Box 1: Within the context of the SRA Collaborative Procedure, products are considered to be the same if the following criteria are met:

- The same qualitative and quantitative formulation;
- The same manufacturing site(s), chain, processes, control of materials and final product;
- The same active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) specifications;
- The same elements of product information (e.g. indications, dosing, storage conditions, primary packing, shelf life, etc.)

With this pathway, WHO's role will be to facilitate cooperation among applicants, participating NMRAs, and SRAs. It will be involved with application of the procedure to a product only if WHO considers the product to be of special public health relevance (e.g. a public health emergency, a request from national governments, etc.). As noted above, the product can be prequalified by the WHO-SRA abbreviated prequalification route, but non-prequalified medicines are also eligible. It is applicable both to innovative and generic medicines.

A manufacturer may participate if they:

- Hold a marketing authorization issued by a participating SRA for the product intended for submission
- Agree with the relevant SRA that the full updated assessment report and inspection report may be shared with the NMRAs to which they intend to apply for registration (see **Box 2** for additional discussion about current challenges with US FDA)
- Agree with the conditions of the procedure and to submit data to NMRAs as defined by the procedure.

Any manufacturer that wishes to participate must seek and secure from the relevant SRA that the holder of the SRA marketing authorization can share the confidential assessment and inspection reports with the relevant NMRAs for the FPP that it intends to submit for accelerated registration. The list of participating NRAS is available here. For additional details about this process including an overview of the steps involved, see **Appendix 5**.

Box 2: Currently, the participating SRAs are limited to the MHRA and EMA due to data sharing issues. **The US FDA currently will not share confidential information with NMRAs through this process, even with approval from the manufacturer.** In August 2018, WHO confirmed in writing to FHI 360 that to date this mechanism has not been used with a US FDA approved dossier, though they continue to advocate with US FDA to change their policies. The Bill & Melinda Gates Foundation has also confirmed in writing this limitation with USFDA-approved products.

5. Accelerated Approval through the Swissmedic Marketing Authorisation for Global Health Procedure

In addition to these pathways, there may also be an opportunity to seek accelerated approval of LNG-IUS product(s) through the Marketing Authorisation for Global Health Procedure (MAGHP) offered through Swissmedic. Swissmedic is the national authorization and supervisory authority for drugs and medical products in Switzerland. In this case, Swissmedic acts as an SRA that reviews a product for either "export registration" in low-income countries or marketing authorization in Switzerland. Once a product has been approved through the MAGHP, an applicant may then seek **WHO Prequalification and/or approval by NMRAs on an accelerated timeline.** See **Appendix 9** for additional details.

Conclusions & Recommendations: WHO Prequalification & WHO Collaborative Procedure for the LNG-IUS

A cost-efficient option to pursue multiple regulatory approvals for an SRA-approved LNG-IUS (e.g., Medicines360's AVIBELA product) in FP2020 countries could be to pursue the **Accelerated Collaborative Procedure for SRA approved products**. However, as of August 2018, the US FDA has not agreed to participate in this initiative due to data sharing concerns. As such, this pathway is only available to manufacturers who want to and are able to use an approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA).

If this pathway is not feasible, a manufacturer could consider applying for **full WHO Prequalification** and then using the **WHO Collaborative Procedure for a fully WHO prequalified product**. However, it is uncertain if this would represent a substantial cost- or time-savings for a manufacturer in comparison to leveraging

regional harmonization initiatives and/or pursuing individual national approvals. Unfortunately, if a product is Prequalified through the Abbreviated pathway, it will not quality for the WHO Collaborative Procedure for fully WHO prequalified products. See below for further discussion of potential alternative registration pathways and their advantages and disadvantages.

Regional Harmonization Initiatives

A second potential pathway is leveraging regional harmonization initiatives, which could lead to accelerated registrations of the LNG-IUS at the country-level. These initiatives may benefit manufacturers by providing standardized guidelines, a CTD, and harmonized inspection procedures. They may also provide technical assistance and reduce the burden on NMRAs with limited resources, which may mean shorter timelines and expedited processes for applicants. However, while the ultimate goal of regional harmonization initiatives is to facilitate a streamlined process for application submission and review among participating countries, in practice, not all initiatives are sufficiently mature. For this reason, interested manufacturers are advised to follow the national registration pathway for the country where they are submitting, but to use regionally harmonized guidelines if they are available. In doing so, manufacturers can be assured that their application will be in compliance with country-level requirements, but they will also be positioned to potentially benefit from regional harmonization if and when the processes are fully implemented (either with simplified guidelines or with mutual recognition).

The following sections provide (1) an overview of the African Medicines Registration Harmonization (AMRH) Initiative; (2) an overview of the Association of Southeast Asian Nations (ASEAN) harmonization procedures; and (3) an overview of the Pan American Network for Drug Regulatory Harmonization (PANDRH) procedures. Within each section, there is a discussion of the level of maturity of each initiative, and of the strategic benefits and limitations to potentially follow the regional harmonization pathway for the LNG-IUS.

Note: Harmonization initiatives included in this report were evaluated only for focus countries included in the FP2020 initiative.

1. African Medicines Registration Harmonization (AMRH) Initiative

Variation in regulatory models and processes across countries is a major obstacle to the approval of medicinal products in some African countries, thereby discouraging manufacturers from pursuing product registrations in these markets.[1] In an effort to harmonize regional regulatory models and processes, the African Medicines Regulatory Harmonization (AMRH) initiative was established. AMRH's main objective is to create regulatory mechanisms that are effective, efficient, and transparent to obtain faster approval and subsequent availability of products in African markets. To achieve this objective, AMRH develops regional regulatory platforms with harmonized regulatory requirements and guidelines, as well as joint regional dossier assessment and Good Manufacturing Practice (GMP) inspections.

The AMRH is comprised of five Regional Economic Communities (RECs) at varying levels of maturity. The following sections will focus on the three RECs in the implementation phase – meaning, harmonization projects have been initiated, at a minimum, and the regional frameworks for harmonization of regulatory policies have been agreed upon. The remaining two RECs (Central Africa and North/Northeastern Africa) are still in early planning stages and are unlikely to be ready for manufacturers to utilize in a short- to mid-term timeframe. Given the variation in harmonization progress in this region, strategic regulatory planning is necessary for successful and timely product approvals.

[1] Luthuli N. and Robles W., Africa Regulatory Harmonization Initiatives. White Paper. 2017

1.1 East African Community (EAC-MRH)

The EAC is comprised of six countries, including: Burundi, Kenya, Rwanda, South Sudan, Tanzania and Uganda. The EAC-MRH has made significant progress to date; in 2014, they approved harmonized guidelines, a CTD, Good Manufacturing Practice (GMP), and the Quality Management System (QMS) compendia.[2] Although there is no mutual recognition in the EAC, the available joint assessment procedure by the NMRAs of the EAC Partner States greatly simplifies the process for manufacturers to apply in multiple EAC countries. Once the assessment of the medicinal products dossier is successfully completed and jointly accepted, the EAC Partner States' NMRAs should grant marketing authorization within three months from the date of joint acceptance.[3]

In 2017, the EAC Joint Assessment Procedure received a total of 32 applications, resulting in four product registrations and 23 applications queried with an estimated 30 - 40% faster completion of evaluation procedure than at the national levels, resulting in significant cost and time savings.[4]

Manufacturers interested in the EAC joint evaluation procedure must submit the following to the EAC Partner States' NMRAs:

1) An Expression of Interest letter (EOI), detailing their interest in participating in the EAC-MRH program;
2) A product dossier, in the format specified in the EAC Guidelines on Submission of Documentation for Registration of Human Medicinal Products;
3) Product samples, to enable visual examination and laboratory analysis;
4) A site master file for each manufacturing site listed in the product dossier, in the required format specified in the EAC harmonized guidance documents for submitting a Site Master File;
5) Evidence of payment to all EAC Partner States' NMRAs where the manufacturer intends to register the product. Fees to be paid by the applicants to the EAC Partner States' NMRAs follow national fees regulations.

Please refer to Appendix 6 for the flowchart detailing the dossier submission procedure under the EAC-MRH.

1.2 Southern African Development Community – SADC - MRH (ZAZIBONA Initiative)

Building on the success of the EAC-MRH joint dossier assessments, the SADC region initiated a platform in 2013 called ZAZIBONA (initially composed of Zambia, Zimbabwe, Botswana and Namibia) to coordinate joint assessments in the region. A total of ten countries, including the four founding members, have now joined the scheme with different membership status including: South Africa, (active), Swaziland (active), Democratic Republic of Congo (active), Angola (non-active), Seychelles (non-active) and Malawi (non-active). The countries with active status participate in dossier assessments while the non-active countries are observers. The ZAZIBONA collaborative process was established with the goal of facilitating the availability of quality medicines through joint assessment of medicines and the inspection of manufacturing and testing facilities. The assessment reports generated during work-sharing are submitted to each NMRA for final product registration at the national level.

[2] AMRH Initiative, Accomplishment & Challenges, presentation by Ms. Ndomondo Sogonda, November 2016. http://www.icdra.co.za/presentation/pre-icdra

[3] Notice to Applicants East; African Community's Procedure For Marketing Authorization Of Medicinal Products http://www.mrh.eac.int/

[4] Ndomondo-Sigonda M. et al. Medical Research Archives, vol. 6, issue 2, February 2018 issue.

Manufacturers wishing to register in one or more countries active in the ZAZIBONA Initiative should follow the ZAZIBONA submission process for all active countries:

1) Submit a cover letter (clearly indicating interest to participate in the ZAZIBONA project);
2) A product dossier in the ICH CTD or the SADC CTD format;
3) Product samples;
4) Site master file; and,
5) Country specific requirements including application fees for each country, statutory forms for each country, and country specific labelling requirements.

Products registered by SRAs are eligible for an abridged review process if access to the assessment reports utilized by the SRA can be provided. Applications may be submitted by any entity that qualifies to be an applicant in each participating country as per national requirements.

The ZAZIBONA collaborative process is designed to achieve registration within a total timeframe of 11 months, during which the applicant will have two windows of opportunity to respond to consolidated lists of regulatory questions over a period of 60 days. At the end of the process, the applicant is provided with an assessment report, which can be used in support of registrations of the respective product in other SADC countries. The ZAZIBONA process design is included in Appendix 7.

The ZAZIBONA initiative does not yet have a central submission process, but the same dossier submitted to ZAZIBONA is submitted to all countries intended for registration based on the harmonized SADC and ICH CTD registration guidelines. Since October 2013, the ZAZIBONA initiative has evaluated 179 product applications over 15 meetings, with a final decision reached for more than 90 products. Average time to obtain a recommendation from ZAZIBONA for product approval is nine months, as evidenced by data from 2013 to 2016.[5]

1.3 West Africa – ECOWAS/UEMOA – MRH

The Economic Community of West African States (ECOWAS) and West African Economic and Monetary Union (UEMOA) have aligned their registration requirements and adopted a CTD.[6] Achieving this is an important milestone, given the diversity between the francophone and anglophone countries in the region. The ECOWAS and EUMOA are working collaboratively to implement this CTD across the West African region. Once fully implemented, the goal is for manufacturers to use this single CTD format for registration in all of the countries in the West African region.[7] Manufacturers should soon benefit from the harmonized CTD requirements, which means that the same product dossier will be acceptable by all NMRAs in this region with differences only in in the administrative section (Module 1), which remains country-specific. Because this initiative is at varying stages of implementation, manufacturers who wish to apply for registration in multiple ECOWAS countries at this time must consult with individual NMRAs to determine whether they have already implemented the standardized CTD format. Of note, ECOWAS is also building the capacity for medicines registration and evaluation of applications, but currently, there is no joint assessment procedure available. This work has been initiated and is expected as a next step.

[5] SADC Collaborative Medicines Registration Initiative (Zazibona), presentation by Sinah M Selelo, November 2016. http://www.icdra.co.za/presentation/pre-icdra

[6] ECOWAS and EOMOA countries include: Benin, Burkina Faso, Cabo Verde, Cote d'Ivoire, The Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, and Togo

[7] The standard ICH-CTD dossier is comprised of five modules and Module 1 is the only section with country-specific requirements. In francophone countries, module 1 needs to be in French.

Benefits and Limitations of the AMRH Initiatives

Among the AMRH initiatives, the EAC and ZAZIBONA are the most developed in their harmonized guidelines for registration processes. As noted, the list of products that are accepted in the EAC and ZAZIBONA regions includes priority medicines for reproductive health. In the EAC, manufacturers submitting registrations in two or more EAC countries can benefit from the joint assessment procedure and mutually recognized GMP inspection. A 2018 study conducted by Janssen Pharmaceutical, Inc. showed a reduction of approval times by 40 – 60% for several branded essential medicines through joint dossier assessments in the EAC.[8] Despite significant progress toward harmonization in this region, however, there is not yet mutual recognition of applications and therefore country-level requirements must still be followed for application submission. The ZAZIBONA Initiative provides an accelerated process for manufacturers seeking marketing authorization in two or more participating countries; however, like in the EAC, applications must still be submitted in accordance with country-level requirements. In West Africa, ECOWAS and UEOMA have merged their guidelines to establish common regional requirements, but country-level registrations must continue to follow local guidelines until the regional requirements are fully implemented. Thus, while in all cases manufacturers must continue to submit applications at the country-level, they may benefit from expedited approval in EAC and ZAZIBONA, and potentially in the future in West Africa. In addition, the available regional guidelines may open a pathway for mutual recognition as harmonization initiatives are further solidified.

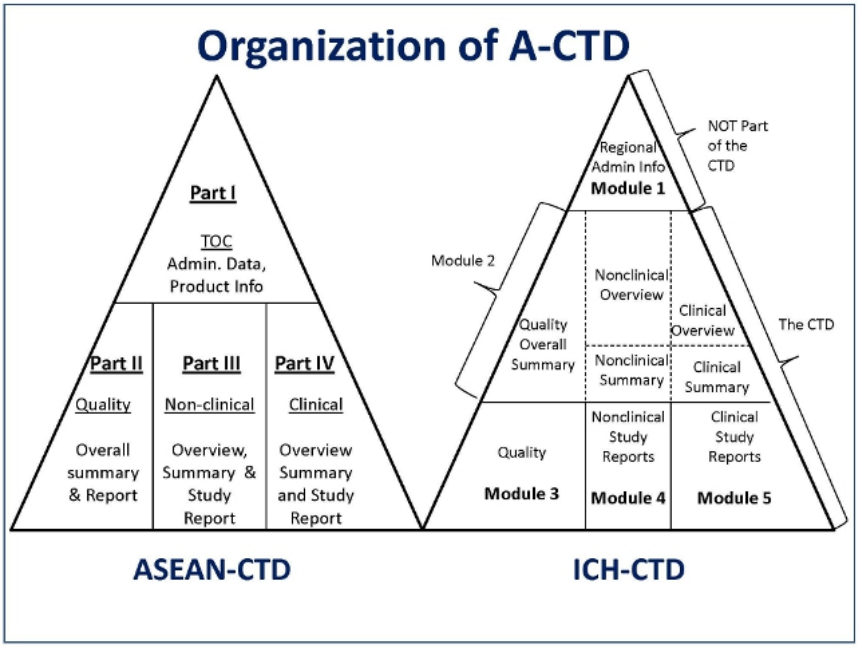
2. Association of Southeast Asian Nations (ASEAN) Harmonization

The ASEAN region consists of 10 countries, including: Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. The Pharmaceutical Product Working Group (PPWG) is the implementing arm of ASEAN and was established with the objective to create regional guidelines for the compilation of product dossiers, including the ASEAN Common Technical Requirements (ACTR)[9] and the ASEAN Common Technical Document (ACTD).[10] The ACTD structure incorporates International Conference on Harmonization (ICH) guidelines and is comparable to the CTD, as described in Figure 2 below.

However, even with the development of the ACTR and ACTD, like in West Africa, it can be difficult for manufacturers to identify a clear pathway for registration in this region. As a result, strategic regulatory planning and discussion with local authorities regarding applicable administrative documents and use of the ACTD is necessary for successful and timely product approvals in this region.

[8] Ndomondo-Sigonda M. et al. Medical Research Archives, vol. 6, issue 2, February 2018 issue. https://journals.ke-i.org/index.php/mra/issue/view/78 accessed on 09 September 2018.
[9] ASEAN ACTR: https://asean.org/?static_post=asean-common-technical-requirements-actr
[10] ASEAN ACTD: http://asean.org/storage/2017/03/68.-December-2016-ACTD.pdf

Figure 2: Comparison of the ASEAN ACTD and ICH CTD component structure[11]



Source: International Pharmaceutical Quality for the ACTD and ICH for the CTD.

At present, there is no centralized submission portal to facilitate dossier submissions across multiple ASEAN member states simultaneously. National online submission portals are only beginning to be used for submissions by some member states. Membership in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) is also part of the region's harmonization strategy. The (PIC/S) is a non-binding, informal, co-operative arrangement between regulatory authorities in the field of Current Good Manufacturing Practices (CGMP) of medicinal product for human or veterinary use. PIC/S is comprised of 49 authorities and aims at harmonizing inspection and facilitating co-operation as well as networking between competent authorities. Indonesia, Malaysia, Thailand and Singapore are members of PIC/S, and Philippines' FDA is currently being assessed for inclusion in the list of accepted ASEAN inspection services. ASEAN member states benefit by avoiding duplication of CGMP inspections within the countries and facilitating quick trade for medicinal products across this region, leading to faster patient access to such products.

Benefits and Limitations of ASEAN Harmonization Initiatives

One of the largest challenges facing ASEAN is harmonization among an extremely diverse group of countries. In addition to financial and social constraints, the ASEAN regulatory industry faces challenges due to a gap between the regulatory legislation issued by national governments and the actual enforcement of these laws at the local-level. Despite numerous challenges, ASEAN harmonization efforts are already beginning to demonstrate a positive impact through the establishment of the regional dossier format (the ACTD) and the harmonized ACTR. Manufacturers wishing to register in multiple countries in this region will benefit from these common guidelines, as it will enable them to prepare a single dossier that is applicable to multiple countries. However, as noted previously, there is no centralized submission

[11] Source: International Pharmaceutical Quality for the ACTD and ICH for the CTD. https://www.ipqpubs.com/wp-content/uploads/2010/12/

portal to facilitate a simultaneous dossier submission across multiple ASEAN member states. Similarly, mutual recognition has not been achieved in terms of medicines registration, so the regulatory framework and approval timelines remain largely country-specific.

3. Pan American Network for Drug Regulatory Harmonization (PANDRH)

The creation of the Pan American Network for Drug Regulatory Harmonization (PANDRH) was approved by governments in the region of the Americas to promote regional drug regulatory harmonization.[12,13]

The sub-regions within the Americas include:

- North America[14]: United States, Canada and Mexico
- Central America + Cuba + Dominican Republic: Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panamá, Cuba, and Dominican Republic
- Caribbean (CARICOM): Antigua and Barbuda, Bahamas, Barbados, Belize, Dominica, Grenada, Guyana, Haiti, Jamaica, Montserrat, St Kitts and Nevis, Saint Lucia, St Vincent and the Grenadines, Suriname, Trinidad and Tobago
- Andean Region: Bolivia, Chile, Colombia, Ecuador, Peru, and Venezuela
- Southern Cone: Argentina, Brazil, Paraguay, Uruguay

According to the PANDRH scope of harmonization, cooperative activities include aligning technical guidelines, regulatory processes, and the strengthening of national regulatory agencies through harmonization of processes and standards to improve drug quality and quality assurance. In this highly diverse region, countries and sub-regions are at varying levels of implementation, with CARICOM at the most advanced stage. Manufacturers who want to register in the PANDRH region will find that regional guidelines are primarily based on WHO documents. Other international guidelines, including ICH and select regional (e.g., EU, American sub-regional) or national technical documents are also used. One requirement to note for national submission in the Caribbean Community CARICOM) is the need to secure a local importer. The establishment of regulations and regulatory tools in the PANDRH region will contribute to the harmonization process of medicines registration to ensure the efficacy, quality, and safety of medicines available in this region. In the meantime, strategic regulatory planning is necessary for successful and timely product approvals. Additional details about the PANDRH dossier format and requirements can be found here.

The Americas' sub-regions can also implement abbreviated review processes in support of the limited regulatory capacity of small states.[15] For example, CARICOM implemented an abbreviated review of priority generic medicines through its Caribbean Regulatory System (CRS) by relying on reference authorities. If a manufacturer wishes to take advantage of this process, applications or dossiers can come to CARPHA/CRS in two ways, either 1) directly or 2) through a Ministry of Health (MOH) that asks the CARPHA/CRS to review the product as an assessor would. In the latter route, the company would sign a waiver to allow the Ministry of Health to release the dossier. This is a good option if a product has been in

[12] Statutes of the Pan American Network for Drug Regulatory Harmonization – PANDRH, PANDRH, Steering Committee, December 2015.
[13] Strategic Development Plan 2014-2020 of the Pan American Network for Drug Regulatory Harmonization (PANDRH), PANDRH Series – Technical Document No. 14, Pan American Network on Drug Regulatory Harmonization, July 2014
[14] The United States, Canada, and Mexico are part of the PANDRH steering committee
[15] Requirements for Medicines Registration in the Americas, PANDRH Series – Technical Document No. 10, Pan American Network on Drug Regulatory Harmonization, June 2013.

backlog and needs timely review. The dossier only needs to contain the CRS submission requirements but can be in a variety of formats. The CRS then reviews, and if favorable, recommends the product to CARICOM Ministries of Health to determine whether to issue a sovereign marketing authorization. This review does not replace the national authorities' evaluation, but it supports and facilitates the evaluation process such that national-level review may be expedited.

Benefits and Limitations of PANDRH Initiatives

Manufacturers wishing to register a product in this region may benefit from simplified application processes that result from harmonized registration guidelines.[16] In the CARICOM sub-region, the CRS abbreviated review of priority generic medicines can be a significant advantage. However, while CARICOM has achieved reliance for the abbreviated application review, other sub-regions in PANDRH are still working toward implementation of similar initiatives. For the Americas sub-region, many challenges remain to achieve effective pharmaceutical harmonization, including limited human and financial resources, as well as cultural and language diversity, among others.

4. Conclusions & Recommendations: Regional Harmonization Initiatives

Although regional harmonization efforts have made great strides over the last ten years, **none are yet operating at the level that an approval from a regional network would be replace the application requirement at the national level.** The most advanced regional networks are the EAC, ZAZIBONA, and CARICOM, due to their harmonized CTD guidelines, joint assessment procedures, and expedited review timelines. At this point, manufacturers primarily can benefit from harmonized and accelerated registration processes that offer a single CTD submission, a single set of questions during the evaluation process and, in principle, a harmonized registration decision (e.g., as part of the regional initiative, the NMRA may follow the recommendations of the collaborative body). However, interested applicants should always meet with local authorities to determine both the country's level of participation in the regional harmonization initiative in question, as well as to identify local requirements including the administrative documents (in Module 1) that must also be submitted.

[16] PANDRH guidelines can be found on the PAHO website here.

National Registration Pathways: An Assessment of Ghana, Ethiopia, and Vietnam

The third pathway to pursue registration for the LNG-IUS in FP2020 countries is by following country-specific registration requirements exclusively via the traditional national registration pathway. In this pathway, registration timelines and difficulty levels may vary significantly by country. Manufacturers that want to register a product in a country that is also part of a regional harmonization initiative, as noted in the previous section, should first identify the country-specific requirements to ensure they are compliant with both local and regional requirements.

To explore national registration pathways and to provide guidance to LNG-IUS supplier(s) who may want to pursue registration in countries identified as a priority in the short term, we selected three countries – Ghana, Ethiopia, and Vietnam—that were identified as high-priority for registration of the LNG-IUS as determined by the criteria below. For each country, we provide a summary of the local regulatory requirements, as well as a discussion of the benefits and limitations of following the national registration pathway. The detailed regulatory assessment for each of these three countries can be found in Appendix 1.

Identification of High-Priority Countries

To identify FP2020 countries that may be priorities for LNG-IUS registration in the short- or mid-term, we considered a number of factors, including:

- Level of local registration difficulty[17]
- Representation of diverse geographic regions
- Information readily available from online sources
- Comparatively strong or increasing IUD and/or implant use
- Diversity in recognition of WHO Collaborative Procedure

In June 2018, input was solicited from a range of stakeholders on priority countries and timelines for LNG-IUS introduction. Respondents included donors, service delivery groups, and Medicines360. Feedback was requested through a short questionnaire administered either by email or phone.

A matrix was then developed which summarized the following information for FP2020 countries: Regional Economic Community membership, regional harmonization membership, regional harmonization maturity level, registration status of AVIBELA, participation in the WHO Collaborative Procedure, local registration difficulty level, IUD and implant use and rates of expansion, priority countries for donors/stakeholders (current or future), and ICA Foundation registration or distribution of LNG-IUS. The LEAP LNG-IUS Initiative team then reviewed the results, and selected Ghana, Ethiopia and Vietnam for the assessment. Additional details about the three countries is included below. Other potentially high-priority countries were also considered, including Senegal, Tanzania, Haiti, Indonesia, Malawi, Burkina Faso, Mali, Cote d'Ivoire, Togo, and Bangladesh.

[17] Difficulty level criteria for local registrations was subjective and determined by: availability of applicable guidelines, timeline and expedited options, MAH requirements, dossier format requirements, GMP requirements, sample requirements, and local study requirements.

1. National Regulatory Assessment #1: Ghana

Ghana was selected for a review of local regulatory requirements based on its participation in the WHO Accelerated Registration of Prequalified FPPs, the availability of online information, and its position as a West African country that is also a high-priority for stakeholders. In addition, it is one of only three countries where the unbranded LNG-IUS product offered through donations by the International Contraceptive Access (ICA Foundation) is registered. Given that there is already some familiarity with the LNG-IUS in Ghana through the ICA Foundation's donation program, it may be an attractive market for Medicines360 and/or donor-funded implementing partners to consider introducing another LNG-IUS product(s) in the future.

We estimate the local level of registration difficulty in Ghana to be moderate based on the fact that requirements are standard, but GMP inspection prior to product approval may be required. Ease of registration in Ghana is facilitated by working groups that specialize in academic and technical regulatory expertise. Ghana is a member of the Economic Community of West African States (ECOWAS) regional harmonization initiative, and as noted previously, ECOWAS does not yet have a joint assessment procedure. For this reason, manufacturers considering registration in Ghana should pursue the country-level pathway. Alternatively, manufacturers with medicinal products that have been prequalified by the WHO/PQP can take advantage of the Ghana Food and Drug's Authority (FDA) fast-track registration of WHO prequalified medicinal products. The Ghana FDA commits to communicating its decision with the applicant and the WHO within 90 calendar days.

The requirements for registration of drug or medicinal products in Ghana is based on the WHO Guidelines on Submission of Documentation for Prequalification of Multi-Source Finished Pharmaceutical Products and the International Conference on Harmonization (ICH) CTD requirements for Registration of Pharmaceuticals for Human Use. Thus, the required dossier format for drug registration in Ghana is the ICH-CTD format. A new application is processed within six months of receipt by the Ghana FDA. Applicants with medicinal products that have been prequalified by the WHO/PQP can take advantage of the procedure for fast-track registration of their prequalified medicinal product by the Ghana FDA.

If a new application is from a new manufacturing site, the Ghana FDA will conduct inspection of the facility to verify whether it complies with CGMP regulations and/or guidelines before a product is registered, regardless of GMP certificates or inspection reports by SRAs. Ghana's requirements for registration and post-registration are readily available online.

Refer to **Appendix 1** for a detailed assessment of the Regulatory Landscape in Ghana.

2. National Regulatory Assessment #2: Ethiopia

Ethiopia was selected for a review of local regulatory requirements due to its strong commitment to reproductive health and increasing prevalence of long-acting reversible contraception (LARC) methods in recent years, which may make the country an ideal setting to introduce the LNG-IUS. From 1990 to 2011, contraceptive use in Ethiopia increased ninefold and the total fertility rate fell from 7.0 to 4.8.[18] This success has been attributed to the 4 factors: political will, generous donor support, nongovernmental and

[18] D. J. Olson et. Al. Ethiopia: An Emerging Family Planning Success story https://pdfs.semanticscholar.org/7f09/993c8d5e08974fb3043d796cf6229ad74d27.pdf accessed on October 24, 2018

public–private partnerships, and the Health Extension Program.[19] In 2015, the results from a survey conducted by the FPwatch Project in Ethiopia, Nigeria, and Democratic Republic of Congo showed that 54% percent of outlets in Ethiopia had LARC commodities or services available at the time of the survey, versus 7% and 8% of outlets in Nigeria and DRC, respectively.[20] Thus, Ethiopia may be an attractive market for Medicines360 and/or donor-funded implementing partners to consider introducing another LNG-IUS product(s) in the future.

We estimate the local level of registration difficulty in Ethiopia to be moderate; while there is no requirement for a local clinical study, timelines for review may be longer than expected based on experience. Ease of country-level registration is facilitated by the Ethiopian Food, Medicines, and Health Care Administration and Control Authority's (FMHACA) online database and application system for product registrations and import permits. While Ethiopia is a member of the International Authority on Development (IGAD) regional harmonization initiative, manufacturers considering registration in Ethiopia should follow the national registration pathway, as IGAD is in early stages of implementation. Ethiopia is a member of the WHO CRP for WHO-prequalified products, which accelerates registration through improved information sharing between the WHO PQP and the FMHACA. Applicants with a registration certificate issued by an SRA (including WHO PQR) are eligible for an abridged registration review, which is processed within 90 days.

Ethiopia requires a CTD-formatted dossier for product registration. Foreign manufacturers must appoint an agent/representative who will be responsible for the import, distribution, and sale of the product in Ethiopia. At the time of importation of the product, the agent representing the manufacturer should hold a license issued by the Ministry of Trade and a Certificate of Competence from FMHACA. The current guidelines state that the timeline for application evaluation is 30 days; however, in our experience, this initial screening process can take 3 - 6 months. According to the current guidelines, there is a fast-track evaluation and registration procedure for certain priority products, including family planning commodities, but specific timelines regarding this procedure are not provided by the FMHACA. Manufacturers of reproductive health products can utilize the fast-track process which could potentially expedite the dossier evaluation process and shorten the timeline for product registrations.

Ethiopia has very strict country-specific labeling requirements and product importation procedures that must be followed before and after product registration. In many instances, the cause for application rejection in Ethiopia is due to label incompliance. It is important to appoint an experienced local agent with strong knowledge of the importation requirements, including customs clearance for shipped products. There are also some notable administrative requirements, as part of Module 1, which the manufacturer needs to be aware of, including: The Agency Agreement, GMP Certificate, Certificate of Pharmaceutical Product (CPP) issued by a competent authority in the exporting country, and the Certificate of Suitability. A sample of actual products with the reference standard substances may also be requested. The quantities of samples and reference standard substances are discussed in FMHACA's current guidelines for medicines registrations. However, the regulatory requirements for registration and post-registration activities are very clear and readily available on the FMHACA website. FMHACA is one of the most well-established NMRAs in Africa, and Ethiopia is one of the few countries with an online registration process.

[19] D. J. Olson et. Al. Ethiopia: An Emerging Family Planning Success story https://pdfs.semanticscholar.org/7f09/993c8d5e08974fb3043d796cf6229ad74d27.pdf accessed on October 24, 2018

[20] K. Thanel et.al. Leveraging long acting reversible contraceptives to achieve FP2020 commitments in sub-Saharan Africa: The potential of implants. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0195228

Refer to Appendix 1 for a detailed assessment of the Regulatory Landscape in Ethiopia.

3. National Regulatory Assessment #3: Vietnam

Vietnam was selected for an in-depth regulatory assessment due to its high IUD use, its non-participation in the WHO Accelerated Registration of Prequalified FPPs, and its position as a country in the ASEAN region. We estimate the local level of registration difficulty in Vietnam to be challenging due in part to the ambiguous and inconsistent regulatory environment, which results in the application of regulations on a case-by-case basis with little overall coordination, including the local clinical trial requirement.

The documents required for product registration application packages in Vietnam include: CPP, Free Sale Certificate from country of origin, GMP certification, product information, a detailed description of the manufacturing process, quality specifications, finished product samples, and packaging information, including a Vietnamese language insert leaflet. Apart from the last requirement, most of the product application can be completed in English.

Because there is no recognition of the WHO Accelerated Registration of Prequalified FPPs in Vietnam, the recommended route of registration is a national-level registration following the ASEAN regional harmonization requirements. The ASEAN regional requirements allow manufacturers to register the product in multiple countries in the region using the same dossier, although it must be submitted in each country separately. Of note, to control rising drug prices, the Vietnamese government requires that pharmaceutical import licenses disclose the price of the product. To comply with country-specific requirements, the appointment of a local Marketing Authorization Holder (MAH) is required. A local MAH with appropriate expertise can also help to avoid or limit government price restrictions.

Refer to Appendix 1 for a detailed assessment of the Regulatory Landscape in Vietnam.

4. Conclusions & Recommendations: National Regulatory Assessments

As indicated above, local registration pathways are nuanced and vary greatly by country. The benefits to pursuing a country-by-country national registration strategy are three-fold. First, following this pathway ensures that applicants provide the exact documentation that the NRA expects and minimizes inefficiencies in the submission process. Second, national registration pathways often have an option for expedited review process that applicants may be able to utilize, such as the fast-track evaluation and registration procedure in Ethiopia. Lastly, national registration processes allow the applicant to work directly with country authorities to determine or negotiate flexibility within the registration requirements on a case-by-case basis. This flexibility can be a significant advantage to applicants following a national registration pathway.

However, there are also challenges when pursuing national registration pathways in FP2020 countries. Some countries may not have clear national guidelines, or they might have guidelines listed online or in their national policy that are no longer applicable in practice. National registration pathways are also highly affected by external factors (e.g. understaffed or resource-limited NRA, political factors, etc.) that can stall or inhibit the application progress. To mitigate the effects of external factors on the application process and to facilitate efficient and effective registration submissions, manufacturers are advised to follow several recommendations: 1) identify and engage an experienced local MAH; 2) request a consultation meeting with local registration authorities early in the application process to confirm the

official guidelines; and 3) identify the dispensing category of the product and as well as required sample quantities.

Taken together, national registration requirements are highly country-specific, and a variety of factors must be considered to determine whether a country-by-country regulatory approach is likely to be the most efficient and successful pathway. Additionally, if a manufacturer wishes to submit for registration to a regional harmonization initiative, it is important to ensure compliance with local regulations first. We offer the following recommendations to LNG-IUS suppliers who are considering applying for national registrations in FP2020 countries:

- Even if requirements are available online, an in-person regulatory landscape assessment can help determine which pathway is best suited for submission, and to identify possible areas of flexibility within the registration process. This will provide applicants with a complete picture of the regulatory landscape for the relevant country.
- If the product is being registered in more than one country (for example, in the EAC, CARICOM or ZAZIBONA regions), file a Joint Assessment application to take advantage of the expedited individual country registrations.
- For local registrations, secure an appropriate local representative to facilitate interaction with authorities and stakeholders, mitigate external delays (e.g., due to environment, politics) and ensure a faster registration timeline.

Overview of LNG-IUS Suppliers

Overview of LNG-IUS Products Currently Available in FP2020 Countries

There are three LNG-IUS products that have been approved by a Stringent Regulatory Authority (SRA) as of October 2018 that are currently available on a limited basis in FP2020 countries:

1. **Mirena®**, a five-year LNG-IUS product manufactured by Bayer Healthcare Pharmaceuticals Inc, is offered on a very limited basis in private, for-profit settings in some developing countries. Recent market assessments conducted in Kenya, Madagascar, Nigeria, and Zambia have documented prices of Mirena® to clients in urban settings ranging from US $60-400.[21] In this price range, the method is prohibitively expensive for most women in LMIC markets. (Note: Bayer Healthcare also manufactures the LNG-IUS products Skyla® and Kyleena®. However, these products are not yet available in FP2020 countries and therefore are not discussed here.)

2. **An unbranded LNG-IUS product** manufactured by Bayer Healthcare is available for free by application through donations made by the ICA Foundation, a private-public partnership between Bayer Healthcare and the Population Council. Since 2005, over 130,000 units have been donated through this mechanism in thirty-six countries. These donated units have been used to support small scale pilot activities, rather than to facilitate access through the health system on a regional or national scale. In addition, the ICA Foundation's LNG-IUS product is only registered in three countries which means that a waiver must be secured when importing in most LMICs.[22]

3. **LILETTA®/AVIBELA®,** a new LNG-IUS is distributed by Medicines360, a non-profit pharmaceutical company, and Allegan. The product approved by the US FDA in 2015, and is sold as LILETTA® there. In the U.S., Allergan and Medicines360 share marketing rights, while Medicines360 has exclusive rights in most FP2020 countries. The product is being sold as AVIBELA® in FP2020 countries, and Medicines360 is currently working with partners to register the product in several countries. In early 2018, this product was approved in Madagascar and Zambia, and more registrations are anticipated in the coming years. The current public sector price to distributors will vary by volume between US$12-16; for an order of 100,000 units, public sector transfer price will be approximately $15/unit.[23]

There are also several LNG-IUS products that are not currently quality assured by a SRA. See **Tables 3** and **4** for more details. **Note**: No LNG-IUS products are currently WHO Prequalified as of October 2018.

[21] Rademacher K.H., Cooley T. What's Next with the LNG-IUS? Updates on Country Activities. Presentation. October 2016. Annual meeting of the Reproductive Health Supplies Coalition, Seattle, WA.

[22] International Contraception Access (ICA) Foundation. http://www.ica-foundation.org/

[23] Rademacher KH, Solomon M, Brett T, et al. Expanding access to a new, more affordable levonorgestrel intrauterine system in Kenya: service delivery costs compared with other contraceptive methods and perspectives of key opinion leaders. Glob Health Sci Pract. 2016;4(suppl 2):S83–S93.

Table 3: Overview of SRA-Approved LNG-IUS Products

Supplier and SRA-approved LNG-IUS Product	Overview of Registration Status in FP2020 countries (as of October 2018)	Overview of pricing in FP2020 countries
Bayer Healthcare - Mirena*	Mirena is registered nearly 30 FP2020 countries.	Provided commercially through private healthcare clinics in some developing countries on a very limited basis. Pricing between ~US$60-$400 has been documented in recent market assessments in urban settings in Kenya, Madagascar, Nigeria, and Zambia.
International Contraceptive Access (ICA) Foundation – unbranded LNG-IUS	Registered in three countries; brought in via waivers in other countries.	Through a public-private partnership between Bayer HealthCare & Population Council, a free LNG-IUS product is provided for small-scale, pilot activities.
Medicines360 (manufactured by Allergan) - Sold in the U.S. under trade name LILETTA. Being registered in FP2020 countries under the trade name AVIBELA	As of mid-2018, registered in Madagascar and Zambia with more registrations anticipated in the coming years.	The current public sector price to distributors for AVIBELA will vary by volume between US$12-16; for an order of 100,000 units, public sector transfer price will be approximately $15/unit.
* Bayer Healthcare also manufactures the LNG-IUS products Skyla and Kyleena. However, these products are not yet available in LMICs and therefore are not discussed here.		

Table 4: Overview of LNG-IUS Products That Have Not Been Approved by an SRA

Supplier and LNG-IUS Product	Overview of Registration Status in FP2020 countries (as of October 2018)	Overview of pricing in FP2020 countries
Pregna – Eloira (based in India)	Being registered in several countries outside of India	Because these products are not SRA-approved or WHO Prequalified, they cannot be purchased by international donors such as UNFPA or USAID. Private sector prices vary by country/supplier.
APCOR Research & Manufacturing - Femilis (based in Belgium)	No current registrations	
Meril - Erinna and Fiona (with different inserters) (based in India)	India	
HLL Lifecare - Emily LNG-IUS.	Being registered in several countries outside of India. Note: The frame shape is modeled after Multiload, which differs from the frames of the other T-shaped LNG-IUS products.	

Conclusions

In conclusion, as LNG-IUS manufacturers and donors consider how to increase the number of LNG-IUS approvals in FP2020 countries, each pathway has specific benefits and limitations. These are summarized in **Table 5** below. Applicants are advised to carefully evaluate which pathway(s) is the most strategic option for their product and target countries in terms of potential time and cost savings.

Table 5: Regulatory Pathways Advantages and Disadvantages

Pathway	Potential Advantages	Potential Disadvantages
WHO Prequalification & WHO-Supported Collaborative Procedures		
Full WHO Prequalification	Once prequalified through this mechanism, it would allow supplier to take advantage of the WHO Collaborative Procedure for a fully WHO prequalified product	More expensive and time-consuming than the Abbreviated WHO Prequalification pathway
Abbreviated WHO Prequalification pathway for SRA-approved generic or innovator products	Less expensive and faster than pursuing Full WHO Prequalification	Would not allow supplier to take advantage of the WHO Collaborative Procedure for a fully WHO prequalified product
WHO Collaborative Procedure for a fully WHO prequalified product	May be faster than filing country-by-country in FP2020 countries	Unclear if would result in substantial time or cost savings especially if target number of registrations is modest
Accelerated Collaborative Procedure for SRA approved products	This could be a cost-effective way to achieve registrations in FP2020 countries if supplier can use approval from the MHRA and EMA	The US FDA has not agreed to participate in this initiative due to data sharing concerns. As such, this pathway is only available to manufacturers who want to and are able to use an approval from the MHRA and EMA.
Regional Harmonization Initiatives		
	Following regional guidelines may be a faster way to achieve registrations in multiple countries in a region once harmonization efforts are mature. Some regions (EAC, ZAZIBONA, CARICOM) offer standardized guidelines and expedited review.	Mutual recognition has not yet reached maturity where a single regional application will be recognized by all countries in a given region. As such, manufacturers who want to register in multiple countries still have to follow country-specific guidelines and submission processes.
National Registration Pathways		
	May be cost-effective and flexible in application requirements. May be options for expedited review in some countries.	Wide variation in country-specific requirements and submissions may be subject to extended delay outside of applicant's control.

Appendix 1: National Regulatory Assessments (Ghana, Ethiopia, Vietnam)

National Regulatory Assessment 1: Ghana

Source: FDA Ghana: https://fdaghana.gov.gh/

General questions

1) **Confirm the current official guidelines for registration of this type of product and include them as attachment at the time of this report.**

The current official guidelines are titled "Guidelines for Registration of Allopathic Drugs-Quality Part, March 1, 2013." Complete guidelines can be found here.

2) **Confirm the classification of the LNG-IUS in a given country.**

The classification of LNG-IUS is an allopathic drug*

** From a verbal discussion with the Ghana FDA representative at the ICDRA 2018 conference: For parties interested in registering the LNG-IUS in Ghana, a letter of interest must be submitted to the Ghana FDA to request appropriate classification. At the time of this report, the LNG-IUS would need to follow a dual regulatory pathway for both an allopathic drug and a medical device. Because the allopathic drug registration requirements are more extensive, requirements for that pathway are provided here.*

Allopathic drug: Any product or substance other than a medical device, which is to be administered to one or more human beings or animals on its own, or as an ingredient in the preparation of a substance, for a medicinal purpose.

Medicinal purpose: means treating or preventing a disease, diagnosing or ascertaining the presence and extent of a physiological function, contraception, inducing anesthesia, altering normal physiologic function permanently or temporarily in any way in humans

Implantable device (medical device): Any device, including those that are partially or wholly absorbed, which is intended to be totally introduced into the human body; or, to replace an epithelial surface or the surface of the eye, by surgical intervention which is intended to remain in place after the procedure. In addition, any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.

3) **Confirm the application process flow of the NMRA vs the applicable Medicines Regulatory Harmonization (MRH) Program.**

National Medicines Regulatory Authority (NMRA)

In Ghana, the NMRA is the Food and Drug Administration (FDA). The Ghana FDA is the country-level agency that is responsible for implementing regulatory practices in Ghana and is the preferred route of regulatory submissions. The application process flow of the Ghana FDA is as follows:

1. An application for the registration of a drug, either locally manufactured or imported, shall be made in writing via a cover letter.
    a. The cover letter submitted with the dossier should include a clear statement by the applicant indicating that the information submitted is true and correct.
2. If the applicant is a foreign company, it shall appoint a local agent through whom an application shall be submitted.
    a. The local agent shall be a registered pharmaceutical wholesale company or an accredited manufacturer's representative in Ghana.
3. Every application shall be accompanied by appropriate fees at the time of submission. Any application that is not accompanied by appropriate fees will not be accepted.
4. The application should be submitted in hard copies and electronic copy through the authorized local agent by the regulatory contact person to the following address:

    The Chief Executive Officer
    Food and Drugs Authority
    P. O. Box CT 2783
    Cantonment-Accra

5. The evaluation of applications is done on a first in first out basis, unless the product meets the expedited review process as set out in "FDA Guidelines for Registration of Allopathic Drugs- Quality Part."
    a. Evaluation reports are peer-reviewed by a second evaluator. During evaluation, additional data and/or samples may be requested.
6. If the new application is from a new manufacturing site, the FDA will conduct inspection of the facility or use other means to verify whether it complies with CGMP regulations.
7. The label review, dossier evaluation, laboratory analysis, and GMP status reports will be presented to the Drug Registration Committee for review and final decision on registration

For purposes of submission to FDA, applications are classified into three categories as follows:

1. New application for registration
2. Application for renewal of registration
3. Application for variation of a registered medicinal product

Medicines Regional Harmonization Program

Ghana is a member state of the Economic Community of West African States (ECOWAS). The major accomplishments of the ECOWAS MRH program to date have been to align the Common Technical Document (CTD) requirements for the West African Health Organization (WAHO) and the West African Economic and Monetary Union (UEMOA) with technical support from WHO. However, for country-level regulatory affairs, the Ghana FDA is the implementing agency.

4) Confirm the required dossier format, e.g. International Conference on Harmonization Common Technical Document (ICH CTD) or country specific format.

The required dossier format is ICH Common Technical Document.

5) If English is not a national language, what are the translation requirements?

All applications and supporting documents shall be in English and legible.

Where material is not originally in English, a copy in the original language and a full translation should be submitted, the accuracy of the translation is the responsibility of the applicant. Authentication of the translation has to be done at the nearest Ghana Embassy or by the National Drug Regulatory Authority of the country from where the document originates.

6) Define the requirements and responsibilities for the Applicant/MAH?

The applicant is defined by the Ghana FDA as the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.

A non-resident applicant would be required to appoint a local agent with the requisite mandate to represent the said applicant. The agent would be required to produce the relevant documentation including, but not limited to, a power of attorney or any other documentation, affirming his/her appointment as an agent.

7) Confirm if there is a recommended distribution category for prescription medicine? e.g. clinics only, hospital or pharmacy distribution only

There is not a recommended distribution category for prescription medicine in the available guidelines. Additional information can be found in "Guideline for Good Distribution Practices" here.

8) What are the sample requirements?

For single pack products like the LNG IUS, 200 samples are required. Additional information can be found in "Sample Schedule for Allopathic Drugs" here.

9) Confirm the estimated application review timelines (if available)

Processing of new applications: A new application will be processed within 6 months of receipt of the application. The applicant will be required to provide any requested additional data within 12 months. In case additional time is required, a formal request must be submitted to the FDA.

10) What is the current product registration fee according to the statutory instrument? Determine if any other costs are involved.

Every application shall be accompanied by appropriate fees at the time of submission. Any application that is not accompanied by appropriate fees will not be accepted. If an application for renewal is not made within three years following the expiration of the registration validity, it shall be considered as a new application for registration.

MINISTRY OF HEALTH
FOOD AND DRUGS AUTHORITY
DRUGS, SAFETY MONITORING & CLINICAL TRIALS DIVISION
Public Health Act, 2012 (Act 851). Fees & Charges (Miscellaneous Provisions) Act. 2009 (Act 793) L.I. 2228 (2016)

NO.	REVENUE ITEMS	APPROVED RATES (USD)	3 YEARS
	Registration Fee for Imported Medicinal Products	***(Cedi Equivalent)***	**USD**
1	Imported Allophatic Products	1,200.00	3,600.00
2	Imported Allophatic new Chemical Entities	1,800.00	5,400.00
3	Imported Herbal Products	1,200.00	3,600.00
4	Imported Food Supplements	500.00	1,500.00
5	Imported Veterinary Medicines	600.00	1,800.00
6	Tobacco and Tobacco Product Registration (Variant)	15,000.00	45,000.00

There are additional fees for Facility GMP Audit and Licensing (Pharmaceuticals). The audit fee of foreign Pharmaceutical Plant by the FDA is US $20,000.[24]

11) Confirm requirement for Authentication (Apostille, Certification, Notarization, or Legalization) of administrative documents such as certificates, power of attorney (POA), letter of authorization (LOA)

The legal information accompanying the dossier should be duly certified and authenticated under the procedure in effect in the country of origin and issued by the appropriate entity. Additional information can be found in "Guidelines for Registration of Biosimilar Products in Ghana" here.

- Document confirming the Senior Executive Officer / Senior Medical or Scientific Officer responsible for the product (under the country's legislation). Submit a document issued by the manufacturer of the biological product giving information on the individuals responsible for the product. The information should include the identity and designation of the authorized person in charge of regulatory activities.
- Certificate of Pharmaceutical Product using the World Health Organization (WHO) model, A free sale certificate (where applicable) should be submitted in addition to the GMP certificate.
- Certificate of Good Manufacturing Practices of other manufacturers involved in the production of the biological product. This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the active ingredient(s), the diluents, and those responsible for labelling and packaging of the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.
- Trademark certificate (optional)
- Proposed brand name and art work for primary and secondary labels. These should be submitted for approval by FDA prior to submission of application, dossier and samples for registration.

[24] http://www.fdaghana.gov.gh/images/stories/pdfs/downloads/drugs%20guidelines/APPROVED%20FEE%20SCHEDULE.pdf

- Invention patent certificate (based on the country of origin's legislation)
- Batch release certificate Refers to the batch release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration. Please refer to the FDA website for the minimum requirements (batch release document).
- Lot release certificate Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration.
- Manufacturer's declaration: A document should be presented certifying that the information provided is the information corresponding to all the studies performed, regardless of their results. This should include all the pertinent information regarding all toxicological and/or clinical tests or trials of the biological product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

12) Are there any country specific labeling requirements?

Country specific labeling requirements are provided in "Labeling Template" here.

13) Verify if there is a consideration for World Health Organization (WHO) Prequalified or Stringent Regulatory Authority (SRA) approved products

Applicants with medicinal products that have been prequalified by the WHO/PQP can take advantage of this procedure for fast track registration of their prequalified medicinal product by the FDA. Guidelines for products with WHO Prequalification be found in "Guidelines for Fast Track Registration of WHO Prequalified Medicinal Products" here. The Ghana FDA also participate in Accelerated Registration of FPPs Approved by SRAs, a pilot facilitated by the WHO Prequalification team.

14) Confirm procedure for submission of application

- An application for the registration of a drug, either locally manufactured or imported, shall be made in writing via a cover letter.
- The cover letter submitted with the dossier should include a clear statement by the applicant indicating that the information submitted is true and correct.
- If the applicant is a foreign company, it shall appoint a local agent through whom an application shall be submitted.
- The local agent shall be a registered pharmaceutical wholesale company or an accredited manufacturer's representative in Ghana.

The application should be submitted through the authorized local agent by the regulatory contact person to the following address:

The Chief Executive Officer
Food and Drugs Authority
P. O. Box CT 2783

Cantonment-Accra

A new application for registration shall include submission of:

- Two electronic copies in a text selectable Portable Document Format (PDF), on a CD Rom and should include MS-Word document for Module 2- see Annex I
- Samples of the FPP as per FDA sample schedule.
- Reference standards and impurity standards along with COAs used in the manufacture of FPPs classified as new drugs, new chemical entities and non-pharmacopeial FPPs as well as APIs with response factors should be submitted. The re-test period of the reference standards should have at least 6months re-test period at the time of submission.
- Non-refundable application fee for registration of medicines (Refer to FDA fee schedule).
- Non-refundable fee for facility GMP Audit and Licensing (Pharmaceuticals) not yet inspected by the FDA (Refer to FDA fee schedule).
- Proposed brand name and art work for primary and secondary labels. These should be submitted for approval by FDA prior to submission of application, dossier and samples for registration.

Additional information can be found in "Guidelines for Registration of Allopathic Drugs- Quality Part" here.

15) What are the requirements for post-approval changes/variations?

All applications for variation to a registered product shall be made according to requirements stipulated in the FDA Application Guideline for Variation of Registered Medicinal Products. All variations with the exception of annual notifications should be approved by the FDA prior to its implementation.

16) What guidance exists for handling of post-approval variations? If variation guidelines exist, please include them as attachment to this report.

Variation guidelines exist for applicants intending to make changes to the quality sections of product dossiers for an API or an FPP. This guidance should be read in conjunction with the FDA Guidelines for the registration of allopathic medicines as well as other related FDA guidelines. All variations with the exception of annual notifications should be approved by the FDA prior to its implementation.

Post-approval variation guidelines are provided in "Variation Guidelines for Allopathic Medicines" here.

Technical questions

1) Is an in-country clinical trial required ?

No

2) If a manufacturer wants to conduct the clinical in this country, what are the requirements?

A clinical trial application made to The Authority to conduct a clinical trial shall be accompanied by the following:

1. Cover letter
2. A non-refundable Application Fee as per the prescribed Fee Schedule.
3. A Clinical Trial Protocol
4. Completed Food and Drugs Authority Application Forms for Conducting Clinical Trials signed by authorized persons
5. A proof of registration with a Clinical Trials Registry (approved by The Authority)
6. Investigator's Brochure (COA, GMP)
7. Ethics Committee / Institutional Review Board Approval
8. Insurance Cover
9. Financial Declaration
10. DSMB Charter
11. Sponsor/PI Contractual Agreement

All clinical trial application documents shall be submitted in hard and soft copies (1 each). Additional information on clinical trial requirements can be found in ("Guidelines for Authorization of Clinical Trials of Medicines, Food Supplements, Vaccines, and Medical Devices in Ghana") here.

1) Is there a specific data package that is required for non-clinical studies?

The data package for non-clinical study reports includes:

1. Pharmacology
    a. Primary pharmacodynamics
    b. Secondary pharmacodynamics
    c. Safety pharmacology
    d. Pharmacodynamic drug interactions
2. Pharmacokinetics
    a. Analytical methods and validation reports
    b. Absorption
    c. Distribution
    d. Metabolism
    e. Excretion
    f. Pharmacokinetic drug interactions (nonclinical)
    g. Other pharmacokinetic studies
3. Toxicology
    a. Single-dose toxicity
    b. Repeat-dose toxicity
    c. Genotoxicity
    d. In vitro
    e. In vivo (including supportive toxicokinetics evaluations)
    f. Carcinogenicity (including supportive toxicokinetics evaluations

g. Long-term studies
h. Short- or medium-term studies
i. Other studies
j. Reproductive and developmental toxicity
k. Fertility and early embryonic development
l. Embryo-fetal development
m. Prenatal and postnatal development, including maternal function
n. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
o. Local tolerance
p. Other toxicity studies (if available)
q. Antigenicity
r. Immunotoxicity
s. Mechanistic studies
t. Dependence
u. Metabolites
v. Impurities
w. Other

2) How many batches or lots are required to be submitted?

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger. Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible. If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control. English translations of executed records should be provided where relevant.

3) Does the National Regulatory Authority require their own GMP inspection or do they accept history of EU/FDA inspections? If so, discuss GMP visits, interval for GMP inspections, e.g. every 5 years or annually? Confirm procedure and cost involved.

If the new application is from a new manufacturing site, FDA will conduct inspection of the facility or use other means to verify whether the facility complies with CGMP Regulations and/or guideline before a product is registered. No product shall be registered unless the facility complies with CGMP. The report of the CGMP inspection will form part of the registration process.

4) **What are the stability testing requirements, long-term storage condition (relevant Climatic Zones), testing frequency, storage conditions and the lengths of studies etc. Is there local Guideline for stability testing, please include as an attachment to this report?**

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate. The WHO guidelines Stability testing of active pharmaceutical ingredients and finished pharmaceutical products should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs. As outlined in the FDA stability guidelines, the purpose of stability testing is to: "provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light." The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions and commitments).

The local guideline for stability testing is provided "Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products" here.

National Regulatory Assessment 2: Ethiopia

Source: Food, Medicine, Health Care, Administration, and Control Authority of Ethiopia
http://www.fmhaca.gov.et/

General questions

1) **Confirm the current official guidelines for registration of this type of product and include them as attachment at the time of this report.**

Guideline for Registration of Medicines, 3rd edition June 2014, found here.

2) **Confirm the classification of the LNG-IUS in a given country.**

In Ethiopia, the LNG-IUS is classified as a Medicine.

3) **Confirm the application process flow of the NMRA vs the applicable Medicines Regulatory Harmonization (MRH) Program.**

Currently there is only one registration process in Ethiopia and it is via the Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA). The regional harmonization program (IGAD) is in early stages and does not offer registration or any other regulatory activities.

4) Confirm the required dossier format, e.g. International Conference on Harmonization Common Technical Document (ICH CTD) or country specific format.

The required dossier format is the Common Technical Document (CTD). To facilitate the preparation of the product dossier, the FMHACA Medicine Registration Guideline is organized in accordance with the structure of Common Technical Document – Quality (M4Q), Safety (M4S), and Efficacy (M4E) Guidelines developed by ICH, and also with the WHO Guideline for submission of documents for multisource and innovator finished pharmaceutical products.

5) If English is not a national language, what are the translation requirements?

Not Applicable. The FMHACA has specified in their current guidelines that all the product dossier and supporting documents must be submitted only in English language.

6) Define the requirements and responsibilities for the Applicant/MAH?

i. An agency agreement should be made between the manufacturer of the product for registration and the agent responsible for the import, distribution, and sale of the product in Ethiopia. Where the company manufactures the product at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such a case, the agency agreement between the local agent and the manufacturer should be the site where the file is kept and the applicant for registration is registered.
ii. The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document for agency agreement.
iii. The agreement should specify the first agent to handle the medicine registration process. In case the manufacturer wishes to have more than one distributor, this has to be mentioned in the agreement, but the maximum numbers of distributors are limited to three. The appointed agent(s) is responsible for correspondence and complete compliance with regulatory requirements pertaining to the product distribution life cycle in the country.
iv. The agreement should state that if any fraud or unsuspected and unacceptable adverse event occurs to the consumer under normal utilization, all the party's (local agents, manufacturer, and/or license holder) mentioned in the agreement will be responsible for collecting the product from the market and will be responsible for substantiating any related consequences.
v. The agreement should specify that both parties are responsible for pharmacovigilance and post-marketing reporting of the product safety, quality, and efficacy follow-up after marketing.
vi. For the purpose of administration, the agreement should remain valid for the period of one year from the date of submission to the Authority unless it is found to be satisfactory for the termination of the agreement.

The agent representing the manufacturer for importation should hold a license issued by the Ministry of Trade and a certificate of competence issued by the Authority at the time of importation of the product.

7) Confirm if there is a recommended distribution category for prescription medicine? e.g. clinics only, hospital or pharmacy distribution only

Information not available.

8) What are the sample requirements?

Where applicable, a sample of actual products may be requested for the purpose of visual confirmation, and/or for the purpose of laboratory testing or analytical performance evaluation of the device. Sample of actual products and reference standard substances can be submitted after document approval and/or along with the dossier for registration.

The quantities of samples to be submitted should be stated on the letter of acceptance for the dossier. For vaginal preparations, 50 units can be requested.

9) Confirm the estimated application review timelines (if available)

Evaluation and Notification: The application submitted for registration will be screened chronologically according to date of submission to the Authority, and the applicant will be notified of the results of its evaluation within 30 days of its submission to the Authority.

Fast Track Registration: Antimalarial, antiretroviral, anti-tuberculosis medicines, reproductive health care products, anti-cancer drugs, vaccines, drugs for —orphan diseases, and drugs for emergent humanitarian aid shall have priority for evaluation and registration.

10) What is the current product registration fee according to the statutory instrument? Determine if any other costs are involved.

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to contact the Authority for the amount and details of mode of payment.

11) Confirm requirement for Authentication (Apostille, Certification, Notarization, or Legalization) of administrative documents such as certificates, power of attorney (POA), letter of authorization (LOA)

The Certificate of Pharmaceutical product (COPP) in the WHO- format must be authenticated by Ethiopia Embassy in the country of origin. If the CPP comes from country where there is no Ethiopian embassy, the Authority will make direct contact with the responsible body that provides the COPP.

12) Are there any country specific labeling requirements?

Labeling requirements (immediate and outer label)
Only original labels or computer-ready color-printed labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

a) The name of the product– brand and generic/International Non-proprietary Name (INN);
b) Pharmaceutical form and route of administration;
c) Qualitative and quantitative composition of active ingredient(s), preservative(s), and antioxidant (s);
d) The volume of the contents, and/or the number of doses, or quantity in container;
e) Directions to consult the package insert or the carton label for complete directions for use;
f) Handling and storage conditions;
g) License number of the manufacturer;
h) Batch number;
i) Manufacturing date;
j) Expiry date; and,
k) Name and address of manufacturer.

Patient Information Leaflet (PIL) or Package Insert
The general content of the PIL should be prepared in line with the content of the SmPC.

13) Verify if there is a consideration for World Health Organization (WHO) Prequalified or Stringent Regulatory Authority (SRA) approved products

Ethiopia is part of the WHO PQ CRP and Accelerated SRA CRP. An applicant claiming to have a registration certificate issued by an SRA (including WHO PQ), as defined in "Guideline for the Registration of Medicines, 2014" should submit complete dossiers in Module 1 through Module 5. At the time of registration by the Authority, the following information needs to be assessed:

1. Full information in Modules 1 and 2
2. Public assessment report(s) and/or final acceptance letter issued by a national regulatory authority in an ICH region and associated countries (e.g., summary of product characteristics and Certificate of Pharmaceutical Product)
3. In the case of a WHO Prequalified product, the final acceptance letter and a copy of the WHO Public Assessment Report (WHOPAR)
4. A Quality Assurance-certified copy of the Marketing Authorization issued by the relevant SRA

5. If the composition/formulation, strength, specifications, etc., are different from the product for which the WHO-type Product Certificate was issued, arguments and/or data to support the applicability of the Certificate(s), and demonstration of pharmaceutical equivalence and bioequivalence
6. If the primary packaging material of the product is different from that approved by the national regulatory authorities of the ICH regions and associated countries or WHO PQP, then all stability testing data
7. Written commitment letter to notify the Authority that whenever a pending variation, notice of concern, withdrawal, or recall is initiated, the same shall be communicated to the Authority
8. Evidence of a minimum of five (5) years of current and continuous manufacturing experience and a copy of the last Annual Product Report.

14) Confirm procedure for submission of application

To register a product, you must bring an authorization letter from your organization to get a user ID and password on behalf of your organization at FMHACA in order to use the Medicine Registration Information System (MRIS) http://www.mris.fmhaca.gov.et/public/registration.

FMHACA Address:
Africa Avenue, near Wolosefer,
Kirkos sub city, 02/03 kebelle,
02 House number
Tel: +251-115-524120/22,
Fax: +251-115-52411392,
Email: regulatory@fmhaca.gov.et

15) What are the requirements for post-approval changes/variations?

Per "Guidelines for Submission of Post-Approval Variation," once a medicine is registered by the FMHACA for sale in Ethiopia, any changes to the original information submitted with the application or set as conditions for registration must be submitted for approval. Variations to details of a medicine may be made to alter or to improve the medicines, to introduce an additional safeguard due to new scientific knowledge or to meet market demands. The conditions of registration of a medicine are therefore considered dynamic considering that variation to the original registered dossier may become necessary during the lifetime of the medicine.

To facilitate the classification of the various types of variations, the following sections explicitly define the classification of variations:
SECTION I of "Guidelines for Submission of Post-Approval Variation" lists major variations. These are classified by the type of variation as such and the applicable conditions. Whenever the conditions are not kept, the variation may either become major variations or may even make a new application necessary.

SECTION II "Guidelines for Submission of Post-Approval Variation" lists minor variations. The minor variations further classified as minor variation require prior approval and minor variations require notification only.

Additional information can be found in "Guidelines for Submission of Post-Approval Variation Medicine Applications" here.

16) What guidance exists for handling of post-approval variations? If variation guidelines exist, please include them as attachment to this report.

Detailed guidance for handling of post-approval variations can be found in "Guidelines for Submission of Post-Approval Variation Medicine Applications, 2015" above.

Technical questions

1) Is an in-country clinical trial required?

No.

2) **If a manufacturer wants to conduct the clinical in this country, what are the requirements?**

Detailed clinical trial requirements can be found in **"**Clinical Trial Authorization Guideline" here.

3) Is there a specific data package that is required for non-clinical studies?

The data package required for non-clinical studies in Module 4 includes:

4.2.1 Pharmacology
4.2.1.1 Primary Pharmacodynamics
4.2.1.2 Secondary Pharmacodynamics
4.2.1.3 Safety Pharmacology
4.2.1.4 Pharmacodynamic Drug Interactions
4.2.2 Pharmacokinetics
4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4 2.2.5 Excretion
4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
4.2.2.7 Other Pharmacokinetic Studies
4.2.3 Toxicology
4.2.3.1 Single-Dose Toxicity (in order by species, by route)
4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
4.2.3.3 Genotoxicity
4.2.3.3.1 In vitro
4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
4.2.3.4.1 Long-term studies (in order by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.3 Other studies
4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) [If modified study designs are used, the following sub-headings should be modified accordingly.]
4.2.3.5.1 Fertility and early embryonic development
4.2.3.5.2 Embryo-fetal development
4.2.3.5.3 Prenatal and postnatal development, including maternal function
4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
4.2.3.6 Local Tolerance
4.2.3.7 Other Toxicity Studies (if available)
4.2.3.7.1 Antigenicity
4.2.3.7.2 Immunotoxicity
4.2.3.7.3 Mechanistic studies (if not included elsewhere)
4.2.3.7.4 Dependence
4.2.3.7.5 Metabolites
4.2.3.7.6 Impurities
4.2.3.7.7 Other

4) How many batches or lots are required to be submitted?

Results from three batches of at least one pilot scale, demonstrating compliance with the FPP manufacturer's API specifications. This information should be provided in Module 3, section 3.2.S.4.4 Batch analysis.

Stability, pilot, scale-up and, if available, production-scale batches on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing. This information should be provided in Module 3, section 3.2.P.5.4 Batch analysis.

5) Does the National Regulatory Authority require their own GMP inspection or do they accept history of EU/FDA inspections? If so, discuss GMP visits, interval for GMP inspections, e.g. every 5 years or annually? Confirm procedure and cost involved.

Principles of GMP Inspections, per "Pharmaceutical Manufacturer GMP Inspection Directive, 2017" can be found here.

1) Pharmaceutical Manufacturing site shall only be visited or registered, if it has been licensed to manufacture medicines by the licensing Authority of the country of origin and it has continued production and marketing of its products continuously in the country of origin for a period of not less than three years.

2) Both local and foreign manufacturers of pharmaceutical shall only be registered if the Authority is convinced by compliance of the manufacturing site with the current Good Manufacturing Practice in the production of Pharmaceutical and Biological products, unless otherwise justified.
3) All finished pharmaceutical facilities shall be subjected to site GMP Inspection once every Five years, unless otherwise notified.
4) Site GMP Inspection shall be carried out after Dossier Evaluation is completed (New and/or Re).
5) Facilities located in countries with stringent NMRAs and WHO prequalified product shall be subjected to document review, unless otherwise required. However, whenever necessary, onsite inspection may be carried out.
6) Whenever necessary, GMP inspection shall be carried out with mutual recognition with identified and selected Regulatory Authorities. The Authority shall accept GMP Inspection report from these regulatory Authorities with pre-agreed preconditions.
7) In response to the application submitted for the inspection of Pharmaceutical manufacturer production sites a 3-member inspection team shall be assigned.
8) All production lines shall be running a major processing activity during the inspection to enable the team to evaluate their performance.
9) Two days or more shall be allocated for the inspection of each manufacturing site depending on the lines available and only onsite Inspection shall be carried out where payment is effective.
10) GMP inspection shall be carried out using Ethiopian National GMP Guideline and/or the World Health Organization (WHO) GMP Guideline.
11) GMP task force shall be organized and members shall be assigned by the Authority.

Application Procedure, per "GMP Inspection Directive, 2017"

1) Local licensed agent, in cases of foreign facilities and local manufacturing facilities shall submit a written application for inspection to responsible Directorate of the Authority.
2) All correspondence and documents required to be submitted shall be in English, and if the document required is not in English, it should be accompanied by a certified translation.

Service Fee, per "GMP Inspection Directive, 2017"

Any person who seeks regulatory service under this directive may be required to pay applicable service in accordance with Regulation No.370/2015. Additional information can be found in "Pharmaceutical Manufacturer GMP Inspection Directive."

6) What are the stability testing requirements, long-term storage condition (relevant Climatic Zones), testing frequency, storage conditions and the lengths of studies etc. Is there local Guideline for stability testing, please include as an attachment to this report?

Stability testing requirements, long-term storage conditions, testing, frequency, and lengths of studies should be performed according to ICH guidelines. There is not a local guideline for stability testing.

National Regulatory Assessment 3: Vietnam

General questions

1) Confirm the current official guidelines for registration of this type of product and include them as attachment at the time of this report.

Complete translations of the below guidelines can be found in Appendix 8.

a. Pharmaceutical Law No. 34/2005/QH11
b. Decree No. 176/2013/NĐ-CP dated 14/11/2013 penalties on administrative violations
c. Circular No. 44/2014/TT-BYT dated 24/11/2014 on drug registration
d. Circular No. 23/2013/TT-BYT dated 13/8/2013 guiding drug processing activities
e. Circular No. 08/2010/TT-BYT dated 26/4/2010 guiding submission of BA/BE report
f. Circular No. 01/2018/TT-BYT dated 08/3/2016 guiding drug labeling
g. Circular No 09/2010/TT-BYT dated 28/4/2010 on drug quality management
h. Circular No. 03/2012/TT-BYT dated 02/2/2012 guiding drug clinical trial
i. Circular No 05/2010/TT-BYT 01/03/2010 on data protection for drug registration
j. Circular No. 03/2013/TT-BTC dated 08/01/2013 on the fees
k. Circular No. 47/2010/TT-BYT dated on 09/12/2010 on export and import

2) Confirm the classification of the LNG-IUS in a given country.

A specific classification of the LNG-IUS was not found in the available guidelines. However, the following classifications were listed on the available guidelines:

a. New Drugs
b. Vaccines
c. Biological Products
d. Generic Drugs
e. Herbal Drugs

No combination product classification was found. For this reason, it is recommended to register as a New Drug.

3) Confirm the application process flow of the NMRA vs the applicable Medicines Regulatory Harmonization (MRH) Program.

Vietnam NMRA – Drug Administration of Vietnam (DAV)

a. Receiving dossiers and collecting registration fee:
-Office of Administration receives drug registration dossiers, then forwards these to the Drug Registration Division.
b. Classification and preparation of dossiers for appraisal:

-Dossiers are classified by - New drug; Vaccines, biological products; Generic drug and Herbal drug to be referred to relevant groups of experts of appraisal.

c. Appraisal of drug registration dossiers:

-New drugs; vaccines and biological products: Appraisal of Administrative data; Quality Profile; Product information; Profile of Safety and Efficacy - Information relating to rational use of drug.

-Generics, herbal drugs: Appraisal of administrative; Quality Profile; and Product information.

d. Post appraisal dossiers:

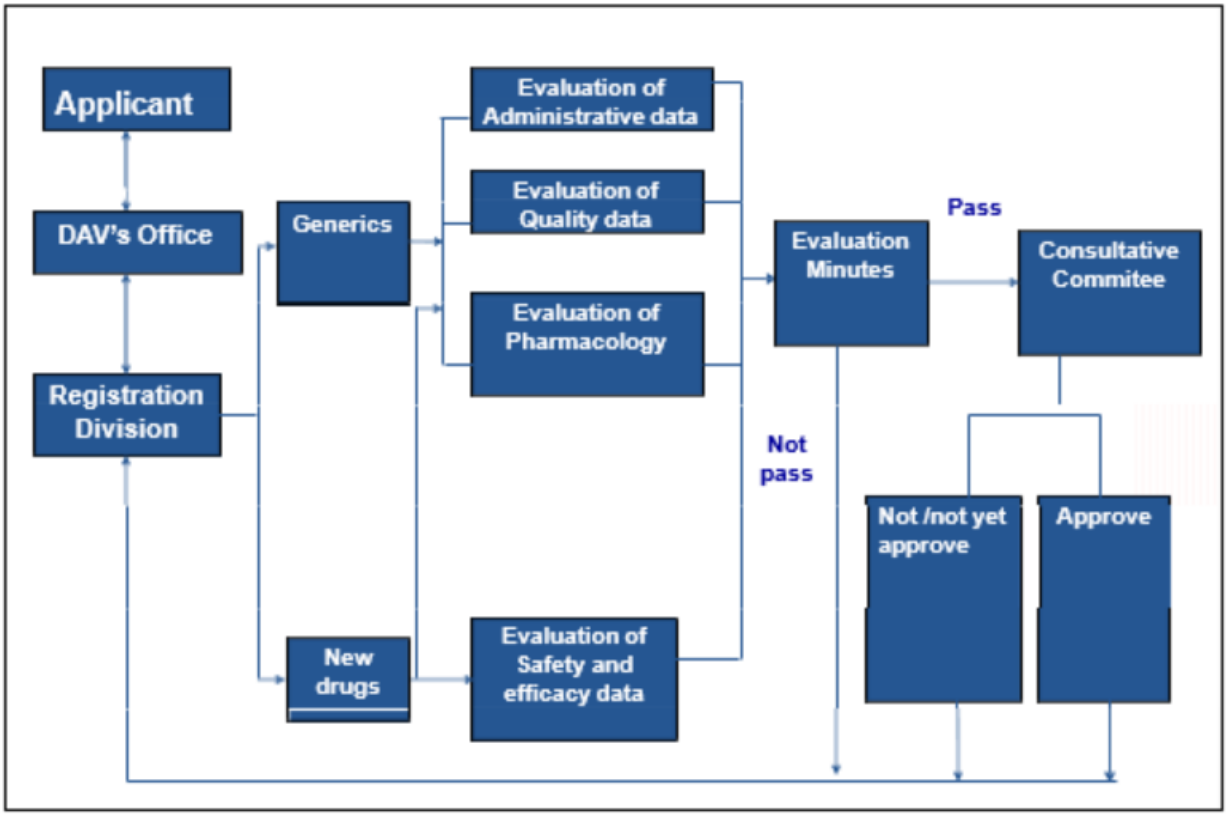
-Focal expert classifies dossiers: Qualified; not yet qualified or not qualified.

-Qualified dossiers collected for meetings of the consultative Committee, not yet or not qualified, inform the applicant.

e. Preparation of contents and dealing with meeting minutes of the consultative Committee, Reporting and note taking of minutes of the Committee's meeting.

f. Preparation of the list and issuance of decision on granting drug registration number.

Figure A1: Drug Registration Process[25]



Expedited registration review (Priority Review) will be given by the MOH for the following situations:

- Drugs meeting needs for ad-hoc treatments belong to the List of Orphan Drugs;
- Drugs meeting needs for treatments in emergencies, disasters, epidemics;
- Local drugs manufactured in new GMP-compliant production lines ≤18 months;

[25] "Drug Registration Process." Source: Drug Administration of Vietnam.

- Vaccines passing WHO's pre-qualification and being considered as eligible for fast-track approval as per the procedure established and published by the DAV.

Vietnam MRH Program – Association of Southeast Asian Nations (ASEAN)

The applicable Medicines Harmonization Program for Vietnam is the ASEAN, which has diverse regulatory requirements for registering drug products. One of the major harmonization achievements is the ASEAN Common Technical Document (ACTD). This is a guideline of the agreed upon common format for the preparation of a well-structured Common Technical Document (CTD) application that can be submitted to ASEAN regulatory authorities for the registration of pharmaceuticals for human use.

Despite regional harmonization efforts, the registration process in Vietnam is mostly country-specific. The ASEAN Pharmaceutical Product Working Group (PPWG) was established by the ASEAN Consultative Committee for Standards and Quality (ACCSQ) with the objective of harmonizing pharmaceutical regulations of ASEAN member countries. However, country-specific requirements persist, with data sharing, mutual acceptance and recognition of current Good Manufacturing Practices (CGMPs), facilitated by ASEAN member countries who become Pharmaceutical Inspection Co-operation Scheme (PIC/S) members.

4) Confirm the required dossier format, e.g. International Conference on Harmonization Common Technical Document (ICH CTD) or country specific format.

ASEAN CTD or ICH CTD (for new chemical drugs, vaccines, biological products).

5) If English is not a national language, what are the translation requirements?

a. Registration dossiers: English or in Vietnamese.
b. Package Insert, Drug Characteristics, Label: Vietnamese.

6) Define the requirements and responsibilities for the Applicant/MAH?

a. Requirements
    1) Local Pharmaceutical Companies (Manufacturers/Importer/Distributors)
    2) Foreign Pharmaceutical Companies:
        a. Foreign Pharmaceutical Companies that have Representative Office in Vietnam;
        b. Foreign Pharmaceutical Companies that have License for conducting pharmaceutical activities in Vietnam granted before January 15, 2015.
b. Responsibilities
    1) Assuring quality, safety, efficacy and consistency of drug marketing with the registration dossier;
    2) Providing sufficiently and accurately all the data, reports and information related to the drug;
    3) Updating information on quality, safety and efficacy of the respective drug;

4) Inform DAV in case the registered drug in Vietnam is recalled in any country within 7 working days;
5) Collaborating with importers, manufacturers to withdraw the drugs failing to meet quality, safety, efficacy regulations;
6) Report on the 15th December every year to DAV the marketing of drug: are manufactured/imported or not.
7) Retaining full dossiers and providing the competent authorities when requested;
8) Cooperating and facilitating the performance of audits, assessments of manufacturing sites;
9) Changing the applicant within 1 month from the date of the applicant stopped operation;
10) Collaborating with manufacturer to carry out specific studies or providing additional information on request of regulatory authority.

7) Confirm if there is a recommended distribution category for prescription medicine? e.g. clinics only, hospital or pharmacy distribution only

Not specified in the evaluated DAV guidelines.

8) What are the sample requirements?

Enough drug product samples to perform three times the release testing.

9) Confirm the estimated application review timelines (if available)

a. First-time registration, renewal: 6 months
b. Extension of MA: 3 months
c. Registration for variations:
   vii. 1 major variation or 2 minor variations or more: 90 days
   viii. 1 minor variation: 60 days
   ix. Variations that need notification only: 20 days

10) What is the current product registration fee according to the statutory instrument? Determine if any other costs are involved.

According to the Circular No. 03/2013/TT-BTC

Name of Fee	Unit	Fee/Drug (1,000 VND)
Pharmaceuticals, vaccines, medicinal products, and herbal medicines		
Registrations that require data confidentiality	Dossier	6,000 (~USD 260)
Registrations that require bioequivalence dossiers and/or clinical dossiers		5,500 (~USD 240)

Other registrations		4,500 (~USD 190)
Major and Minor Variations		1,000 (~USD 45)

11) Confirm requirement for Authentication (Apostille, Certification, Notarization, or Legalization) of administrative documents such as certificates, power of attorney (POA), letter of authorization (LOA)

Only Certificate of Pharmaceutical Product (CPP) and Certificate of Good Manufacturing Practices (GMP) require legalization. However, in recent experience with Levoplant, the NRA requested that the artwork and POA also be legalized by the Vietnamese embassy.

12) Are there any country specific labeling requirements?

Refer to Appendix 8 - Circular No. 01/2018 / TT-BYT

13) Verify if there is a consideration for World Health Organization (WHO) Prequalified or Stringent Regulatory Authority (SRA) approved products

At this time, the DAV does not participate in the World Health Organization Prequalification of Medicines Programme - Collaborative Procedure in the Assessment and Accelerated National Registration of WHO-prequalified Pharmaceutical Products.

14) Confirm procedure for submission of application

The Drug Registration Department receives drug registration dossiers in their office. The name of the product and related information is registered.

The Drug Registration Department processes dossiers in a first-in-first-out sequence. After having received comments from all groups of specialists, a letter is issued informing the applicants of the evaluation results. After receiving this letter, applicants must provide supplementary information (if required). If the drug registration dossiers meet all requirements, a registration number is issued, and a Marketing Authorization Letter is issued.

15) What are the requirements for post-approval changes/variations?

a. A major variation means a variation which directly and greatly affects quality, safety and efficacy of a drug.
   Part I. An administrative dossier and drug information
   Part II. A quality report
   Part IV. A clinical report
b. A minor variation means a variation which slightly affects quality, safety and efficacy of a drug.
   Part I. An administrative dossier and drug information

Part II. A quality report

c. Other variation means a variation other than major variation or minor variation.
Part I. An administrative dossier and drug information
Part II. A quality report
Part III. A pre-clinical report
Part IV. A clinical report

16) What guidance exists for handling of post-approval variations? If variation guidelines exists, please include them as attachment to this report.

Refer to the Appendix 8 Circular 44/2014/TT-BYT.

Technical questions

1) Is an in-country clinical trial required?

According to the Article 89 of the Law on Pharmacy 105/2016/QH13 of Vietnam:

Pharmaceutical products which are subject to full clinical trials:

a. Pharmaceuticals that contain a new active ingredient or products with new combination of a marketed ingredient.
b. Newly developed biologics or biologics with a new combination of a marketed ingredient.
c. Pharmaceuticals, biologics which have been legally marketed but for a period of less than 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory).
d. Pharmaceuticals, biologics for which a clinical trial has been conducted before the effective date of this Circular but which has not met the requirements of Ministry of Health's good practice
for clinical trials or those of international guidelines on good clinical practice for trials on medicines recognized by Ministry
of Health.

Pharmaceutical products which are exempt from clinical trials:

a. Pharmaceutical drugs with non-proprietary name (Generic drugs).
b. Foreign drugs for which a registration number for marketing in Vietnam has not been granted but which have been legally marketed for at least 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority, for the same route of administration, formulation and indications with those intended for use in Vietnam.
c. Foreign drugs for which a registration number for marketing in Vietnam has been granted, but have undergone modifications or supplementations in relation to indications, route of administration, dosage forms identical with those of the same drugs which have been legally

marketed in the country of origin for at least 5 years (or a reference country if provided for by international treaties to which Vietnam is a signatory).

However, according to feedback received from local partners in Vietnam, the Drug Administration Department of Vietnam (DAV) evaluates this requirement on a case by case basis. A consultation with the DAV to confirm this requirement prior initiating the registration activities is recommended.

2) Is there a specific data package that is required for Clinical Data non-clinical studies?

Refer to Appendix 8 Circular No. 03/2012/TT-BYT

3) How many batches or lots are required to be submitted?

Batch selection requirements are established according to the ASEAN Guideline on Stability Study of Drug Product.

At the time of submission, stability data should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

For New Chemical Entity (NCE), stability data should be provided on at least three primary batches of the drug products.

For Generics and Variations, the following will apply: For conventional dosage forms (e.g. immediate release solid dosage forms, solutions) and when the drug substances are known to be stable, stability data on at least two pilot scale batches are acceptable. For critical dosage forms (e.g., prolonged release forms) or when the drug substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be at least of a pilot scale; the third batch may be smaller, if justified.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specification as that intended for marketing.

Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

4) Does the National Regulatory Authority require their own GMP inspection or do they accept history of EU/FDA inspections? If so, discuss GMP visits, interval for GMP inspections, e.g. every 5 years or annually? Confirm procedure and cost involved.

The foreign drug manufacturer must satisfy at least "Good Manufacturing Practices" (GMP) requirements as recommended by the World Health Organization (GMP-WHO). In case the GMP certificate or the Certificate of pharmaceutical products (CPP) does not specify that the manufacturer satisfies GMP-WHO requirements, the drug establishment shall provide evidence that it satisfies the GMP requirements which are equivalent to GMP-WHO requirements. With respect to IVD products, the drug manufacturer must satisfy GMP requirements or ISO standards or obtain other equivalent certificates. In case there is some doubt about the manufacturing conditions or quality of the drug, the Drug administration of Vietnam or the Department of Medical Equipment and Health Works (regarding IVD products) shall carry out the inspection at the manufacturer's facility before or after the drug registration number is granted.

5) What are the stability testing requirements, long-term storage condition (relevant Climatic Zones), testing frequency, storage conditions and the lengths of studies etc. Is there local Guideline for stability testing, please include as an attachment to this report?

Stability requirements are established according to the ASEAN Guideline on Stability Study of Drug Product.

The stability testing should be biased towards more stressful rather than less stressful conditions so as to provide a margin of error in favor of the patients and to increase the likelihood of identifying substances or formulations that pose particular stability problems. The objective of a stability study is to determine the shelf-life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.

The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the specifications of the drug product packed in its specified packaging material and stored at the established storage condition within the determined time period.

The general conditions for long term stability testing are the Zone IVb conditions (30 °C / 75% RH).

Appendix 2: Full WHO Prequalification: Summary of Key Steps and Requirements

The following steps are required for a manufacturer to pursue full WHO Prequalification:

1. Expression of Interest (EOI) submitted by applicant to participate in WHO Prequalification of Medicines Programme (WHO PQP)
1. Receipt and processing of EOI by WHO PQP
2. Parallel assessment of clinical and quality components of the dossier by WHO. Results are communicated to applicant if corrective action is required. Applicants are expected to submit responses to comments and any additional information that may be requested as soon as possible and within a month, inform WHO of the estimated time frame to address and respond to all queries.
3. Inspections in three parallel tracks: finished product manufacturing site, API manufacturing site, and the clinical research site. Results from the inspections are communicated to the manufacturer or Clinical Research Organization (CRO). If corrective actions are required WHO will postpone its final decision.

WHO screens the information submitted for evaluation for Prequalification, using a screening checklist. This is an in-house list of dossier characteristics that need to be confirmed to be acceptable before a dossier is assigned a WHO reference number and accepted for full assessment. The checklist provides insight into what aspects are considered to be the key elements of an assessment of a FPP. The screening may lead to a request or requests for additional information.

WHO provides technical support to applicants, and applicants may request a meeting with the WHO experts involved in the assessment a dossier to clarify issues identified by the WHO experts. WHO can provide technical assistance to applicants regarding appropriate product information to be submitted as well as production and control requirements.

In addition, there is a model dossier which is an example medicines dossier. The product chosen for the model dossier is a prequalified solid oral product, levonorgestrel 0.75 mg tablets. However, the model dossier is intended to have general applicability across therapeutic areas and can be broadly useful, including for example to new drugs.

Once both product dossier and inspected manufacturing and clinical sites are found to be acceptable then a final decision on prequalification is made.

Appendix 3: Abbreviated WHO Prequalification Pathway for SRA-Approved Generic or Innovator Products – Summary of Key Steps and Requirements

The following steps are required for a manufacturer to pursue Abbreviated WHO Prequalification for either a generic or innovator product:

1. A cover letter submitted by applicant which includes a statement confirming that for WHO Prequalification, the FPP will (at the time of submission and after Prequalification), in all respects be the same as the product registered with the reference SRA. This includes but is not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information. The cover letter should also include a statement indicating that the product is actually on the market of the reference SRA's country or region.
2. A copy of the marketing authorization, or the equivalent thereof, issued by the reference SRA to demonstrate that the product is registered or licensed in accordance with the reference SRA requirements.
3. A copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
4. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.
5. A list of the SRA-approved manufacturer(s) of the FPP, including manufacturers of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s) (and unit if applicable).
6. A list of the SRA-approved manufacturer(s) of the active pharmaceutical ingredient(s) (API(s)) used in the manufacture of the FPP, with the physical address of the manufacturing site(s) (and unit if applicable).
7. If available, a public assessment report, issued by the reference SRA. Assessment report(s) issued by the reference SRA that are not publicly available may be requested.
8. A tabular listing of the batches manufactured for the market of the reference SRA's region or country since approval or during the past five years, whichever is shorter. The table should include at least the batch number, batch size (number of units), date of manufacture and pack type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.
9. A sample(s) of the product in market packaging(s). This should be provided with the submission to enable visual inspection thereof. Attach the respective certificate of analysis.
10. A copy of the currently approved FPP specifications (release and shelf-life), dated and signed or certified by authorized personnel, with the analytical test procedures.
11. The quality information summary (QIS-SRA). The QIS-SRA template, available on the WHO Prequalification Programme website (http://apps.who.int/prequal/), should be fully completed and submitted with the application. The QIS-SRA provides a condensed summary of key information on the FPP as approved by the reference SRA at the time of application for prequalification of the FPP.

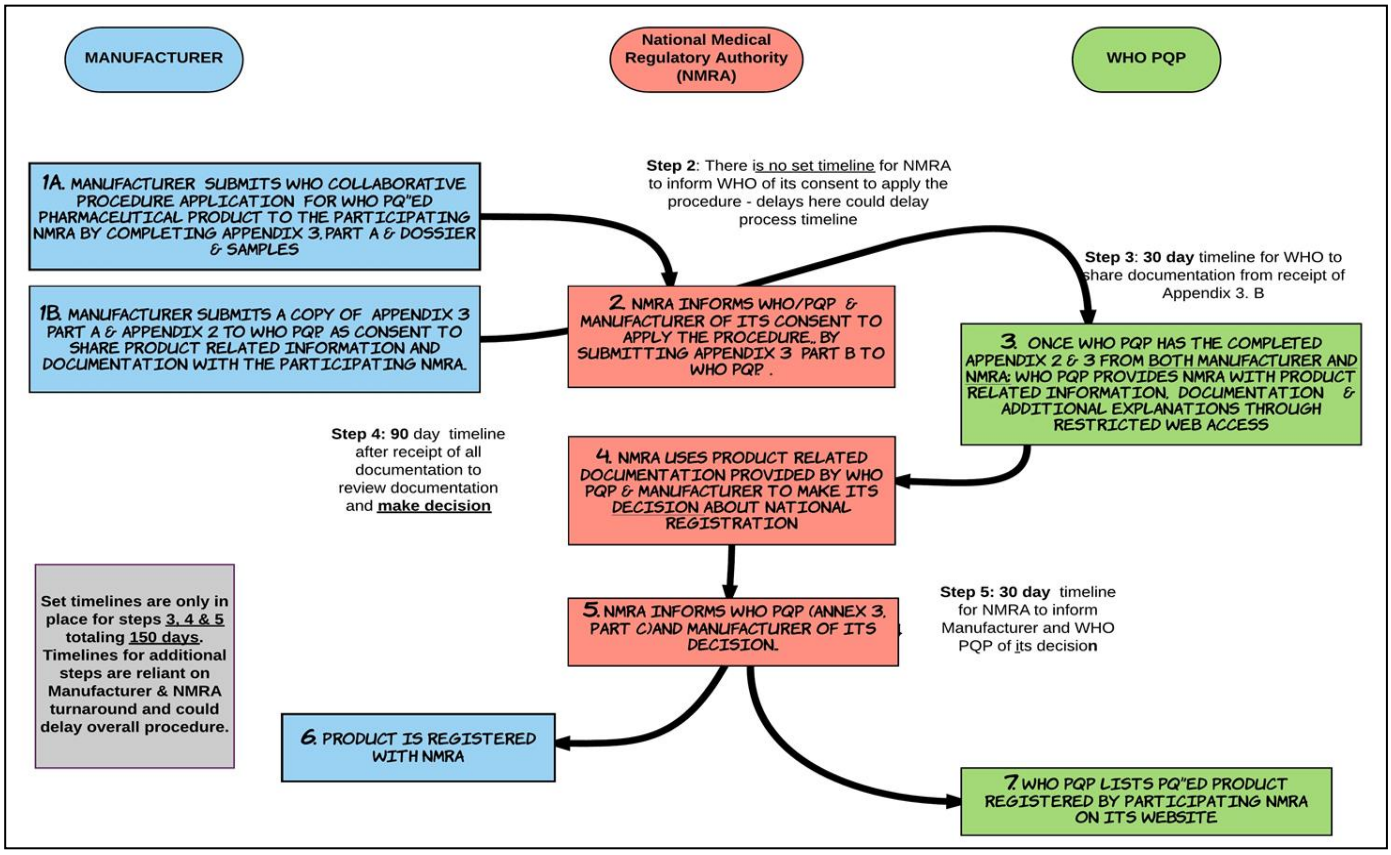
In addition, the preferred storage condition for WHO-Prequalified products is "do not store above 30 °C," based on demonstrated stability at long-term storage conditions IVB. If this storage condition is not

indicated on the SmPC, PIL and labels of the product, applicants are encouraged to apply for a variation in this respect with the relevant SRA. This could also be done after prequalification of the product.

WHO would normally not inspect the manufacturing site(s) of an SRA-approved product; however, there may be circumstances necessitating an inspection to be conducted in collaboration with the reference SRA, upon application or after Prequalification of the product.

Appendix 4: WHO Collaborative Procedure for a Fully WHO Prequalified Product

The steps required for a manufacturer to use the WHO Collaborative Procedure if they have full WHO Prequalification are illustrated in the following schematic illustration:[26]



[26] Illustration created by T. Brett, 2018.

Appendix 5: Accelerated Collaborative Procedure for SRA Approved Products

Information on this procedure has been summarized from the WHO website on WHO Prequalification - https://extranet.who.int/prequal/. **The SRAs currently participating are EMA and UK MHRA.**

Pharmaceutical companies may participate in the pilot if they:

- Hold a marketing authorization issued by an SRA for the finished product intended for submission
- Agree with WHO on:
    - selection of the finished product for which the procedure is to be organized
    - the SRA that will be invited to share its full assessment and inspection reports for the product
    - participating NMRAs to which they intend to apply for registration and proposed date(s) of submission(s) in the relevant countries,
- Agree with the relevant SRA that the **full updated assessment report** and **inspection report** may be shared with the NMRAs to which they intend to apply for registration,
- Agree with the conditions of the procedure and to submit data to NMRAs as defined by the procedure.

The countries of NMRAs that are currently participating in the procedure are:

Botswana, Burkina Faso, Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Georgia, Ghana, Kenya, Malawi, Mali, Mozambique, Namibia, Nigeria, Senegal, Sierra Leone, Tanzania, Uganda, Zambia, Zimbabwe

Additional NMRAs may be invited to participate by WHO if applicants express interest in registering their FPPs in countries the NMRAs of which are not yet participating in the procedure.

The steps for the applicant include the following:

The interested holder (applicant) of the SRA marketing authorization:

1. Agrees with WHO by submitting Annex 6 below which both parties sign. This indicates that the procedure will be applied to the specific product and that WHO will have access to the data shared with NMRAs (Annex 6):

Annex6-WHO-Agreement (1).doc

2. Grants the SRA permission to share information concerning the product with the relevant NMRAs and WHO (Annex 3A):

Annex 3A-Data sharing consent to S

3. Requests SRA permission to share the SRA's assessment and inspection reports with NMRAs and WHO (Annex 3B):

Annex3B-Request-SRA_DataSharing (7).

4. Submits an application for registration of the product, with the same set of technical data they submitted to the SRA electronically and/or in hard copy, to participating NMRAs in a synchronized way, in line with the procedure and respecting specific national requirements (Annexes 4, 5 and 8):

Annex4-Documentation-SRA_Collaborat

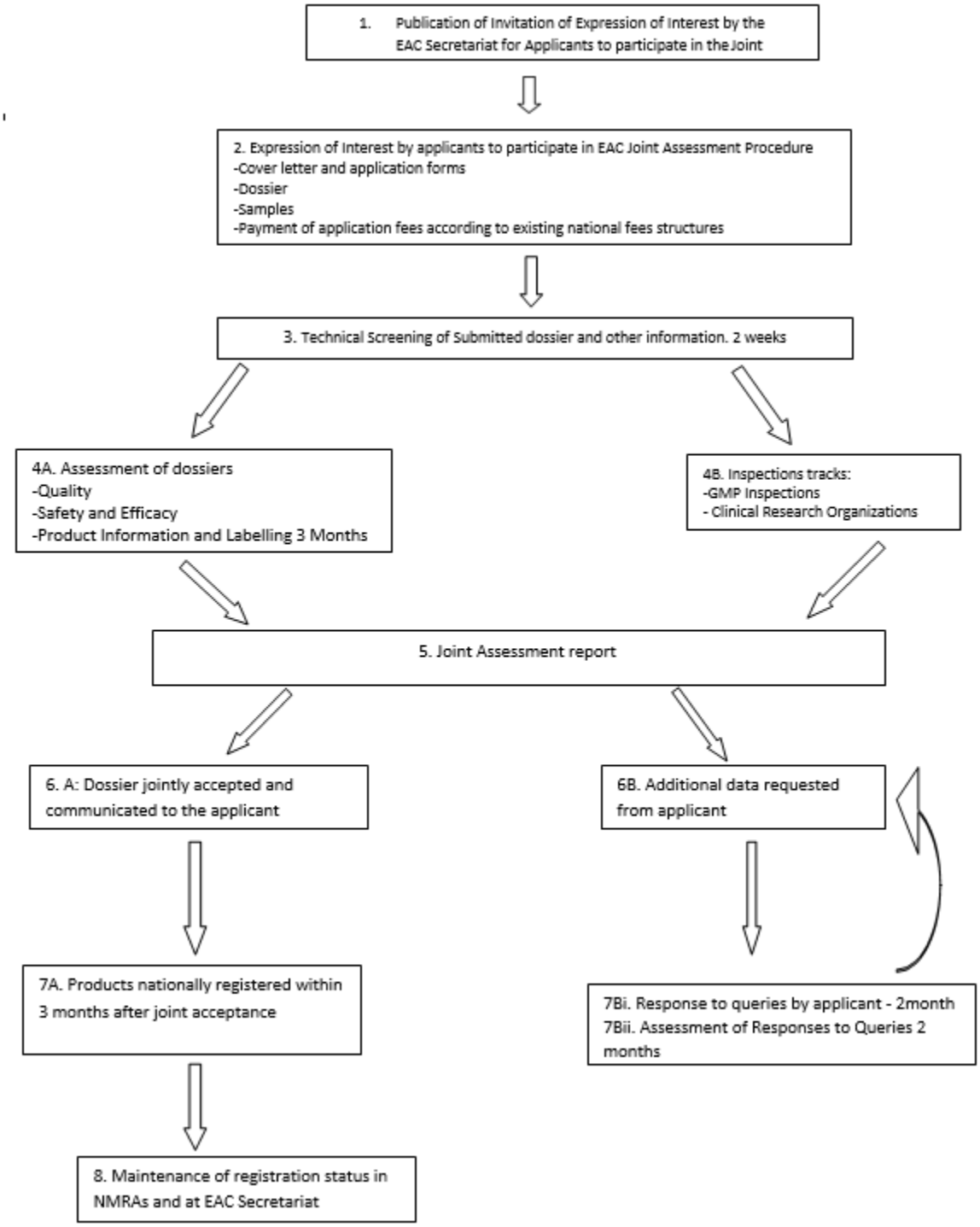
Annex5-CompanyDeclaration (1).docx

Annex8-ConceptNote_0.docx

According to WHO guidance, the time taken by each NMRA for data analysis, review, preparation of questions, and comments should not exceed 60 days. If required, WHO will assist an NMRA by appointing a rapporteur to prepare the draft assessment report, to be based on the original SRA reports, and including any questions to be forwarded to the applicant. The applicant should be prepared to respond quickly to any questions raised and provide any additional information requested. Within the following 30 days, the NMRAs should adopt its regulatory decision, inform the applicant of the outcome and notify WHO.

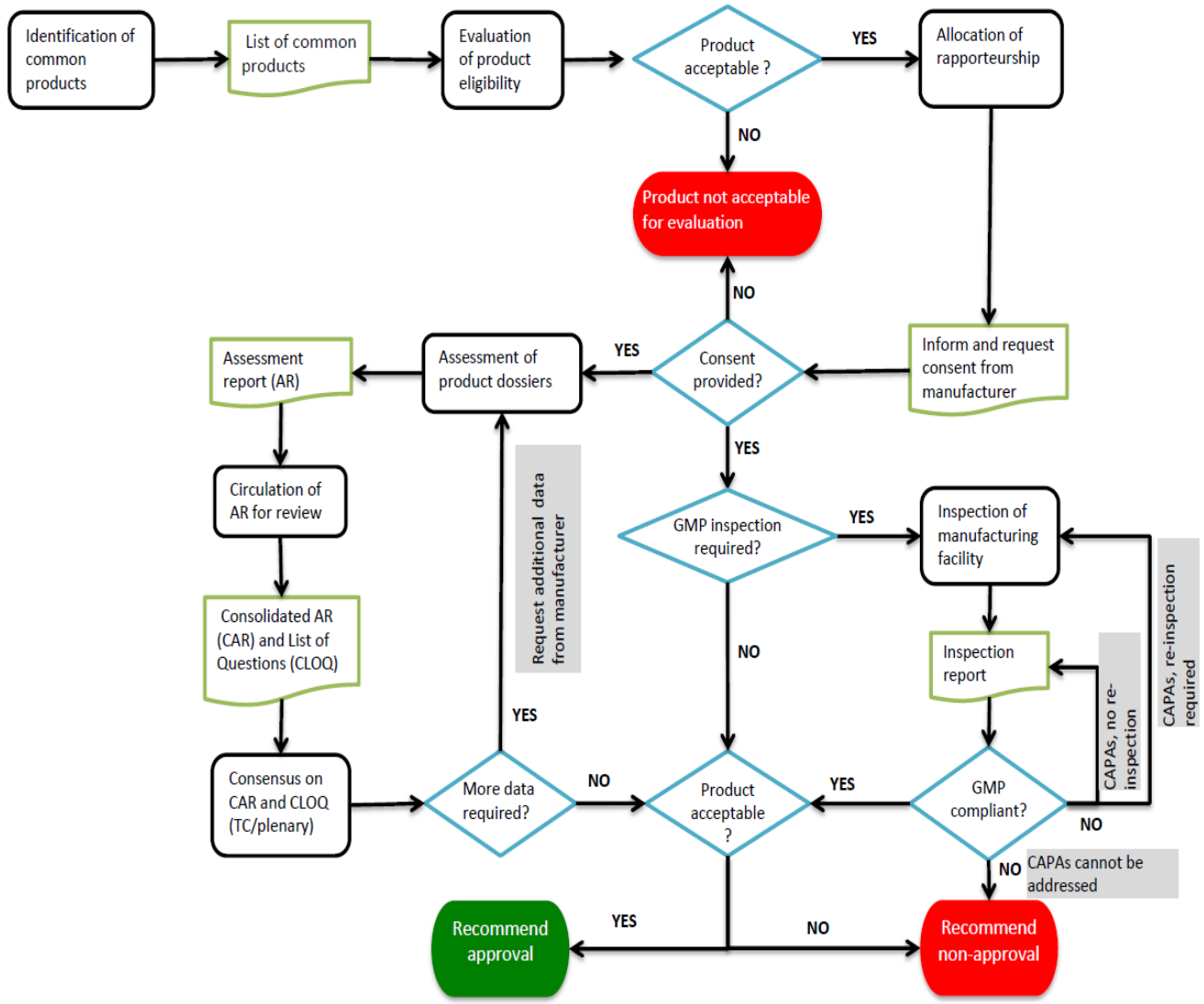
Further information can also be found in appendix 11 of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (available here: http://apps.who.int/iris/handle/10665/272452).

Appendix 6: EAC Procedure for Marketing Authorization[27]



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

Appendix 7: ZAZIBONA Procedure for Marketing Authorization[28]



[28] Source: S. M Selelo, SADC Collaborative Medicines Registration Initiative, Presentation at the 17th International Conference of Drug Regulatory Authorities, 27 November 2016

Appendix 8: Translation of Vietnamese Regulatory Guidelines

1. Circular No. 01/2018/TT-BYT: Regulation on Labeling of Medicines, Medicinal Materials and Directions for Use of Drugs

01_2018_TT-BYT Labeling guideline.p

2. Circular No. 03/2012/TT-BYT: Guidelines for Clinical Trials on Drugs

03_2012_TT-BYT Clinical trials.pdf

3. Circular No. 03/2013/TT-BTC: Fees

03_2013_TT_BTC Fees.pdf

4. Circular No. 05/2010/TT-BYT: Guiding the Keeping of Confidentiality of Trial Data in Medicine Registration

05_2010_TT_BYT Data protection on (

5. Circular No. 08/2010/TT-BYT: Guiding Report of Bioavailability/Bioequivalence Study Data When Registering Drugs

08_2010_TT_BYT BA and BE studies.pdf

6. Circular No. 09/2010/TT-BYT: Guiding the Management of Medicine Quality

09_2010_TT_BYT Management of dru

7. Circular No. 23/2013/TT-BYT: Guidance on Drug Processing Activities

23_2013_TT_BYT Drug processing act

8. Circular No. 44/2014/TT-BYT: Registration of Drugs

44_2014_TT-BYT
Registration of drug

9. Circular No. 47/2010/TT-BYT: Guiding the Export, Import of Medicines and Packaging in Direct Contact with Medicines

47_2010_TT_BYT
Export and import.p

10. Circular No. 176/2013/ND-CP: Penalties for Administrative Violations Against Medical Laws

176_2013_ND-CP
Penalties for admini

11. Pharmaceutical Law No. 34/2005/QH11

Pharmaceutical Law
No. 34 2005 QH11.p

Appendix 9: Marketing Authorisation for Global Health Procedure through Swissmedic

In 2014, a Memorandum of Understanding (MoU) was signed between the Bill & Melinda Gates Foundation and the Swiss Federal Department of Foreign Affairs and the Federal Department of Home Affairs. This MoU provides the basis for the involvement of **Swissmedic** – the Swiss Agency for Therapeutic Products which is the Swiss surveillance authority for medicines and medical devices –to help increase access to high-quality, essential medicines for populations living in low-income countries. The aim is to increase the efficiency of the regulatory review and registration process and to strengthen regulatory authorities.

A critical component of this partnership is the Marketing Authorisation for Global Health Procedure (MAGHP) which builds on the existing authorisation process at Swissmedic. The marketing authorisation can be requested for Switzerland or as a so-called **export registration**, which allows the product to be marketed only outside of Switzerland. However, the requirements in terms of the necessary data and documentation, as well as the review process, are the same for both types of marketing authorisations. Swissmedic acts as a Stringent Regulatory Authority (SRA) in this process.

The key benefit of this process is that, following approval of a product through the MAGHP, an applicant may then seek **WHO Prequalification and/or approval by NMRAs on an accelerated timeline** (see below for details). The initial focus of the MAGHP been on approvals of NMRAs located in the of the East African Community; however, this is now being extended to other NMRAs in low-resource settings.

Key requirements:

For all applications, including those for export only, a Swiss marketing authorisation holder is required. However, an applicant does not necessarily need to be based in Switzerland, but can work through a representative, e.g. a regulatory office. Fees for the application have to be paid according to the Ordinance on the Fees levied by Swissmedic and national Fees regulations of the NMRAs concerned. The application must include the comprehensive and complete documentation for quality, preclinical and clinical aspects in line with articles 3, 4 and 5 of the Medicinal Products Authorisation Ordinance. The requirements are further detailed for the specific type of application; see here for more information: https://www.swissmedic.ch

The documentation for this procedure shall be submitted in English. Also, assessment reports and Lists of Questions (LoQ) and correspondence will be written in English.

The Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) have to be submitted in English and the correspondence language of the applicant (German or French). Swissmedic will review and correct the SmPC, PIL and the packaging in the correspondence language (German or French). However, the English version of SmPC corrections by Swissmedic will also be made available to the NMRAs, the WHO and the applicant. The applicant must commit to provide WHO PQ-conforming data (e.g., stability data 30° / 75% RH, 6 months real time data).

Application process:

A written request for an MAGHP procedure shall be sent to Swissmedic up to six months prior to planned submission but not later than three months, and must include the following details:

- Product name / International Non-proprietary Name (INN)
- Anatomical Therapeutic Chemical classification (ATC) / Therapeutic Index (IT group)
- Indication(s) and dosage recommendation (i.e, SmPC in English)
- List of preclinical and clinical trials, in particular with essential information about the pivotal trial(s)
- Completed form: "Status of marketing authorisations abroad"
- Planned submission date of the application and – in the case of submission in eCTD-format - date for submitting the eCTD test sequence
- Proposed date for a pre-submission meeting or justification why such a meeting is not necessary
- List of preferred EAC markets for which a marketing authorisation is intended (active participation of NMRAs possible).
- List of preferred markets outside the EAC
- Confirmation that fees will be paid according to national fees regulations of the NMRA concerned and / or the WHO PQP Guidelines (if a PQ listing is intended)
- Permission to exchange confidential information, including the submitted application dossier, Swissmedic evaluation reports, correspondence with NMRAs concerned, experts and WHO PQP, during the whole process on an electronic platform

Timelines & information sharing:

Swissmedic commits to a timeline of 330 days to come to a decision. From day 0 to day 330, Swissmedic is the leading party for the evaluation, timelines, and decisions. Communication until day 330 (decision) will be between the applicant and Swissmedic.

Communication in the affirmation phase (post-Swissmedic decision) will be between the NMRAs concerned and the applicant directly. Swissmedic will facilitate the contact between the applicant and the NMRAs concerned.

Information regarding the application, including evaluation reports, will be shared on an electronic platform with Swissmedic reviewers and the assigned NMRA and, where applicable, WHO experts involved in the evaluation of the specific application. Confidentiality and the avoidance of any conflict of interest of participating experts will be assured. The affirmation phase to require market authorisation in the NMRAs concerned/WHO PQP is expected to last 90 days at the end of the process. A fast-track procedure is not feasible due to the increased coordination with NMRAs and WHO PQP in the pilot phase. Therefore, a decision by the participating NMRA and WHO PQP should be available within a total of 420 days.