

INTRODUCING NEW CONTRACEPTIVE OPTIONS:



Product Registration Basics for Global Health Program Managers



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Acronyms

AMRH	African Medicines Regulatory Harmonisation
ASEAN	Association of Southeast Asian Nations
CARICOM	Caribbean Community
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DCVR	Delivering Contraceptive Vaginal Rings
EAC	East African Community
ECTD	Electronic Common Technical Document
EECO	Expanding Effective Contraceptive Options
FP	Family Planning
FP2020	Family Planning 2020
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAH	Marketing Authorization Holder
NAFDAC	National Agency for Food and Drug Administration and Control
PC	Population Council
PQ	Prequalification
PVR	Progesterone Vaginal Ring
SFH	Society for Family Health
SRA	Stringent Regulatory Authority
USAID	United States Agency for International Development
WCG	WCG Cares
WHO	World Health Organization

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Introduction

New contraceptive products have the potential to help women and girls plan the families and lives they desire. Among the 214 million women in developing countries with an unmet need for family planning (FP),ⁱ many cite method-related reasons for not using contraception. Some women want methods with different side effects, or no side effects at all. Others need discreet methods, or methods they can use while breastfeeding.ⁱⁱ Ensuring that women have access to a broad range of methods is one critical component of meeting their contraceptive needs. In almost all cases, **registration of contraceptive products is a prerequisite for access.**¹

Regulatory requirements and processes are complex, evolving, and vary by country. As a result, many global health program managers lack the regulatory expertise needed to plan for registration as a part of new contraceptive product introductions. The goal of this guide is to demystify regulatory affairs for non-experts. Readers will learn the basics of product registration and how this information can support good decision-making by program managers in consultation with regulatory experts.

To support sound regulatory strategies in places where unmet need for contraception is highest, this guide focuses specifically on Family Planning 2020 (FP2020) countries.

EXPANDING EFFECTIVE CONTRACEPTIVE OPTIONS (EECO)

Expanding Effective Contraceptive Options (EECO) is a USAID-funded project that supports the introduction of new contraceptive options and dual protection methods in FP2020 countries where they are most needed. Each product in the EECO portfolio is designed to address one or more method-related reasons for non-use of contraception. Led by WCG Cares (WCG), EECO works with market players along the supply chain from product manufacturers to providers and clients, as well as the stakeholders who influence the policy environment.

The five stages in EECO's product introduction model are outlined in Figure 1.

This guide focuses on the first stage in EECO's product introduction model. ■

Figure 1. **EECO PRODUCT INTRODUCTION MODEL**



¹ Under certain circumstances, some national regulatory authorities authorize special permits for importation of unregistered products. These circumstances are discussed in the Special Import Permits section of this guide.





Basics

WHY REGISTRATION MATTERS

Regulatory authorities protect public health by ensuring the safety, efficacy, and quality of drugs, medical devices, and other regulated products. Through the process of registration, these authorities review key information about the product, including clinical trial data, to determine if it should be allowed on the market. Once registration is granted, regulatory authorities continue to monitor the product throughout its lifecycle in the market.

WHO REGULATES

Regulatory authorities, like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, are responsible for reviewing and granting or rejecting registration applications in the countries where they have the legal authority to do so. Outside of the U.S., these authorities are commonly a branch of the Ministry of Health. Yet in some cases, the regulatory authority is an entirely separate entity.



ROLE OF THE WORLD HEALTH ORGANIZATION (WHO) IN REGULATORY AFFAIRS

The WHO supports access to essential medicines in many ways, including by making it easier for manufacturers to apply for registration in multiple countries and easier for national regulatory authorities to review those registration applications. In many FP2020 countries, shortages of human, technical, and financial resources weaken and slow local regulatory systems, preventing people from accessing high quality contraceptives and other essential medicines when they need them. Manufacturers often lack interest in pursuing registration in these markets because it can be time-consuming to comply with regulatory requirements that vary at the country level.

The WHO enables more efficient registration of products in several ways:

- The WHO sets norms and standards, develops guidelines, and advises Member States on issues related to quality assurance of medicines for national and international markets.
- The WHO assists countries in building national regulatory capacity through networking, training and information sharing.
- The WHO offers “prequalification” (PQ) of health products to ensure that they meet global standards. WHO experts review information about the product, test it, and visit the manufacturing site. The United Nations Population Fund, USAID, and other procurement agencies make purchasing decisions based in part on whether a product has WHO PQ.
- The WHO also offers “collaborative procedures” to facilitate the accelerated national registration of products that have WHO PQ or approval by a Stringent Regulatory Authority (SRA). ■

² The list of countries participating in the collaborative procedure for accelerated registration can be found on the WHO website here: <https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>



WHO PQ of medicines was first established in 2001 in response to the HIV/AIDS pandemic. Its aim was to guide United Nations agencies and other international organizations with respect to the quality of antiretroviral medicines for supply to low-income countries.

STRINGENT REGULATORY AUTHORITIES

SRAs provide expertise and resources for the proper evaluation of regulated products. The WHO listed these regulatory authorities as SRAsⁱⁱⁱ:

- Australia
- European Free Trade Association
- European Union Member States
- Health Canada
- Iceland
- Japan
- Liechtenstein
- Norway
- United States

WHO COLLABORATIVE PROCEDURES

The WHO has established collaborative procedures to facilitate faster national registration of pharmaceutical products that have:

- WHO PQ, or
- approval from an SRA.

In general, products that receive approval through the WHO Collaborative Procedure can expect more streamlined registration processes (e.g., fewer requirements, shorter timelines) at the national level for participating countries.²



Pathways to Registration



REGIONAL HARMONIZATION INITIATIVES

Variation in regulatory requirements and processes across FP2020 countries can discourage manufacturers from pursuing registration in different types of markets where their products may be most needed. Modifying registration applications for country-by-country submission is resource-intensive, and can be difficult for manufacturers with limited capacity. In Africa, Asia, and the Americas, regional regulatory initiatives encourage harmonization of regulatory requirements across countries. While these initiatives are still evolving and vary in their level of maturity in different regions, they offer important benefits that may increase as they become more established. In the future, if mutual recognition is achieved, registration by a regional platform

may take the place of or accelerate national-level registration, providing benefits such as:

- reduced market entry barriers (e.g., the cost and administrative burden of registration) to manufacturers, which can lead to lower prices of products, encourage manufacturers to register their products in more countries, and contribute to a more sustainable total market for health products;
- reduced burden on national regulatory authorities because they can have confidence in common standards for scientific evaluation and inspection; and,
- faster access to health products for those who need them.

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 replace the application requirement at the national level. Currently, standardized guidelines and expedited review are offered in three regions:

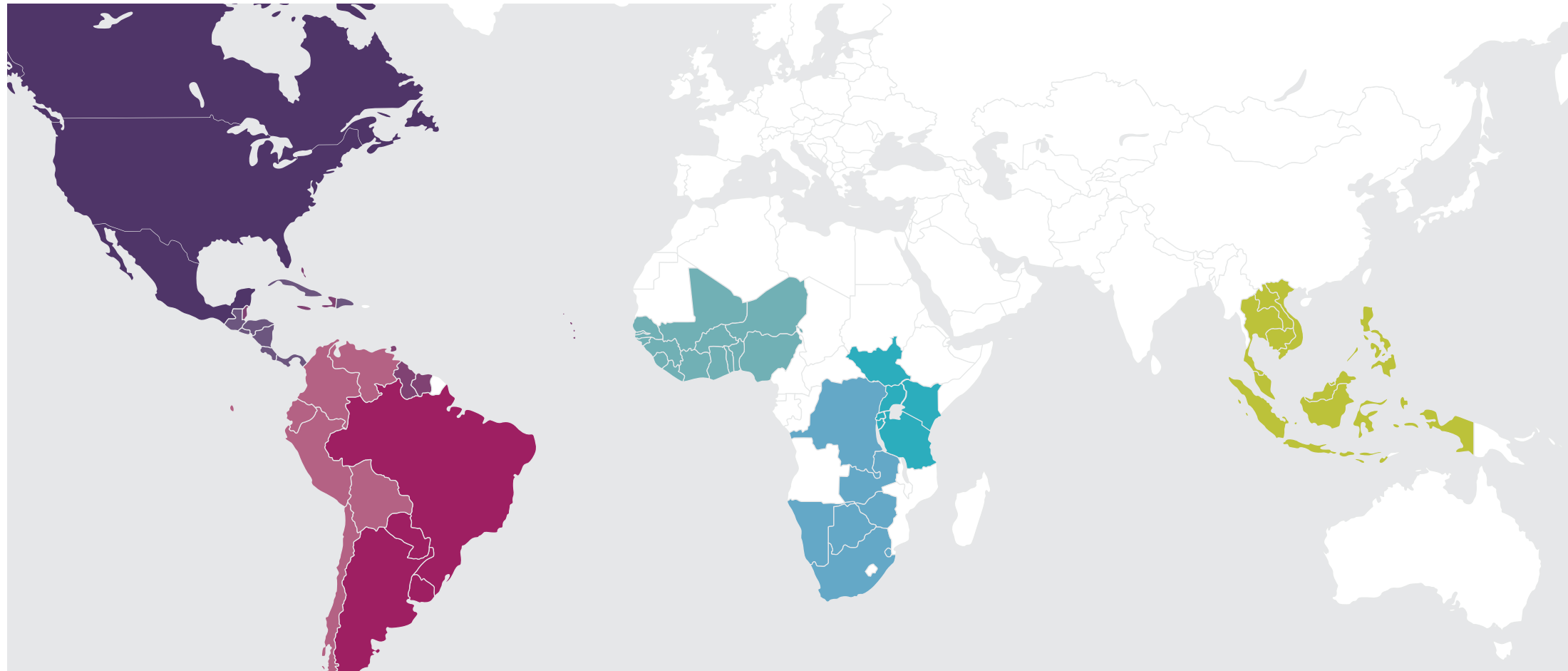
- The East African Community (EAC)
- The ZAZIBONA Initiative
- The Caribbean Community (CARICOM)

The three regions listed above offer a regional harmonization initiative assessment report. As such, if an applicant (e.g., a manufacturer) submits a product registration application to one of these three regional harmonization initiatives, they will receive an assessment report that indicates whether or not the product is recommended for registration. When an applicant secures an assessment report with

a positive recommendation prior to pursuing national registration, national regulatory authorities can review the dossier more quickly and easily, with some variation by country. A pilot study showed that drug approval times were reduced by 40% to 60% in a set of sub-Saharan African countries using a collaborative registration procedure as part of the African Medicines Regulatory Harmonisation (AMRH) initiative.^{iv}

With the goal of facilitating access to essential medicines, donor funding supports several of these initiatives. For example, the World Bank, the Bill & Melinda Gates Foundation, and the United Kingdom's Department for International Development have contributed to regional harmonization efforts through the AMRH program.

Figure 2. **COUNTRIES INVOLVED IN REGIONAL HARMONIZATION INITIATIVES**



PAN AMERICAN NETWORK FOR DRUG REGULATORY HARMONIZATION:

North America:

- United States
- Canada
- Mexico

Central America + Cuba + Dominican Republic:

- Costa Rica
- El Salvador
- Guatemala
- Honduras
- Nicaragua
- Panamá
- Cuba
- 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
- Venezuela

Southern Cone:

- Argentina
- Brazil
- Paraguay
- Uruguay

AFRICAN MEDICINES REGULATORY HARMONISATION (AMRH) INITIATIVE:

East African Community (EAC):

- Burundi
- Kenya
- Rwanda
- South Sudan
- Tanzania
- Uganda

ZAZIBONA:

- Zambia
- Zimbabwe
- Botswana
- Namibia
- South Africa
- Swaziland
- Democratic Republic of Congo

ECOWAS/UEMOA:

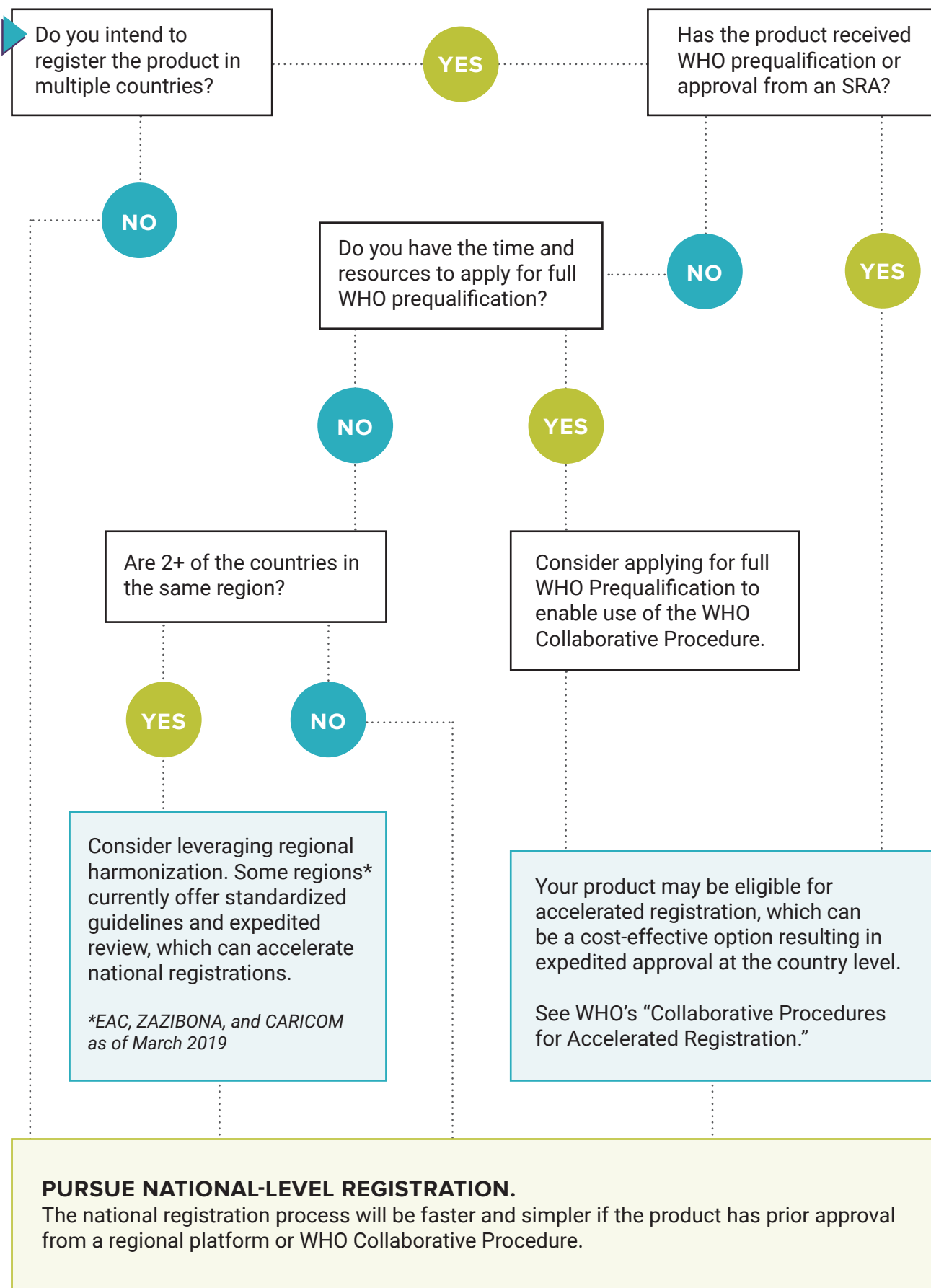
- Benin
- Burkina Faso
- Cabo Verde
- Côte d'Ivoire
- The Gambia
- Ghana
- Guinea
- Guinea Bissau
- Liberia
- Mali
- Niger
- Nigeria
- Senegal
- Sierra Leone
- Togo

ASSOCIATION OF SOUTHEAST ASIAN NATIONS (ASEAN)

Harmonization Initiative:

- Brunei Darussalam
- Cambodia
- Indonesia
- Lao PDR
- Malaysia
- Myanmar
- Philippines
- Singapore
- Thailand
- Vietnam

Figure 3. **REGULATORY PATHWAY DECISION TREE**



Manufacturers and others wishing to register products may have several potential regulatory pathways open to them, including: (1) working toward WHO PQ or leveraging one of the WHO collaborative procedures; (2) making use of one of the regional harmonization mechanisms; or (3) applying for country-level registration directly. Program managers may wish to work with regulatory experts to determine which registration pathway is most advantageous to pursue and for assistance with navigating the requirements of that strategy. Figure 3 (on the following page) outlines some of the important considerations that can guide this decision.

SPECIAL IMPORT PERMITS

In certain circumstances, a special import permit can be requested to import a product for short-term use, such as for research (e.g., a pilot study for a new drug) or medical

emergencies (e.g., an Ebola outbreak). Import permit application requirements are country-specific but typically require supporting documents such as:

- a Certificate of Pharmaceutical Product (CPP) to help the importing country assess the quality of the pharmaceutical product,
- a Good Manufacturing Practice (GMP) Certificate to attest that the product manufacturer is compliant with established guidelines, and
- the applicable Certificate of Analysis to demonstrate the product quality.

National regulatory authorities vary in their willingness to approve import permits for unregistered products. If approved, import permits can be a faster—albeit temporary—way to get a product in country. ■





Before & After Registration

COMPONENTS OF A REGISTRATION APPLICATION

Common Technical Document (CTD) is a standardized format for registration applications. The U.S., European Union, and Japan originally developed the streamlined format. Many national regulatory authorities have since adopted it, and some now require an electronic version (eCTD) for submission. The WHO has also adopted the CTD format for the PQ process.

The CTD format includes five modules:

- **Module 1:** Administrative and prescribing information (e.g., application letter/form, labeling/packaging, CPP, GMP Certificate)
- **Module 2:** Overview and summary of modules 3 to 5
- **Module 3:** Quality data (e.g., product

- manufacturing and quality controls)
- **Module 4:** Non-clinical study reports
- **Module 5:** Clinical trial reports

As part of the registration application process, many national regulatory authorities also require samples of the product for testing or retention, and conduct GMP audits of the facility where the product is manufactured.

PRODUCT LIFE STAGES

Contraceptive product development can take a decade or more. It is a long and complex process that typically involves the stages outlined in Figure 5. It is good practice to involve regulatory specialists throughout the process of product development to ensure product quality, safety and efficacy as well as reduce the risk of delays as the product approaches readiness for registration.

Figure 4. REGISTRATION APPLICATION DOSSIER IN CTD FORMAT

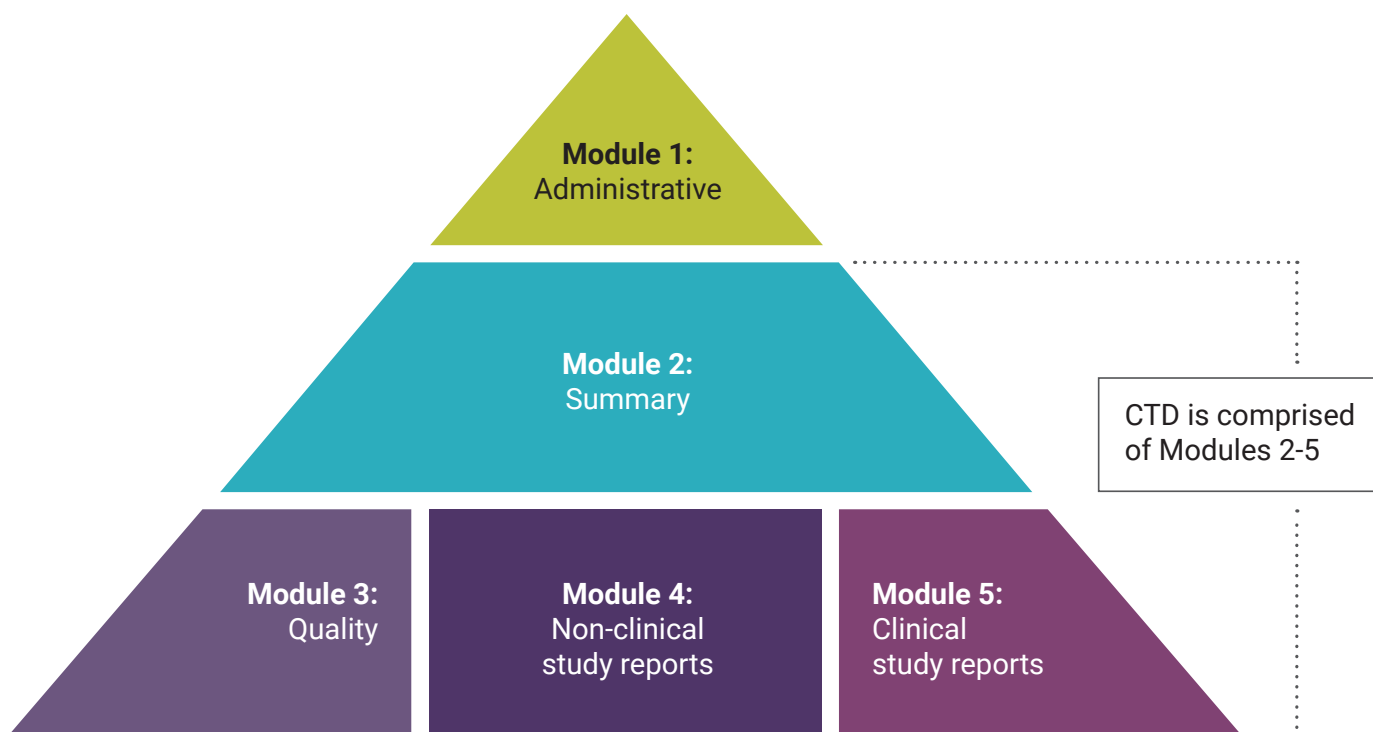
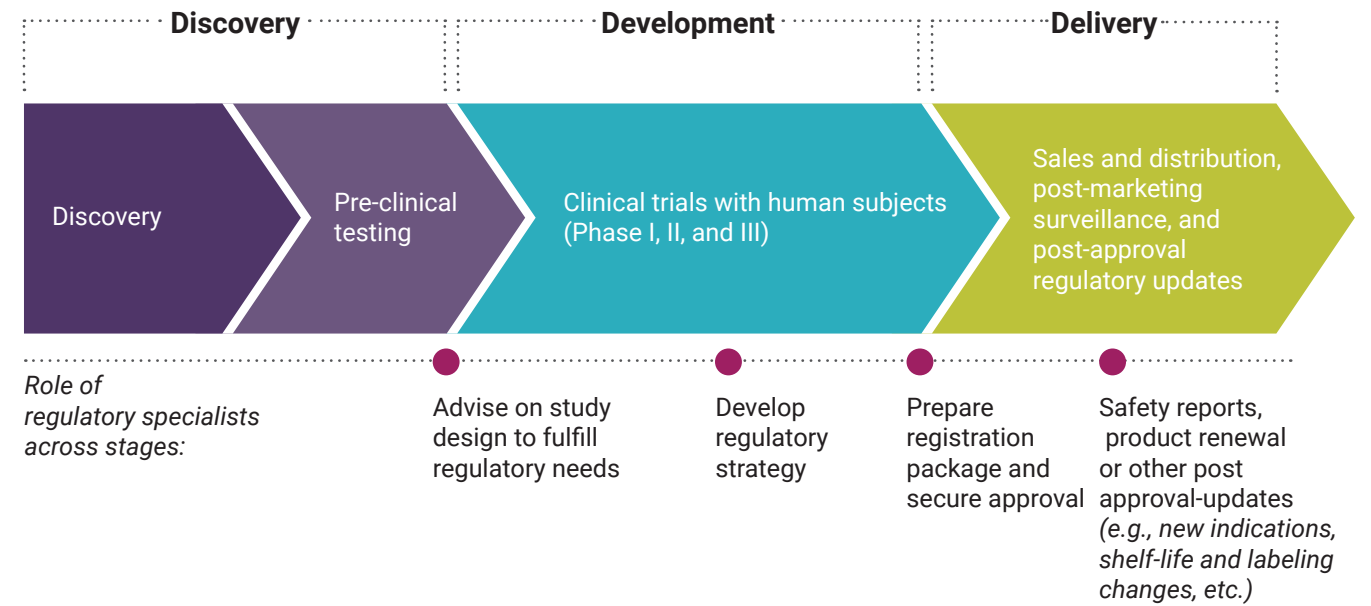


Figure 5. ROLE OF REGULATORY SPECIALISTS IN THE STAGES OF CONTRACEPTIVE PRODUCT DEVELOPMENT



AFTER REGISTRATION

Once a health product is registered in a given country, it can be imported, marketed, sold, and distributed to address important health needs, such as the need for contraceptive choice, in that country.

After granting Marketing Authorization, the national regulatory authority continues to monitor the product, including reports of adverse events collected by the MAH and shared with the product manufacturer. Furthermore, any changes to the product's indications, shelf-life, labeling, MAH or any other change requiring reporting, must be approved by the national regulatory authority.

Lastly, when the product's Marketing Authorization expires, typically in three to five years, it must be renewed with the national regulatory authority. ■

A critical role:



MARKETING AUTHORIZATION HOLDER

Program success can be greatly influenced by the selection of a Marketing Authorization Holder (MAH), which is a mandatory component of the registration application.

In some countries, the MAH must be a local entity while in others, it can be a foreign supplier or manufacturer. The MAH may be the product distributor or may choose a distributor. The national regulatory authority grants Marketing Authorization to an organization or company for a given period (typically three to five years). The MAH is responsible for compliance with the conditions of the market authorization, including post-approval surveillance as well as documentation and reporting of adverse events within the legislative framework of the registration.

It is essential for manufacturers to select an MAH with the motivation and capacity to fulfill these functions. Many manufacturers are open to input from global health program managers to guide their MAH selection. Global health program managers are well-positioned to identify the added advantages of potential MAH candidates, like national scale and experience with public sector tenders.





Real World Example

REGISTERING THE PROGESTERONE VAGINAL RING (PVR) IN NIGERIA

In support of Nigeria’s commitment to FP2020, WCG facilitated the registration of PVR in Nigeria with through the USAID-funded Delivering Contraceptive Vaginal Rings (DCVR) project led by Population Council (PC). The registration process for the PVR in Nigeria provides an example to contextualize the regulatory basics reviewed in this guide.

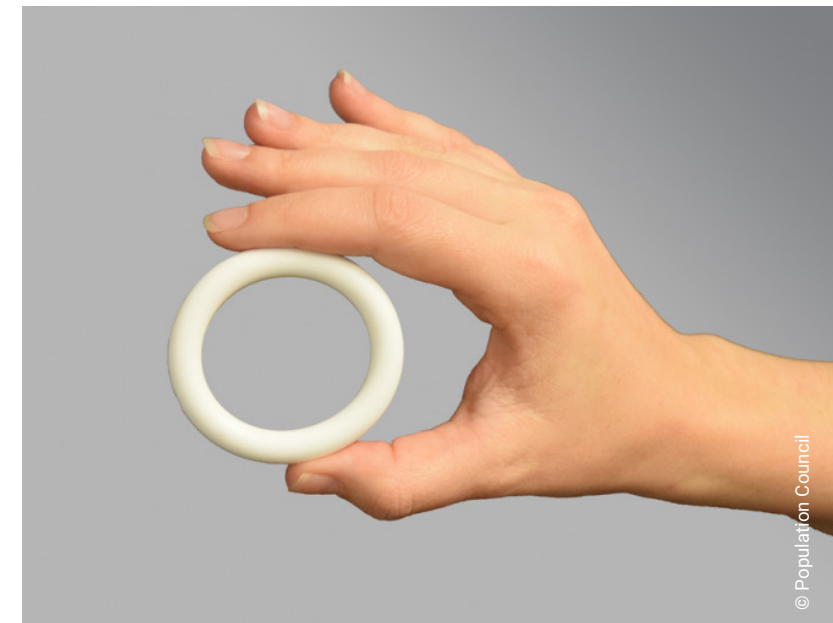
The PVR was developed by PC in partnership with experts for use by breastfeeding women for up to one year postpartum. Women can insert the PVR vaginally for continuous use for up to three months, using a maximum of four rings in one year. The PVR provides a steady release of 10mg of progesterone

daily to suppress ovulation and enhance the contraceptive effect of breastfeeding.^{vii} The PVR is manufactured by Grünenthal Chilena Ltda. in Chile under the brand name Progering®. The PVR has been successfully registered in 10 countries in Latin America.³

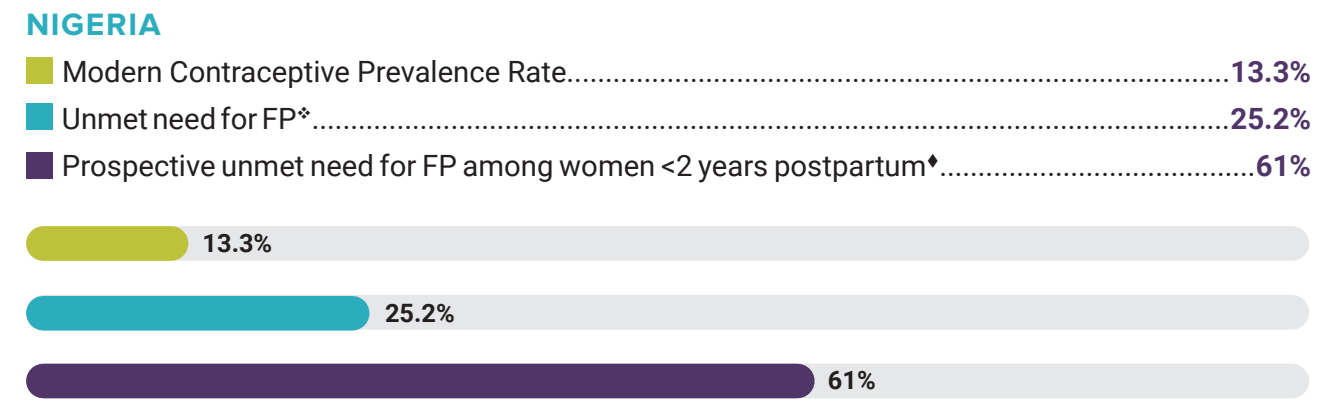
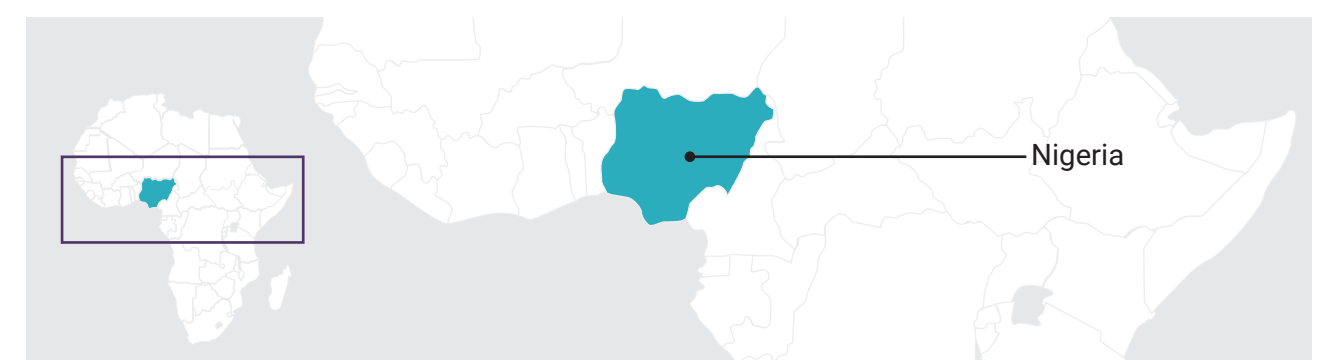
As an initial step in the registration process, WCG completed a regulatory assessment in-country to determine the registration requirements and timelines. WCG recommended pursuing registration at the country-level rather than one of the alternative routes described in the Regulatory Pathway Decision Tree (Figure 3). This was because the PVR does not yet have WHO PQ or approval by an SRA, and the West Africa regional harmonization initiative is not yet sufficiently mature to expedite country-level registrations.

WCG’s regulatory assessment also reviewed how the PVR is classified in Nigeria. The registration process differs depending on the product’s classification as a medical device, drug product or combination product. According to Nigeria’s National Agency for Food and Drug Administration and Control (NAFDAC), the PVR is considered a drug product, which has additional requirements for clinical data, testing and fees as compared to medical devices. As of 2018, there is no combination product classification in Nigeria.

To support the registration process, WCG engaged with PC, NAFDAC, the Federal Ministry of Health, and other key family planning stakeholders, as well as potential MAH candidates. To serve as the MAH for the PVR registration, candidates needed to meet the minimum requirements (e.g., be a local agent with the required certifications and licenses) and have the interest and capacity to occupy this role. Ultimately, WCG recommended the



Society for Family Health (SFH) of Nigeria as the MAH because they met the requirements and have the capacity to eventually procure and market the PVR at scale in Nigeria.



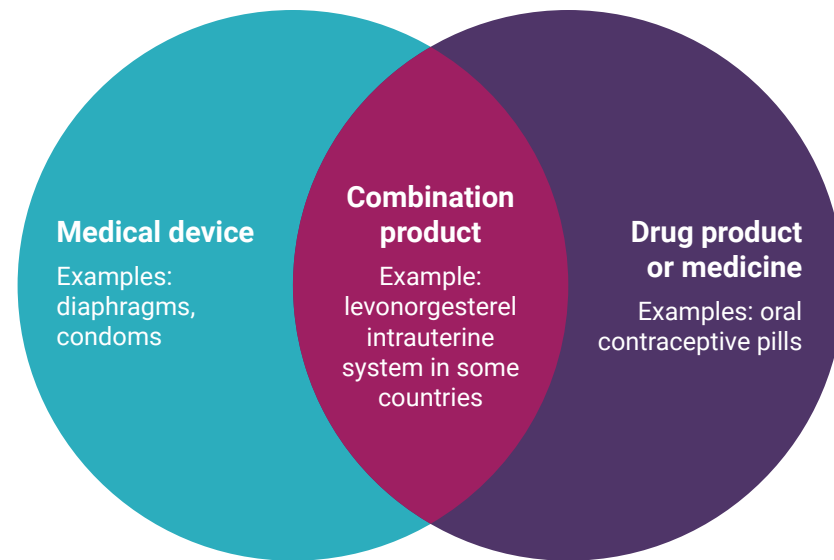
Sources: FP2020,^{vii} MCHIP^{viii}

^{*}Among married women.
[†]Prospective unmet need is based on the woman’s desired timing of her next pregnancy and her current contraceptive use, if any. Using this information, Unmet Need for FP among postpartum women is 61% while only 15% of postpartum women are using any form of FP in Nigeria.

³ As of 2018, the PVR Progering® is registered in Chile, Bolivia, Colombia, Ecuador, El Salvador, Honduras, Nicaragua, Panamá, Peru and Dominican Republic.



Figure 6.
**PRODUCT CLASSIFICATION
CATEGORIES FOR
REGULATORY
APPLICATIONS**



Of note, while WCG was preparing the registration application package for Nigeria in 2018, NAFDAC changed its regulatory application requirements, adopting the use of the CTD-formatted dossier instead of the local dossier format.⁴ This change could have set back the timeline for registration of the PVR in Nigeria. Fortunately, with support from the EECO project, WCG and Grünenthal Chilena had recently completed the first version of the CTD-formatted dossier for PVR as part of the process of pursuing WHO PQ. WCG was able to leverage this version of the CTD-formatted dossier and update the modules required for Nigeria to avoid delays.

In October 2018, WCG traveled to Nigeria to finalize and submit the electronic copy of the registration application package on

behalf of the SFH. After a successful initial review, NAFDAC moved to the next step in its regulatory process, requesting a copy of the paper application and issuing an import permit for a specific number of samples to be sent by the manufacturer for evaluation in Nigeria. As of December 2018, NAFDAC had issued the import permit for the PVR samples.

Once the samples are evaluated, NAFDAC and its expert committee responsible for product approvals will review the entire registration application package. If the application is found to be acceptable, NAFDAC will provide Marketing Authorization Approval, allowing SFH to market the product in Nigeria. Typically, the entire regulatory review process in Nigeria takes 3-8 months. ■

STEPS IN THE PVR REGULATORY PROCESS IN NIGERIA

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

⁴ As described above, the CTD-format requires standardized information on the quality, safety and efficacy of the PVR which must be provided by several different parties, including the product developer, manufacturer and MAH.



Conclusion

Registration is a critical first step in introducing new products into markets to meet essential health needs. By collaborating closely with regulatory specialists, global health program managers and manufacturers can set products up for success—deciding whether to pursue a special import permit to initiate activities in the country and/or registration, choosing an efficient regulatory strategy, selecting an appropriate MAH, and navigating regulatory challenges as they arise. ■

For more information about global regulatory affairs, review the introductory courses and resources available through:

- The Regulatory Affairs Professionals Society (RAPS): <https://www.raps.org/>.
- The Organisation for Professionals in Regulatory Affairs (TOPRA): <https://www.topra.org/>.



Cheat Sheet for Program Managers



PRODUCT REGISTRATION STEPS

These steps are typically performed by regulatory specialists to register new contraceptive products:

1. Conduct a desktop assessment to review country-specific registration requirements available online and to identify local stakeholders and potential MAH candidates.
2. Perform an in-country regulatory landscape assessment (if needed).
3. Assist the manufacturer or sponsor to select and appoint an MAH.
4. Communicate with the manufacturer to obtain required documents for registration.
5. Submit registration dossier on behalf of manufacturer.
6. Request import permit for any samples needed as part of the registration process.
7. Upon receipt of import permit, coordinate shipment of samples from manufacturer to regulatory authorities in country.
8. Communicate receipt of marketing authorization letter with internal and external partners.
9. Prepare requests for post-registration updates as the need arises. ■

Glossary

Common Technical Document (CTD): is a specific way of formatting relevant quality, safety and efficacy information for product registration. It was originally developed by U.S., European Union and Japan, and adopted by the WHO. Increasingly, other countries are adopting this streamlined format. The electronic version of the CTD is called the eCTD.

Certificate of Pharmaceutical Product (CPP): is issued by the national regulatory authority from the exporting country and used to assess the quality of the product by the importing country.

Good Manufacturing Practices (GMP): refers to a system of controls to ensure that medicinal products are consistently manufactured according to quality standards.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): comprised of members from regulatory authorities and the pharmaceutical industry to provide harmonized guidance on the scientific and technical aspects of product registration. ICH currently maintains the CTD guidelines.

Marketing Authorization Holder (MAH): a company, firm, legal person or non-profit organization that has the right to market a specific product in a given country. The MAH is selected by the product manufacturer and listed on the product registration application. The national regulatory authority grants marketing authorization to the MAH. Typically, marketing authorization must be renewed every few years (varies by country).

Stringent Regulatory Authority (SRA): is defined by their status as a member or observer of the ICH. SRAs are recognized for having the highest standards for quality, safety and efficacy of pharmaceutical products. As such, national regulatory authorities and the WHO take the approval of a product by an SRA in consideration during their review processes.

WHO Prequalification (WHO PQ): is a process that involves the review of health products' quality, safety and efficacy data, as well as testing the product and auditing the manufacturing site(s). If a product secures WHO PQ, it may be eligible for accelerated registration processes at the country level. ■



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^{vii}Nigeria. (2019). *Family Planning 2020 (FP2020)*. <https://www.familyplanning2020.org/nigeria>

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