USAID GLOBAL HEALTH
SUPPLY CHAIN PROGRAM
Procurement and Supply Management

Roadmap for the manufacture of injectable contraceptives in sub-Saharan Africa

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FROM THE AMERICAN PEOPLE

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ABBREVIATIONS

API	active pharmaceutical ingredient
AU	African Union
BMGF	Bill and Melinda Gates Foundation
CAGR	compound annual growth rate
CIFF	Children's Investment Fund Foundation
EBITDA	earnings before interest, tax, depreciation, and amortization
FP	family planning
GHSC-PSM	Global Health Supply Program-Procurement and Supply Management project
GMP	Good Manufacturing Practice
MPA-IM	medroxyprogesterone acetate intramuscular
MPA-SC	medroxyprogesterone acetate subcutaneous
NRA	national regulatory authority
PAVM	Partnerships for African Vaccine Manufacturing
SRA	Stringent Regulatory Authority
SSA	sub-Saharan Africa
UNFPA	United Nations Population Fund
USAID	United States Agency for International Development
USD	United States Dollar
WHO	World Health Organization

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1.0 INTRODUCTION

Local manufacturing of pharmaceuticals is seen as a way to aid localization, improve pandemic preparedness, diversify the supply chain, and promote growth in the local economies.[1] In recent years, local manufacturing in sub-Saharan Africa (SSA) has been the subject of different plans and roadmaps. Perhaps the most well-known is the Pharmaceutical Manufacturing Plan for Africa, endorsed by the African Union (AU) in 2012.[2] More recently, the African Development Bank Group,[3] Partnerships for African Vaccine Manufacturing (PAVM),[4] and the World Bank Group[5] have published plans to support local manufacturing.

However, these plans primarily focus on support for the manufacturing of oral solids and/or vaccines while also proposing broad-based solutions that could benefit all manufacturers. These include pooled procurement, regulatory support, platforms to facilitate understanding, and access to finance and technologies.[2-5] No recent plan yet focuses on contraceptive or hormonal product manufacturing.

The USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project contracted IQVIA Government Solutions to assess the economics of establishing an injectable and oral contraceptive manufacturing facility in SSA and develop a model that estimates the construction costs, operating expenditures, and the financial impact of factors such as corporation tax and depreciation, as well as the future market size and likely revenue. The model restricted sales to FP2020 SSA countries[6] and South Africa.

The initial model indicated that a commercial return is likely impossible for the manufacture of oral contraceptives, given the market size estimated for FP2020 SSA countries and South Africa. Early discussions also indicated that achieving a commercial return on an injection system similar to the one used for the subcutaneous presentation of medroxyprogesterone (MPA-SC) would be challenging. As a result, the final model focused only on analyzing the costs and revenues associated with manufacturing and selling an intramuscular formulation of medroxyprogesterone acetate (MPA-IM). Therefore, this document focuses specifically on outlining the steps to promote the manufacture of MPA-IM, one of the most popular contraceptives used by women in SSA.[7]

This document drew insights from discussions with three pharmaceutical manufacturers located in SSA, two international pharmaceutical manufacturers, a national quality control laboratory located in SSA,

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[1] USAID Regionalization Workshop, May 2-3, 2023.

[2] AUC-UNIDO Partnership. Pharmaceutical Manufacturing Plan for Africa. Business Plan. 2012

[3] African Development Bank Group. A new frontier for African Pharmaceutical Manufacturing Industry, 2022

[4] Partnerships for African Vaccine Manufacturing (PAVM) Framework, 2022

[5] Africa Gets a $1 Billion Shot in the Arm to Boost Health Systems, Emergency Preparedness and Response

[6] FP2020 SSA countries defined as: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Djibouti, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, South Sudan, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe. FP2020 countries refers to those that made commitments to expand access to contraceptives by 2020 http://2015-2016progress.familyplanning2020.org/page/fp2020-partnership

[7] Reproductive Health Supplies Coalition. Landscape and Projection of Reproductive Health Supply Needs, 2022

three SSA pharmacy university departments, and one development bank. A review of relevant literature complemented these interviews.

The document is organized into five sections. Section one summarizes the economic assessment of establishing an MPA-IM manufacturing facility in SSA. Section two outlines four key challenges in establishing such a facility, followed by a discussion of possible solutions to overcome these challenges in section three. The next section assigns a priority level to each proposed solution, and the final section five highlights the key points and study limitations.

2.0 MODEL OUTPUTS AND ASSUMPTIONS – RETURN BELOW COMMERCIAL EXPECTATIONS

The model suggests that over 20 years, an investor would receive a return representing approximately 6.01 percent compound annual growth after loan payments, depreciation, royalty payments, and corporation tax. This figure excludes any impact from inflation. This projected return falls considerably below manufacturers' reported profits in at least one SSA country, which range between 11 and 22 percent,[8] and well below the level indicated in interviews by local manufacturers.

Key assumptions behind the model are described below. A more detailed description of the model is provided in Annex 1.

Sales Volumes Dominated by Donors

Between 80-90 percent of the market in FP2020 SSA countries is donor-funded,[7] except in South Africa, where it's largely government-funded. World Health Organization (WHO) prequalification or Stringent Regulatory Authorities (SRA) approval is a prerequisite to participate in donor-funded tenders. According to the model, obtaining WHO prequalification and registration through the relevant Collaborative Procedure would take eight years, with the launch of an intramuscular formulation in the ninth year.

Dedicated Building on Existing Pharmaceutical Factory Site

Hormones are regarded as highly active pharmaceutical ingredients (API), and facilities must adhere to specific Good Manufacturing Practice (GMP) guidelines, with a particular focus on air-conditioning and ventilation systems.[9] The model assumes the MPA-IM manufacturing facility is a dedicated building on a site already operating as a pharmaceutical factory. Such a facility is compatible with WHO guidelines[10] and represents the lowest cost option, with some costs and staff shared or covered by other pharmaceutical manufacturing activities on the site. We assume the facility is located in an industrial park to ensure a

[8] Chaudhuri S and West A): Can local producers compete with low cost imports? A simulation study of pharmaceutical industry in low-income Africa, Innovation and Development, 2014: DOI: 10.1080/2157930X.2014.921273

[9] WHO. Guideline to the inspection of hormone product manufacturing facilities. February 2008.

[10] Fabio P et al. The requirements for manufacturing highly active or sensitising drugs comparing Good Manufacturing Practices. Act Biomed 2019; (90(2): 288-299.

consistent supply of electricity and water as well as appropriate facilities for wastewater management. API, excipients, and equipment would be imported.

Required $14.5 million Loan, 50 Percent to be Funded by a Development Bank

With a size of 850 square meters and 34 staff, the modeled facility is not large. However, an estimated loan of approximately $14.5 million is still required for building and operating costs before product launch. The model assumes that a development bank provides half the loan at an annual interest rate of 8.5 percent while the remaining 50 percent comes from an alternative source (commercial or other). The model suggests that this alternative investor would not recover that capital until 14-15 years after the initial investment.

Based on this model, it appears that this facility faces four key economic barriers: (i) Market uncertainty, (ii) WHO prequalification, (iii) Access to capital, and (iv) Access to foreign currency.

In the next section, we explore these challenges in greater detail.

3.0 KEY BARRIERS

3.1 Market Uncertainty

The MPA injectable contraceptive market in SSA is experiencing significant disruptions relating to both administration methods and pricing. The potential expansion of the private sector also adds to the uncertainty. These various issues are described in more detail below.

Potential MPA-IM Volume Decline

Forecasts suggest the market for injectable contraceptives in SSA will continue to grow, driven by injectable contraceptives' enduring popularity and population growth.[6] Volumes of injectable MPA are, however, split between the intramuscular and subcutaneous presentations. Donor purchases of MPA-SC increased by 49 percent from 2021 to 2022, reaching 34 percent of total MPA donor purchase volumes in 2022.[11] Donor funding for country-level initiatives aimed at expanding the use of MPA-SC continues.[12] Pfizer Inc., moreover, committed to supplying MPA-SC at its current price of $0.85 to public sector buyers through 2030.[13] MPA-SC manufacturing capacity is also unlikely to be an issue with the anticipated launch of a generic MPA-SC in the near to mid-term and following the Bill and Melinda Gates Foundation (BMGF) commitment to fund MPA-SC manufacturing capacity expansion.[12,14]

The model predicts that the MPA-SC market share will peak at 50 percent, reaching this point before the launch of the intramuscular product from this facility. However, future sales volumes of MPA-SC could exceed this projection. If MPA-SC were to reach 70 percent of volume, the model suggests that estimated returns over 20 years would fall by approximately two percent.

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[11] Analysis of GFPVAN data (August 2023)

[12] The DMPA-SC Access Collaborative. https://www.path.org/articles/dmpa-sc-collaborative/. Accessed 6th July 2023

[13] BMGF. Bill & Melinda Gates Foundation, Children's Investment Fund Foundation, Pfizer and Becton, Dickinson & Company Expand Partnership for Greater Access to Injectable Contraceptive for Women in Low- and Lower-Middle-Income Countries. August 3rd, 2023

[14] Bill and Melinda Gates Foundation. Committed Grants. DMPA-SC - Capacity Expansion at Incepta. Incepta Pharmaceuticals Ltd | Bill & Melinda Gates Foundation

Low Public Sector MPA-IM Prices

The United Nations Population Fund (UNFPA) Product Catalogue price for MPA-IM was 76 cents per vial in 2022.[15] However, in March 2023, the Ethiopian Procurement Supplies Authority announced that it accepted an offer for the supply of a WHO-prequalified MPA-IM manufactured in Bangladesh at approximately 61 cents per vial.[16] This suggests that the price of MPA-IM to public sector buyers may range from 61 cents to 76 cents per vial. This range may shrink in the future, especially considering Pfizer's recent announcement to sell its products, including MPA-IM, to 45 low-and middle-income countries on a not-for-profit basis.[17]

The current model assumes that sales will be made at an average of 61 cents per vial.

Growth of the Private Sector

Several donor programs focus on growing the private sector share of the total contraceptive market in SSA. Without regulatory control over the quality of the MPA-IM distributed in the private sector, WHO-prequalified manufacturers, or at least those aiming to make a profit, may be disadvantaged due to potentially higher incurred costs.[18] Discussions with a national quality control laboratory regarding the MPA-IM testing suggest that the required equipment or expertise is not unusual or extensive. However, it has been suggested that regulators in SSA do not have the capacity to ensure that only quality-assured products are sold in their countries.[2] This apparent lack of capacity, combined with the potential expansion of the private sector, adds uncertainty regarding the extent to which a WHO-prequalified supplier will benefit from the private sector's growth.

3.2 WHO Prequalification

WHO prequalification applications can only be made once registration is complete in the country of manufacture. The model assumes that construction, commissioning, and registrations will take eight years. This breakdown includes three years to build and commission the factory, two years for local registration, two years for WHO prequalification, and one year for product registration in all other relevant countries through the Collaborative Procedure process. However, the timeframe for WHO prequalification is somewhat uncertain and may be particularly challenging for an MPA-IM manufacturing facility located in SSA, as described below.

Uncertain Time for WHO Prequalification

The time for manufacturers to achieve WHO prequalification varies considerably. Quality Chemical Industries Ltd. (QCIL), a Ugandan manufacturer, declared it took four years to construct and commission a greenfield factory and achieve WHO prequalification for antiretroviral products.[19] Universal, a Kenyan manufacturer, stated it took seven years to achieve WHO prequalification for an antiretroviral product, including construction, commissioning, and regulatory approvals.[20] An international manufacturer already approved by multiple SRAs noted it took them two to three years to receive WHO prequalification, while another manufacturer of both oral and parenteral products suggested nine years to launch. Thus, the period assumed in the model (nine years) may be optimistic.

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[15] UNFPA Product Catalogue. Accessed 2022.

[16] Ethiopian Procurement Supply Service. Award Result (ICB/EPSA6/MOH-SDG-MOFED/FH/PH/15/22. March 22, 2023

[17] Pfizer Inc. Pfizer Expands 'An Accord for a Healthier World' Product Offering to Include Full Portfolio for Greater Benefit to 1.2 Billion People in 45 Lower-Income Countries. January 17th, 2023

[18] Shocken C. Business Case. Investing in production of high-quality misoprostol for low-resource settings. 2014. https://www.conceptfoundation.org/wp-content/uploads/2015/06/BusinessCase_Misoprostol_web.pdf

[19] CiplaQCIL. Presentation. West African Medicines Regulatory Harmonization (WA-MRH). Key Milestones. Provided by USAID.

[20] Universal Corporation Ltd. Presentation to Virtual Joint Meeting 28 November -1 December 2022. Provided by USAID.

Since WHO prequalification or SRA approval is required for donor procurement and WHO prequalification is also required in several SSA countries like Kenya[21] and Ethiopia,[22] such a wide range in the time needed to obtain WHO prequalification may undermine investor's confidence in achieving the estimated returns anticipated by the model.

Challenging WHO prequalification

Hormonal manufacturing is complex, with one manufacturer comparing it to vaccine manufacturing. Moreover, the process for achieving WHO prequalification has been described as a "marathon" and as much of a cultural as a technical challenge, given the focus on documentation and data integrity.

Several manufacturers in SSA make both large and small-volume parenterals.[23,24,25] None of these manufacturers has been through the WHO prequalification process. Moreover, the PAVM Framework for Action highlights the need to expand the workforce by more than 800 percent to meet the anticipated or hoped demand for vaccines and a shortage of skills in process development.[4] An analysis of training needs in the Southern African Development Community also suggests the labor pool is "usually low-skilled" due to high employee turnover caused, in part, by emigration and training that often focuses on regulatory requirements rather than operations such as formulation development, plant engineering, and supply chain management.[26]

This limited pool of expertise and the complexity of hormonal manufacturing suggest that WHO prequalification may represent an even greater challenge for an MPA-IM manufacturing facility based in SSA. As such, the interviewed manufacturers indicated that a technology transfer would be required to establish a WHO-prequalified MPA-IM manufacturing facility in SSA.

3.3 Access to Capital

The model suggests a total investment of just over $14 million is needed to construct and commission this facility. An investor taking on 50 percent of that investment would not see a return on capital for 14 years and, in 20 years, would see a return of just 6.01 percent on a compound annual growth rate (CAGR). By the time of product launch, the factory would also be the fifth WHO prequalified supplier of MPA-IM.[27] Thus, its appeal to social impact investors may be less than it would have been before the entrance of WHO-prequalified generic MPA-IM suppliers to the market.

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[21] Kenya Medical Supplies Authority. Open International Tender (OIT). Tender document for the supply of family planning commodities. Invitation for Tender (IFT) Number. KEMSA/OIT01/2020-2022. 16th June 2020. https://www.kemsa.co.ke/wp-content/uploads/2020/05/SBD-KEMSA-OIT1-2020-2022-FAMILY-PLANNING-COMMODITIES.pdf

[22] Ethiopian Procurement Supply Service. Tender Amendment (AMENDMENT)ICB/EPSA6/ MOH-SDG-MOFED/FH/PH/15/22). 22nd December 2022.

[23] Kenya - Tasa Pharma, Laboratory & Allied Ltd and B Braun Pharmaceuticals*. Source: PPB Database of Registered Products, accessed 22/6/23 ** Large volume parenterals only.

[24]Nigeria - Biomedical Ltd*, Dana Pharmaceutical Ltd*, ECWA Central Pharmacy Ltd, Barker Alfanxo Pharmaceutical Industries, Juhel Nigeria Ltd, Reagan Remedies, Drugfield Pharmaceuticals Ltd, Fidsons Healthcare, Med-In hospital & Pharm Services Ltd*, Unique Pharmaceuticals* Source: NAFDAC List of inspected local pharmaceutical manufacturers, 2021. *Large volume parenterals only.

[25] Ethiopia – Ethiopian Pharmaceutical Manufacturing S.C (EPHARM), Addis Pharmaceuticals Factor S.C. (APF), Pharmacure Pvt Ltd, MedSol Pharmaceuticals Manufacturing*, Humanwell Pharmaceutical Ethiopia PLC, Sansheng Pharmaceutical PLC. Source: EPMSMA, 2022, *Large volume parenterals only.

[26] Southern African Generic Medicines Association (SAGMA). Analysis of training needs in the generic medicines sector in the South African Development Community. June 2014.

[27] WHO prequalified suppliers of MPA-IM as of 22nd August 2023: Pfizer Manufacturing Belgium NV/SA, Mylan Laboratories Limited, Incepta Pharmaceuticals Ltd and Tunggal Idaman Abdi. https://extranet.who.int/pqweb/medicines/finished-pharmaceutical-products/prequalified. Accessed 23rd August 2023.

The size of the investment, the potential decline in social impact, and the time and size of the return will likely limit the types of investors willing and able to invest in this facility. These issues are examined in more detail below.

Investment Size, Capital Return Time, and Total Return

The investment size is probably beyond the amount most social impact investors are willing or able to invest. Investors hesitate to commit all their funds to a single project, with many imposing so-called "concentration limits" of around 10 percent of their total funds.[28] Therefore, for the social investment fund to consider investing in a facility manufacturing MPA-IM, it would have to be $65-100 million. A literature review and website search suggest that only a few social impact investments of that size also focus on healthcare or pharmaceutical manufacturing.[29] Moreover, only six percent of larger social impact investors are willing to accept below-market returns.[30] With a 6.01 percent projected return over 20 years, excluding the impact of inflation, this falls below the average returns sought by impact investors seeking a return in emerging markets (typically 10 percent).[30]

This relatively unimpressive rate of return also means manufacturers are unlikely to invest. In interviews, local manufacturers consistently claimed to look for a 12 percent or higher return on the capital invested within five to eight years.

Development bank loans may be more accessible due to these institutions' focus on promoting specific industries, with pharmaceutical manufacturing consistently identified as a priority sector. However, national development banks will only invest a proportion of the total funds to be invested. For example, the Ethiopian Development Bank's limit is 50 percent,[31] while the Kenyan Development Corporation's is somewhat higher at 67 percent.[32]

These limits mean an additional investor to the development bank is needed, and as discussed above, the estimated rate of return, the size of the investment, and the level of social impact may make this challenging.

3.4 Access to Foreign Currency

Construction materials, equipment, and ongoing supplies of API, excipients, and likely, primary packaging will require access to the United States Dollar (USD) or a similarly robust currency. Lack of access to foreign currency would likely delay the construction and commissioning of the factory and interrupt production, adding further delays and costs. Several major manufacturing hubs in SSA are currently restricting access to foreign currency, notably Ethiopia and Kenya.[33,34]

Fear of being unable to access foreign currency also affects local companies' ambitions. One local manufacturer interviewed had gone so far as to eschew export markets because the management was not confident of being able to access sufficient foreign currency to supply the export market and the domestic market on an ongoing basis.

Limited access to foreign currency is, thus, another challenge to an export-oriented MPA-IM manufacturing facility.

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[28] Financing4Development. Building bridges between Impact Investing and Reproductive Health. Deliverable #4. Dossier of investors and estimated investment appetite. September 18th, 2015.

[29] IQVIA's analysis, based on literature and website search. Presentation to GHSC-PSM.

[30] Global Impact Investing Network. Annual Survey 2020. June 2020

[31] Development Bank of Ethiopia. A short guide to access DBE's loans. https://www.dbe.com.et/BusnessPromotion/Policy/DBENewPolicyEng.pdf Accessed 6th July 2023

[32] Kenya Development Corporation. https://kdc.go.ke/loan-facilities/. Accessed 6th July 2023

[33] https://www.africanews.com/2022/10/16/ethiopia-restricts-use-of-foreign-currency//

[34] https://qz.com/why-is-kenya-running-out-of-dollars-1850194509

4.0 PRIORITY ACTIONS

This section proposes potential actions to address the barriers outlined above. These are summarized below (Table 1) and explained in more detail in the following sections.

Table 1: Summary of key barriers and priority actions

Key Barrier	Priority Action
Market uncertainty	Forecast for MPA by presentation
	Implement volume and/or price guarantees and/or other market-shaping interventions
	Assess diversification and export potential
	Leverage PAVM Framework for Action (regulatory support)
	Assess the impact of modular factories on hormonal production
	Leverage PAVM Framework for Action (forum for investors and manufacturers)
Access to capital	Develop a social impact argument for a diversified portfolio, including family planning (FP)
	Develop social impact metrics for supply security
	Provide investment advice and support, including consideration of capital guarantee
Access to foreign currency	Continue to pay the manufacturer in USD

4.1 Easing Market Uncertainty

Managing Volume Decline

As noted above, the extent to which MPA-SC will penetrate the injectable contraceptives market is currently unknown. Growth is rapid, and donor-funded programs continue to promote its use. Pfizer's decision to provide MPA-SC and MPA-IM at a not-for-profit price and the entrance of generics may lead to a price reduction. It is recommended to conduct forecasting of long-term injectable contraceptive demand by formulation across public and private sectors in FP2020 SSA countries and South Africa to provide greater certainty of likely volumes required. Unitaid has funded similar forecasts for artemisinin-

based combination therapies since at least 2012 to ease market uncertainties.[35] BMGF also funds forecasts for a wider set of antimalarial commodities.[36]

However, long-range (i.e.,15-20 years) forecasts can be unreliable. If donors wish to promote local manufacturing of MPA-IM, then, given the projected rate of return and the market uncertainty, they will need to consider market-shaping interventions. For example, if a volume guarantee were to assure that 30 percent of the volume procured by donors for FP2020 SSA countries would be sourced from this facility, it would increase the CAGR over 20 years from 6.01 percent to 7.9 percent. The current model assumes 20 percent of the volume procured by donors would be from this facility. Donors have made similar commitments in the past. For example, the BMGF and the Children's Investment Fund Foundation (CIFF) partnered with Pfizer in 2014 to ensure a price of $0.85 per unit of MPA-SC for public-sector purchasers in low- and middle-income countries. In 2023, this agreement was renewed until 2030, with Pfizer committing to increasing its production capacity by 65 percent.[37]

An alternative risk mitigation solution to MPA-IM volume decline is to explore diversification of the facility's product portfolio and then provide support to that manufacturing facility to help it develop the necessary infrastructure and skills. This would first require an examination of the markets in SSA for other highly active pharmaceutical ingredients, including hormonals and steroids, to determine the size and potential of those markets and implementation of a similar exercise to that carried out for this contraceptive facility to understand the likely profitability of such a broad-based facility.

On the other hand, a more limited diversification strategy might simply focus on expanding the warehouse capacity to allow for contract secondary packaging activities such as overbranding and kitting. Secondary packaging activity includes taking a product (any product, not just a hormonal contraceptive) in its primary packaging (i.e., a product in a blister or vial) and putting that product in an alternative secondary packaging (i.e., a carton or box).[38] Again, the feasibility and impact of such a strategy would need to be established in a separate study.

Competitive Pricing

Competitive pressures will likely keep the donor and/or public sector price for MPA-IM in SSA near 61 cents. At this price, it is anticipated that this new facility located in and serving exclusively FP2020 countries and South Africa would make 6.01 percent over 20 years on a CAGR basis, well below manufacturers' expected rate of return.

Therefore, a price guarantee restricted to the period of loan capital and interest repayment may be appropriate. To achieve a return of capital within 10 years and a rate of return of 15 percent CAGR over 20 years, the price would need to be guaranteed at approximately $1.90 per vial (i.e., more than one dollar than the current price offered to Ethiopia). At such a price, the price guarantee would cost approximately $160 million over the 20 years.

A more acceptable alternative may be for donors to simply cover the loan principal and interest directly. This would increase the return to 7.9 percent CAGR over 20 years and cost donors $11.1 million. This rate of return would not be attractive to commercial investors but might attract impact investors for whom the average realized rate of return in emerging economies is 8-18 percent. [30]

Alternatively, the facility could generate further revenues through exports to countries beyond South Africa and FP2030 countries in SSA. At present, the model does not account for such exports. If our

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[35] UNITAID. Policy brief. ACT Demand Forecast 2012-2013. April 2012.

[36] Clinton Health Access Initiative. Annual global forecasts for malaria commodities to help global community navigate increasingly complex markets. January 21, 2022. https://www.clintonhealthaccess.org/blog/annual-global-forecasts-for-malaria-commodities-to-help-global-community-navigate-increasingly-complex-markets/. Accessed 22nd August 2023.

[37] https://www.gatesfoundation.org/ideas/media-center/press-releases/2023/08/injectable-contraceptives-ciff-pfizer-bd-expand-partnership

[38] Health Sciences Authority Regulatory Guidance. Guidance on secondary packaging of therapeutic and medicinal products. Singapore. 7th May 2021 https://www.hsa.gov.sg/docs/default-source/hprg-ald/guide-mqa-031.pdf

market share assumptions are correct, the model predicts the facility could produce a further two million doses. Since this facility is assumed to achieve WHO prequalification, export to higher-priced countries should not require changes in production processes. Import tariffs may also not be a barrier, given agreements that provide preferential rates for exports from SSA countries, such as the African Growth and Opportunity Act.[39] Nonetheless, given the limited experience of manufacturers located in SSA in exporting to high-priced markets, support to identify and screen appropriate agents in those markets may be required.

National governments might permit preferential pricing of a locally manufactured MPA-IM; indeed, many countries already provide incentives to local manufacturers. For example, in Kenya, legislation allows the Kenyan Medical Supplies Authority to offer a 6-15 percent margin of preference depending on the extent to which products are manufactured in Kenya and/or the extent to which the manufacturer is owned by Kenyan citizens.[21] Most national governments in SSA are not, however, responsible for direct procurement of MPA-IM. Even if they were, in all but one or two cases, the domestic market is too small for preferential pricing to impact the overall rate of return.[7] The AU or a regional economic community might consider this type of preferential pricing, but it can distort the production economics. This can lead to manufacturing failure if the preferential pricing policy is removed.

Managing Private Sector Growth

A commercial return on a WHO-prequalified MPA-IM manufacturing facility is only possible if poor quality alternatives do not undercut prices and if private sector sales are not displaced by the product leakage from the public sector.

Testing for the quality of MPA-IM does not require novel or unusual equipment. The Pharmaceutical Manufacturing Plan for Africa suggested in 2012 that not all countries have sufficient capacity to regulate the market effectively.[2] As of November 2022, only five national regulatory authorities (NRAs) in Africa had reached maturity level 3,[40] the level required for WHO-prequalified vaccine manufacturing.[4]

Given the existing number of programs focused on building the capacity of national regulators, initiatives focused on MPA-IM, or hormonal products in general, must build on the current programs. Moreover, due to the similarities between hormonal and vaccine manufacturing, it may be most effective to collaborate with PAVM. PAVM calls for support for all NRAs in Africa to achieve maturity level 3 and suggests programs (i) harmonize operating frameworks, (ii) increase knowledge and expertise-sharing mechanisms, (iii) upskill leadership, (iv) develop sustainable financing, and (iv) develop regional centers of regulatory excellence that could be responsible for capacity building programs.[4]

4.2 Supporting WHO Prequalification and Registration Processes

Our model assumes it will take eight years to construct, commission, and achieve WHO prequalification and multiple country registrations. Years 1-3 are dedicated to the construction and commissioning of the site, years 4-5 to gaining registration in the country of manufacture, years 6-7 to securing WHO prequalification and year 8 to cross-country registration using the WHO Collaborative Procedure.

In the next paragraphs, we examine potential strategies for shortening each of these phases.

Site Construction and Commissioning

Several of the local manufacturers interviewed confirmed that a typical timeline for the construction and commissioning of manufacturing sites is three years. However, there are multiple examples of delays in

[39] Kategekwa J. Recalibrating US economic engagement with Africa. The Wilson Quarterly, Spring 2023.

[40] WHO. List of National Regulatory Authorities (NRAs) operating at maturity level 3 (ML3)1 and maturity level 4 (ML4)2 (as benchmarked against WHO Global Benchmarking Tool (GBT) (in alphabetical order) - As of November 2022. https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4. Accessed 22nd August 2023.

factory construction in SSA due to an inability to source relevant expertise and materials.[41] Therefore, a modular approach to the factory's construction may be appropriate.

In this approach, the factory is built in sections, or modules, in a different location with easier access to relevant expertise and materials. Each module is tested before shipping to the manufacturing site to ensure that the equipment is installed correctly. Modules are then shipped and tested again once installed to ensure consistency with pre-site testing results.

This modular approach is relatively novel and used to advance vaccine manufacturing in SSA.[4] A modular approach can save up to 20 percent on total construction and commissioning costs, as well as on time. The duration for operational qualification is reported to take 15-18 months.[42]

Whether this modular approach would lead to higher total capital costs when applied to hormonal manufacturing remains uncertain. However, the model suggests that for every year of construction and commissioning through the modular approach, earnings before interest, tax, depreciation, and amortization (EBITDA) increase by an average of $3.6 million.

A modular approach, thus, offers the potential to reduce construction and commissioning time. However, due to its novelty, manufacturers and investors would benefit from sensitization to its potential impact. This may be achieved through targeted forums and or the commissioning of a study to explore the potential of a modular factory for hormonal manufacturing.

Domestic Registration

The product registration timeline varies by country in SSA and, on average, takes approximately 1.5 years.[43] This timeline could likely be improved, at least in some countries where experience suggests it may take up to 10 years. Fast-track registration for locally manufactured products is available in at least three key manufacturing hubs in SSA,[44,45,46] and product marketing can occur before formal registration in at least one SSA country. As noted above, hormonal manufacturing is complex, similar to vaccine production. The PAVM Framework for Action aims to promote regulatory excellence in vaccine manufacturing. Expanding this initiative to include regulatory excellence in hormonal or highly active pharmaceutical ingredient product manufacturing would prevent regulatory delays.

WHO Prequalification Process

The WHO prequalification process is a challenge, even for manufacturers with previous experience of SRA approvals. Several programs offer support to local manufacturers in GMP, notably those run by US Pharmacopeia[47] and the WHO Local Production team.[48]

Although the model assumes many key operational positions are filled by expatriates with appropriate experience, WHO prequalification would be made more certain through a partnership with an existing MPA-IM manufacturer to provide support. Such support may include the provision of a product dossier for submission to the national regulator, secondment of expert staff, and early training of local staff to build expertise and experience.

Such agreements can take many years to arrange. For example, the Sanofi technology transfer of the trivalent influenza vaccine to the Butantan Institute in Brazil took nearly 10 years to complete,[4] while the

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41 https://fabtechnologies.com/pharmaceutical-manufacturing-facility/. Accessed 6th July 2023

42 Personal Communication. Unizima. 2023.

43 GHSC-PSM. Personal Communication

44 Pourraz J. Making medicines in post-colonial Ghana: State policies, technological transfer and pharmaceuticals market. Social Science & Medicine, 2022,311: 115360

45 Pharmaceuticals Export Promotion Council of India. Regulatory and market profile of Kenya. https://pharmexcil.com/uploads/countryreports/Kenya_Regulatory_Market_Profile.pdf Accessed 31st July 2023.

46 Ethiopian Food and Drug Authority. Guideline for Registration of Medicines. Fourth Edition. May 2020.

47 https://www.usp.org/global-public-health/promoting-quality-of-medicines-plus

48 https://www.who.int/teams/regulation-prequalification/lpa

technology transfer of the Hib vaccine from GSK to Bio-Manguinhos, also in Brazil, took nearly eight years. Timelines may have been extended in these cases due to the involvement of parastatal/public sector organizations.

Given the small size and scope of a single MPA-IM manufacturing facility, it is appropriate for its initiatives to be included within existing efforts by the PAVM Framework for Action to establish a "Vaccine Technology Transfer & Intellectual Property Brokering Service to link technology providers and recipients to an ecosystem of support for tech[nology] transfer".[4]

Collaborative Procedures

WHO launched its collaborative procedure for accelerated registration of prequalified finished pharmaceutical products in 2013. The collaborative procedure "accelerates registration through improved information sharing between WHO prequalification and national regulatory authorities". By leveraging assessment and inspection outputs already produced by WHO prequalification, and thereby eliminating duplicative regulatory work, it speeds up in-country registration of quality-assured products and contributes to their wider availability."[49]

WHO targets a timeline of 90 days for registrations under the collaborative procedure.[50] However, one supplier of MPA-IM experienced a registration timeline of 1-12 months leveraging this procedure, depending on the country. Manufacturers interviewed suggested the procedure could be further streamlined by ensuring consistent rules around packaging and post-registration testing and having a single point of contact in each country's regulator.

4.3 Easing Access to Capital

The ease of raising capital to support this facility depends on the business case. Similarly, the business case depends on market-shaping interventions such as volume or price guarantees. The facility may, however, also need to consider the type of capital it seeks (i.e., debt or equity) and from whom it seeks to receive such capital (i.e., bank or impact investor). These topics are explored further below.

Social Impact Argument

Access to modern contraceptives has a significant social impact. In a study conducted in 2021 examining a range of investments focused on health and development in Africa, access to modern contraceptives was deemed the most cost-effective intervention for the continent. Considering the demographic dividend, the cost-effectiveness ratio of access to modern contraceptives was adjudged to be almost 110:1.[51]

Our model facility would be the fifth WHO-prequalified facility making MPA-IM globally. As such, a social impact investor may deem its impact limited. A diversified factory focusing on a combined portfolio of hormonal and steroid-containing products may be more attractive to an impact investor, given that it may address a wider range of supply challenges.

Lastly, developing a formal metric to measure the social impact of supply security in SSA would benefit investors and help to facilitate investment decisions.

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[49] WHO. Collaborative procedure for accelerated registration. https://extranet.who.int/pqweb/vitro-diagnostics/collaborative-procedure-accelerated-registration Accessed 31st July 2023.

[50] Doerr P. Presentation. Overview of collaborative procedures and initiatives to register therapeutic products. 23rd February 2021. https://www.shareweb.ch/site/Health/aboutus/Documents/Online-events-documents/4_WHO_Overview%20of%20collaborative%20procedures%20and%20initiatives%20to%20register%20therapeutic%20products.pdf. Accessed 6th July 2023.

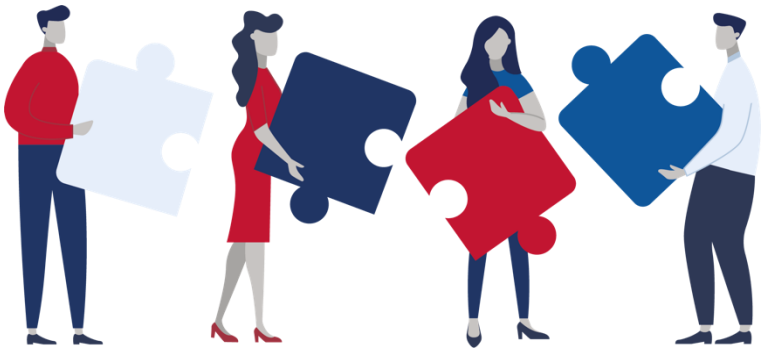
[51] Copenhagen Consensus Center. Identifying best buys for Africa. Comparing costs and benefits. 2021.

Capital Type

A technology transfer may lead to the payment of royalties or equity. Based on a conversation with a local manufacturer, the model assumes that royalties constitute eight percent of revenues. However, an international manufacturer indicated that a technology transfer from an existing MPA-IM manufacturer would only interest them if there were a transfer of equity in return. Transfer of equity allows the company transferring the technology to retain some measure of control over how that technology is used and/or where it is sold. Many SSA manufacturers are family-owned and operated. Therefore, a transfer of equity may be a challenge, both from a cultural perspective and because of the need to structure and value the company appropriately. A local manufacturer may hence require support to swap equity for technology.

Emzor, a WHO-prequalified manufacturer located in Nigeria, recently issued a corporate bond. A corporate bond is an alternative to raising capital via a loan or technology transfer.[52] A corporate bond is a guarantee from the issuing corporation that it will pay bond holders a set percentage return. Thus, it requires the corporation to be viewed as sufficiently robust to guarantee repayment of the capital plus the interest. Pharmaceutical manufacturers in SSA are likely unfamiliar with corporate bonds; thus, technical and financial support may be required if the manufacturer is deemed sufficiently robust to issue a corporate bond. Donors interested in promoting local manufacturing of hormonal products might consider underwriting such a bond to guarantee capital repayment.[53,54]

4.4 Easing Access to Foreign Currency



The lack of foreign currency reserves afflicting several SSA countries results from many different factors, and measures to address them are beyond any roadmap for a single MPA-IM manufacturing facility.

USAID's procurement agent, GHSC-PSM, pays manufacturers for products in USD. This eliminates any foreign exchange risk for the manufacturer and provides a ready supply of USD required to purchase equipment, API, and other manufacturing inputs.

5.0 RECOMMENDATIONS

This section proposes activities in Table 2 to support local manufacturing or reproductive health commodity supply in SSA. Table 2 assigns a level of priority to each of the proposed solutions. The highest priority is given to actions that ease market uncertainty. Without greater confidence in the size or trends of the MPA-IM market in SSA, investors are unlikely to support the establishment of an MPA-IM manufacturing facility in SSA. Priorities ranked "2" are of equal importance to those ranked "3" but would likely need to be completed before those ranked "3" could begin.

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[52] https://sec.gov.ng/wp-content/uploads/2021/12/Emzor-Series-1-Pricing-Supplement-200121-executed-approved.pdf

[53] Galitopoulou S and Noya A. Understanding social impact bonds. OECD, 2016.

[54] Center for Global Development. Investing in Social Outcomes. Development Impact Bonds, Investing in Social Outcomes: Development Impact Bonds | Center For Global Development | Ideas to Action (cgdev.org). Accessed 6th July 2023.

Table 2: Recommended actions and priority

Key Barrier	Action	Priority
Market Uncertainty	Assess the impact of modular factories on hormonal production	1
	Implement volume and/or price guarantees and/or other market-shaping interventions	1
	Assess diversification and export potential	1
	Leverage PAVM Framework for Action (regulatory support)	3
	Forecast for MPA by presentation	3
	Leverage PAVM Framework for Action (forum for investors and manufacturers)	3
Access to capital	Develop a social impact argument for a diversified portfolio, including FP	2
	Develop a social impact metric for supply security	2
	Provide investment advice and support, including consideration of capital guarantee	3
Access to foreign currency	Continue to pay the manufacturer in USD	3

Table 3 suggests timelines for these various activities. As noted above, construction and product registration will take eight years. Construction cannot start without funds being available, and as such, we propose that all activities associated with business case review and argumentation occur within one year. Given the complexity of the marketplace and the varying interests of different donors, we suggest a meeting to agree on the way forward. Timings for those activities associated with the PAVM Framework for Action are tentative. The PAVM Framework for Action has not yet suggested when these should start, but we hope that hormonal manufacturing can be incorporated as soon as they do.

Table 3: Recommended timeline based on priority

Priority Action	Year 1	2	3	4	5	6	7	8	9	10
Stakeholder meeting										
Assess impact of modular factories on hormonal production										
Assess diversification and export potential										
Forecast for MPA by presentation										
Re-assess need for, and if appropriate, agree to offer volume and/or price guarantees and/or other market shaping interventions										

Develop of social impact argument for diversified portfolio including family planning										
Develop of social impact metric for supply security										
Provide investment advice and support, including consideration of capital guarantee, if appropriate										
Leverage PAVM Framework for Action (regulatory support)										
Leverage PAVM Framework for Action (forum for investors and manufacturers)										
Continue to pay manufacturer in USD										
Implementation of volume and/or price guarantees and/or other market shaping interventions										

6.0 KEY POINTS AND LIMITATIONS

This work focused on the economics of building an MPA-IM manufacturing facility in SSA to serve FP2020 SSA countries and South Africa only. The study indicates that such a facility will not earn a commercial return, making it dependent on donor, government, or social impact investor support. However, this study did not thoroughly examine the impact of exporting surplus capacity to higher-priced markets or portfolio diversification on the business case, although these are offered as potential solutions for interested stakeholders to consider. The study also did not consider potential challenges related to the ease of doing business or logistics, as these tend to be specific to site location.

Interest in supporting local manufacturing of FP commodities remains considerable, but it's possible that the time for an MPA-IM facility has passed. Previously, supply was constrained, but this is no longer the case. Without donor support, it seems likely that sustainable manufacture of MPA-IM will only be possible if it can either be part of a larger hormonal or highly active pharmaceutical ingredient portfolio or it can serve markets on other continents where prices are higher.

Annex 1: Model Details

Introduction

The model attempts to estimate the costs and revenues associated with manufacturing and selling an intramuscular formulation of MPA only. The model assumes the facility will be located in SSA and the product will be sold in the 38 SSA countries that made commitments to expand access to family planning in 2020 (FP2020)[6] plus South Africa.

The model incorporates estimates of the costs associated with the construction of the facility, its operating expenditures, and likely revenues. The size, layout, and equipment required for the facility is based on similar costs for pharmaceutical factory design, construction, and audit. Costs for equipment and packaging are sourced from equipment and packaging suppliers. Costs for API and excipients are sourced from Indian import and export data. Staff costs are based on interviews with five SSA manufacturers in Ethiopia and Kenya, while registration costs and challenges are estimated based on discussions with three SSA NRAs, one local and two international manufacturers. Marketing and distribution costs are estimated based on interviews with two SSA-based importers and distributors, and utility and land rental costs are estimated based on published literature relating to the pharmaceutical parks established in SSA, particularly in Ethiopia. Revenues are estimated based on secondary literature, notably Reproductive Health Supply Coalition's Landscape and Projection of Reproductive Health Needs report,[55] tender data from South Africa, Kenya, and Ethiopia, and IQVIA's private sector datasets covering South Africa and Kenya. The financial impacts included in the model include corporation tax, depreciation and loan interest and repayment based on published literature and commonly used conventions (for depreciation). More details on model inputs are outlined in Annex 2.

Analysis of the model suggests eight cost inputs contribute to 96 percent of operational costs before tax (Table 1). Assumptions used to estimate these costs and those used to estimate revenues are discussed below.

Product Scope, Market Volumes and Growth

For this study, the model restricted production of the intramuscular formulation of the three-monthly injectable contraceptive, the active ingredient of which is MPA. The model also restricts sales to the 38 countries in SSA that made commitments in 2020 to expand access to modern contraceptives (FP2020 SSA countries), plus South Africa. Approximately 140 million injectable contraceptive doses are estimated to be needed in 2030, with volume growth at 3.9 percent on a CAGR basis between 2019 and 2030.[54] However, the model assumes no further growth beyond 2030, and to this extent, the model may be conservative.

Table 1: Average contribution to operating expenditure in the 6 years following product launch (Years 9-15), before tax

Agency and Marketing Costs	23.2%
Interest and Loan repayment	18.5%
API and Excipients	13.3%
Packaging	13.3%
Technology Transfer Fee	9.7%
Equipment and Construction	7.5%
Salaries	6.6%
Insurance and Distribution to Port	4.2%
Other†	3.8%

† Includes product registration, product retention, WHO Prequalification inspections, land rental, utilities, equipment repair and maintenance, site insurance and IT costs

[55] Reproductive Health Supplies Coalition. Landscape and Projection of Reproductive Health Supply Needs, 2022

MPA dominates injectable contraceptive volumes in the selected country markets, and those volumes are, in turn, dominated by donor-funded purchases. In 2019, 88 percent of injectables across these markets were supplied through the public sector or through the private sector as subsidised product.[55] Market volumes are however split between MPA-IM and MPA-SC. Donor funding for country-level initiatives aimed at expanding the use of MPA-SC continues.[56] Donor purchases of MPA-SC increased by 49 percent from 2021 to 2022, reaching 34 percent of total MPA donor purchase volumes in 2022.[57] As of 2023, donors pay approximately 39 percent more for MPA-SC than the lowest published SSA price for a WHO-prequalified MPA-IM ($0.85[58] versus $0.61[59]). This price difference may act as a break in market penetration by MPA-SC. The model assumes that MPA-IM will take only 50 percent of total MPA volumes and that the sale price will be $0.61.

Product Pricing and Market Share

As noted above, MPA-IM volumes are dominated by donor funding. The lowest published public sector price for a WHO-prequalified MPA-IM was offered to Ethiopia in 2023. A combination of MPA-IM plus syringe was offered (and accepted) for $0.66.[59] Allowing $0.05 for the syringe, this gives an approximate price per vial of MPA-IM of $0.61, reflecting a 20 percent decrease from the price listed in the 2022 UNFPA Product Catalogue. This indicates that the price of MPA-IM to public sector buyers in the future may range from between $0.61 to $0.76 per vial. As noted above, the model uses the lowest price (i.e., $0.61) for donor and public sector procurements in the FP2020 countries. Given this price and given this facility would produce the fifth WHO-prequalified MPA-IM product, the model assumes the facility will achieve a 20 percent market share of total donor and subsidized volumes.

The National Department of Health (NDOH) manages procurement in South Africa, not donors. The NDOH publishes the price at which contracts are awarded. The NDOH also publishes the formula used to allocate volumes between competitive bids.[60] The model uses this information to calculate the maximum price capable of securing a 30 percent share of volume in 2021. That price is $1.25 (excluding value-added tax).

South Africa also regulates prices in the private sector and sets the Single Exit Price (SEP). Analysis of historical data describing generic penetration of the private sector suggests generic penetration can be rapid.[61] Twelve generics launched between 2014 and 2021 were identified. In these examples, market shares were generally above 20 percent by the second year following the launch and continued to rise. In comparison, the median difference between the generic and the originator price at launch was 26 percent. An oral contraceptive achieved similar progress when it launched with a price 20 percent lower than the originator's.

The model assumes a price 20 percent lower than the originator's SEP throughout the period. The model also assumes an average volume share of 20 percent for the private sector in South Africa.

Prices in the FP2020 SSA countries in the private market are unregulated. In this case, the model uses prices from IQVIA's Kenyan audit (after subtracting the estimated distributor margins (see Annex 2)). Marketing to the private sector in the FP2020 SSA countries is thought to be more complex and challenging than in South Africa due to the number of channels and distributors and the reported

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[56] The DMPA-SC Access Collaborative. https://www.path.org/articles/dmpa-sc-collaborative/. Accessed 6th July 2023

[57] Analysis of GFPVAN data (August 2023)

[58] BMGF. Bill & Melinda Gates Foundation, Children's Investment Fund Foundation, Pfizer and Becton, Dickinson & Company Expand Partnership for Greater Access to Injectable Contraceptive for Women in Low- and Lower-Middle-Income Countries. August 3rd, 2023

[59] Ethiopian Procurement Supply Service. Award Result (ICB/EPSA6/MOH-SDG-MOFED/FH/PH/15/22. March 22, 2023. ~5 cents allowed for syringe cost.

[60] Department of Health, South Africa. HP03-2020CHM/01: Supply and delivery of contraceptives and hormone modulating agents to the Department of Health for the period ending 30 September 2023.

[61] IQVIA. South Africa Total Pharmaceutical Market audit, 2014-2021. IQVIA's analysis of private sector generic penetration in South Africa, 2014-2021. Copyright IQVIA. All rights reserved.

preference for international brands.[62] Therefore, the model assumes an average market share of 10 percent in the FP2020 SSA countries, which is half of what is assumed for South Africa.

Agency and Marketing Costs

As noted in Table 1, agency and marketing activities constitute approximately 23 percent of operational costs. Agency and marketing activities include helping to work with the national regulatory authority to register the product, acting as the marketing authorization holder or local trade representative in the country, marketing the product into the private sector, and submitting tenders to the relevant authority when appropriate. A Kenyan distributor with experience in marketing hormonal contraceptives suggests such activities might cost 15 percent of the price charged to pharmacists for the product. In the private sector in South Africa, stakeholders suggest a higher fee of 30 percent. The public sector fee for agency and marketing services in South Africa may be closer to 15 percent. These figures are used in the model.

Interest and Loan Repayment

The model assumes it will take three years to build and commission the factory,[63,64] two years to receive local registration,[65] two years to gain WHO prequalification,[66] and one year to register the product in all other relevant countries through the WHO Collaborative Procedure process for prequalified products.[67] In other words, it assumes the product could be launched in more than one country in the ninth year following the beginning of construction. Funding is required to cover the costs incurred during years 1-8. The model assumes 50 percent of the required funding would be sourced from a development bank and the remaining 50 percent from another source. This other source could be a manufacturer or, perhaps, an impact investor. Impact investors invest with "intention to generate positive, measurable social and environmental impact alongside a financial return."[68] Some impact investors accept below-market returns.[30]

The Ethiopian Development Bank will lend a maximum of 50 percent, [69] although the Kenyan Development Corporation will lend up to two-thirds of the capital required.[70] The interest rate charged for pharmaceutical manufacturing investments in Ethiopia is 8.5 percent, which is used in the model. The model assumes the loan must be paid back within 15 years, with repayments beginning in year nine (the first year of assumed sales).

Construction and equipment costs drive the size of the initial loan. The model assumes the MPA-IM manufacturing facility to be a dedicated building on a site already operating as a pharmaceutical factory. A separate, dedicated facility is compatible with WHO guidelines[71] and represents the lowest cost option, with some costs and staff shared across other pharmaceutical manufacturing activities on the site. Construction costs are estimated at approximately $1,470 per square meter. This amount is almost twice

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[62] Adebis YA, Nwogu IB, Alaran AJ et al. Revisiting the issue of access to medicines in Africa: Challenges and recommendations. Public Health Challenges, 15th June 2022. https://doi.org/10.1002/puh2.9

[63] CiplaQCIL. Presentation. West African Medicines Regulatory Harmonization (WA-MRH). Key Milestones. Provided by USAID.

[64] Interview with local sterile injectable manufacturer in Ethiopia

[65] GHSC-PSM. Personal Communication

[66] Hodges EU, Crissman K, Hsiung P, Kenol P, Nishi JB, Silimperi D and Udayakumar. Navigating complexity to improve global access: Supporting a more efficient and effective World Health Organization prequalification programme. August 2022. Duke Global Health Innovation Centre and Global Health Technologies Coalition.

[67] Doerr P. Presentation. Overview of collaborative procedures and initiatives to register therapeutic products. 23rd February 2021. https://www.shareweb.ch/site/Health/aboutus/Documents/Online-events-documents/4_WHO_Overview%20of%20collaborative%20procedures%20and%20initiatives%20to%20register%20therapeutic%20products.pdf. Accessed 6th July 2023.

[68] Global Impact Investing Network. What is impact investing? https://thegiin.org/impact-investing/need-to-know/#what-is-impact-investing. Accessed 14th August 2023.

[69] Development Bank of Ethiopia. A short guide to access DBE's loans. https://www.dbe.com.et/BusnessPromotion/Policy/DBENewPolicyEng.pdf Accessed 6th July 2023

[70] Kenya Development Corporation. https://kdc.go.ke/loan-facilities/. Accessed 6th July 2023

[71] Fabio P et al. The requirements for manufacturing highly active or sensitising drugs comparing Good Manufacturing Practices. Act Biomed 2019; (90(2): 288-299.

that reported in one 2023 study[72] for a high technology factory/laboratory in Nairobi and 16 percent higher than the costs of building a heavy-duty factory in Nairobi in 2022, according to another study.[73] Equipment costs are based on supplier price lists.

Time to launch is also a key driver of the loan amount due to the need to fund the site before any revenue earnings. While the time for registration through the Collaborative Procedure for WHO-prequalified products appears relatively consistent within one year, published data and interviews suggest that the time from construction to WHO prequalification can vary. As noted above, the model assumes that product launch will take up to nine years.

Technology Transfer Fee

The challenges of achieving WHO prequalification are well documented.[74] The challenge for an injectable hormonal manufacturing facility located in SSA may be even greater since there are no such facilities currently in SSA. Moreover, none of the existing parenteral manufacturers have experience with the WHO prequalification process. It is important to note that in an interview with one international manufacturer with experience in contraceptive manufacturing described hormonal product manufacturing as being similar in complexity to vaccines.

Therefore, the model assumes the facility requires support (such as dossier preparation, training of production staff and supervision) from an existing injectable contraceptive manufacturer. Stakeholders interviewed suggest that equity in the company or a fee (estimated at 8 percent) would be required in exchange for such support. For ease, the model assumes an 8 percent fee.

Salaries

Due to the challenges of achieving WHO prequalification and manufacturing hormonal products, the model assumes certain positions will be staffed with experienced expatriates. These positions include Technical Manager, Production Manager, Production Supervisor and Production Operator (also see Annex 2). Salaries for expatriate and local staff are gleaned from stakeholder interviews.

Two shifts per day are assumed in the model. The impact of running two shifts rather than one is shown in Annex 2.

API and Excipients

The list of required API and excipients for MPA-IM manufacturing is sourced from secondary literature.[75] API and excipient prices were sourced from available 2019 Indian import and export data. The price of MPA-IM used in the model is the average of that exported by a WHO-prequalified API supplier to a WHO-prequalified manufacturer in 2019, inflated by 10 percent (to $765 per KG). This price closely matches the price calculated from anonymised Indian import data concerning supplies from the same country from 2013 to 2016.

Packaging

Prices for a 1ml vial with rubber stopper and flip-off cap were sourced from an international vial manufacturer supplying multiple multinational pharmaceutical companies. Two different-sized cartons were priced. Shipment information indicates that the bulk of donor-funded shipments are packed in a carton of 20 vials, while private sector volumes tend to be packed as one vial per carton. For pricing

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[72] Integrum Construction Managers. Construction costs in Kenya 2023. Building rates per square metre/Ft, March 20th, 2023. https://integrum.co.ke/construction-costs-in-kenya-2023/

[73] Statista. Industrial building costs in African cities as of July 2022, by building type. www.statista.com. Accessed 11th August 2023.

[74] Hodges EU, Crissman K, Hsuing V et al. Navigating complexity to improve global access. Supporting a more efficient and effective World Health Organization prequalification program. Duke Global Health Innovation Centre and the Global Health Technologies Coalition (GHTC). August 2022.

[75] World Health Organisation. Additional guidance on submission requirements for medroxyprogesterone acetate depot injection products using the Common Technical Document (CTD format). 01 August 2015.

purposes, it is assumed that 80 percent of the volume would be packed 20 vials per carton and 20 percent of the volume with one vial per carton. An additional 10 percent was added to these prices to cover the patient leaflet and export carton cost. Stakeholder interviews suggest the cost of the patient leaflet is negligible, with an average unit cost of $0.00095, according to manufacturer interviews.

Insurance and Distribution to Port

USAID, the major funder of contraceptive commodities to SSA, pays for the transport of the product from the manufacturer's facility, insurance during transport, customs clearance and delivery to the final destination. In some cases, the costs described above may include warehousing. However, the model includes an allowance for insurance and distribution to the port in the host country. This is based on a published survey of 24 Kenyan manufacturers, using the ratio between the cited transport costs and other costs (API and excipients, labor, packaging, utilities and maintenance).[76]

Inflation and Country Investment Incentives

The model assumes that both product prices and input prices rise by the same amount over the model period and, therefore, are not impacted by inflation. This may not be the case in reality. Estimating product prices and input prices over 20 years is challenging. However, if the model underestimates the effect of inflation, it is important to note the model is rather conservative in other respects. First, the model assumes no volume growth (as explained above) despite evidence that injectable volumes will increase by 3.9 percent on a CAGR basis between 2019 and 2030. Second, the model does not include tax and/or other incentives available to those investing in pharmaceutical manufacturing in SSA. Expatriate salaries are, for example, subsidized for five years in Ethiopia, and Ethiopia and Kenya offer tax holidays or time-limited tax reductions, particularly for those able to invest in the industrial parks.

[76] Vugigi SK. Assessment of the pharmaceutical manufacturing industry in Kenya to forecast local production sufficiency. Thesis, School of Pharmacy of Kenyatta University. October 2017 http://ir-library.ku.ac.ke/handle/123456789/18353. Accessed 15 September 2019.

Annex 2: Model Inputs

Costing Element	Area	Detail
Equipment and Design Costs	Engineering Works	Concept and detailed design
	Construction	Civil and architectural works
	Mechanical, Electrical and Plumbing Works (Material + Installation)	Clean utilities (e.g., HVAC, water, clean compressed air), black utilities (e.g., chiller, boiler, compressor), high and low voltage supply, control systems, etc.
	Water System	Purified water + storage, water for injection + storage
	Filling Line	Preparation (preparation and transfer vessels), filling and packaging (vial washing, depyrogenation, filling machine, capping machine, labeling machine, cartoning), ancillary equipment (e.g., autoclave)
	Quality Control Laboratory	Apparatus, equipment, utensils, stability equipment, accessories
	Cleanroom Fittings	Walls, ceiling, doors/windows, flooring, benches etc.
	Warehouse	Racking system, loading equipment etc.
	Validation	Qualifications
Costing Element	**Area**	**Comment**
Production Capacity	Active Days per Year	300 days
	Active Hours per Shift	Up to 3 shifts per day
	Effective Hours per Shift/Production	Assume 5 hours per shift to account for cleaning
	Effective Hours per Shift/Packaging	Assume 6 hours per shift
	Efficiency Factor - Liquid Vial Filling	Efficiency factor refers to realisable activity level versus theoretical capacity of equipment
	Efficiency Factor - Packaging Line	Efficiency factor refers to realisable activity level versus theoretical capacity of equipment
	Liquid Vial Line - Preparation Vessel, Batch Capacity	Taking into account efficiency factor
	Vial Filling Line - Output per Hour	Taking into account efficiency factor/2 shifts in campaign mode
	Vial Filling Line - Output per Year	Taking into account efficiency factor
	Purified Water Production Capacity	

	Purified Water Storage Capacity	
	Water for Injection - Production Capacity	
	Water for Injection Storage Capacity	
	Facility Sizing	Production Unit (sterile): 350 square meters; Packaging Unit (sterile) 300 meters; Warehouse 300 meters
	Vial and API Wastage - as a Percentage of Target Volume Following Launch	
	Estimated Electrical Consumption - Mega Watt Hours (MwH)	
	Estimated Yearly Water Consumption	
Costing Element	**Detail**	**Comment**
Product Costs	API - MPA	2019 price, inflated by 10%
	Excipient - Polyethylene Glycol 3350	
	Excipient - Polysorbate 80	
	Excipient - Sodium Chloride	
	Excipient - Methyl Paraben	
	Excipient - Propyl Paraben	
	Water for injection	
	Excipient - Hydrochloric Acid for pH adjustment	
	Excipient - Sodium Hydroxide for pH adjustment	
	Vial + Carton A	1 vial/stopper/cap, 1 vial per carton
	Vial + Carton B	20 vials/stopper/cap per carton, price associated with each vial
Costing Element	**Position**	**Number of additional staff needed to run shared facility for 2 shifts**
Staff Costs	Technical Manager (Expatriate)	1
	QA Officers (Local)	3

	QC Officers (Local)	4.5
	Production Manager (Expatriate)	1
	Production Supervisor (Expatriate)	2
	Packaging Supervisor (Local)	2
	Operators (Expatriate)	9
	Maintenance Technician (Local)	2
	Warehouse Operators (Local)	2
	Janitors (Local)	1
	Security Personnel (Local)	1
	Human Resource Officer (Local)	1
	IT Officer (Local)	1
	Logistics Procurement Assistant (Local)	1
	Miscellaneous (Local)	2
	Regulatory Affairs Supervisor (Local)	1
	Business Developments (Local)	1
	Accounting/Finance Assistance (Local)	1
Costing Element	**Detail**	**Comment**
Utilities/Land Rental	Electricity	Subsidized in Ethiopian industrial parks. 2018 price $0.03, 2021 price $0.045.
	Water	Highest tariff for Ethiopian industrial park used (11.6 Ethiopian birr)
	Land Rental	Based on 850 square meter site, average price 2019-2050, Ethiopian industrial park
Costing Element	**Detail**	**Comment**
Miscellaneous	Inspection - WHO Prequalification Fee	1 product line - registration fee
	Inspection - WHO Prequalification Fee	1 product line - annual fee
	Inspection NRA Fee	38 countries, 1 product line
	Registration - FP2020 SSA Country	38 countries, 1 product line

	Registration - South Africa	1 country, 1 product line
	Retention - FP2020 SSA Country	38 countries, 1 product line
	Retention - South Africa	1 country, 1 product line
	Bioequivalence Study	Based on published protocol for MPA-IM approved by WHO
	IT system per annum	
	Site Insurance per annum	
	Repair and maintenance	Increases with age of equipment
Costing Element	**Detail**	**Comment**
Marketing and Distribution	Agency for marketing, warehousing and distribution in FP2020 SSA	
	Agency for marketing, warehousing and distribution in South Africa	
	To domestic port of exit only (as other costs taken by donor or by agent)	Expressed as % of cost of raw materials, packaging, labor, utilities and maintenance
Costing Element	**Detail**	**Comment**
Finance	Percentage of capital requirements to be loaned by Development Bank	Development Banks will not loan 100% of the requirements. Set thresholds (50% Ethiopia, 67% Kenya)
	Percentage annual interest charged by Development Bank	Pharmaceutical investments often offered better rates, as in Ethiopia
	Depreciation/replacement fund - structure	Guidance suggests 39 years for most construction elements
	Depreciation/replacement fund - equipment	Guidance varies from 5 (compressors) to 39 (e.g., HVAC) years to 5 years for technological equipment, regardless of actual class life. An average of 15 years is assumed, particularly given minimal usage over the first 9 years from purchase.
	Fee for technology transfer	Expressed as % of revenues
Costing Element	**Detail**	**Comment**
Market Size and Growth	Product scope	MPA-IM formulation
	Geographic scope	FP2020 countries + South Africa

	Market growth	Injectable market size at 2030 as shown in RHSC LEAP report kept constant for model horizon
	Share of MPA-IM of injectable market	MPA-SC not yet launched in South Africa, but model assumes it will be
	Market shares - FP2020 SSA (Donor volumes)	4-5 other prequalified suppliers
	Market shares - FP2020 SSA (Private sector)	
	Market share - South Africa (Public sector)	
	Market share - South Africa (Private sector)	
	Price - FP2020 SSA (Donor volumes)	
	Price - FP2020 SSA (Private sector volumes)	
	Price - South Africa (Public sector)	
	Price - South Africa (Private sector)	
	Price - South Africa (Public sector)	
	Price - South Africa (Private sector)	