Strategic Insights For New Vaccine Manufacturing Initiatives

Bridie Telford, Thomas Johnston, Reid Adler and Julia Barnes-Weise

Global Healthcare Innovation Alliance Accelerator

April 2022

Introduction

As we enter the third year of the COVID-19 pandemic, there is a ten-fold difference in administration of vaccine doses between higher- and upper-middle income countries and low-income countries, and the WHO interim goal of 40% vaccination by the end of 2021 was missed by 90 countries. There is a range of underlying factors contributing to the stark global contrasts in vaccination rates, including inadequate local infrastructure and funding for managing mass vaccination campaigns, vaccine hesitancy and a lack of timely access to vaccines, the latter being the focus of this paper.

The issues that have contributed to the disparity in access to COVID-19 vaccines between higher- and lower-income countries include:

- The greater negotiating power of the governments of higher-income countries to purchase early access to multiple vaccines, based on existing relationships with vaccine developers (particularly in the U.S.);
- The greater of availability of funds for higher-income countries to make early, at-risk investments in a portfolio of vaccines through development funding and advance purchase agreements;
- A global funding mobilization failure, leaving COVAX under-resourced to negotiate timely vaccine supplies for the countries that were unable to negotiate their own bilateral agreements;
- The reliance of lower-income countries on imported vaccines due to insufficient local and regional manufacturing capabilities. This has been particularly true of the African continent, which imports 99% of its total vaccine supplies; and
- An unwillingness or delay on the part of many vaccine developers to share their proprietary know-how with manufacturers in low- and middle-income countries.

In February 2022, COVAX reported for the first time that it had more vaccines available to distribute than were requested by the 92 AMC eligible countries. However, the vaccines being made available now are not necessarily the most suitable or preferable for use in lower-resource settings. Further, the supply of vaccines now does not compensate for the lack of timely and predictable supplies to low- and middle-income countries throughout the pandemic. Unpredictable COVAX delivery timelines and supplies of almost-expired vaccine doses have compounded the challenges of managing mass vaccination campaigns faced by many countries. As some countries begin recommending second booster doses, and work continues to develop vaccines against emerging variants, there remains a strong need to not only address the near-term availability of COVID-19 vaccines, but also timely, affordable and appropriate vaccine availability for lower- and middle- income countries for future disease outbreaks.

Rather than buying vaccines manufactured in high-income countries (whether through COVAX, bilateral purchase agreements and/or pooled procurement arrangements), a more effective path to satisfying long-term vaccine requirements may be to expand the ability of underserved regions to manufacture vaccines themselves. This can be achieved through building

manufacturing partnerships with existing vaccine producers, as well as by developing the capacity to manufacture novel vaccines independently.

The purpose of this paper is to offer a framework for assessing regional manufacturing capacity building opportunities to address the problem of insufficient and delayed vaccine supplies that many countries have experienced during the COVID-19 pandemic. The analysis in this paper has a particular emphasis on Africa, which has heavy reliance on vaccine imports and where the majority of countries are currently at risk of missing the target of vaccinating 70% of the population against COVID-19 by September 2022. This discussion is intended to provide strategic insights and some examples for potential vaccine manufacturers and for the funders who seek to facilitate production and equitable distribution of COVID-19 and other vaccines.

Part I: Strategic Planning

Any country, organization or funder contemplating building new or expanding existing manufacturing capacity (a "new manufacturing initiative") should consider beginning with a comprehensive baseline capability assessment and establishment of a clear set of goals. The assessment framework outlined below sets out some key strategic planning considerations organized into four main steps:

1. Assess current vaccine manufacturing capabilities
2. Identify target outcomes in the context of national and regional vaccine production needs
3. Identify essential resources and conduct a gap analysis
4. Develop and implement capacity building plans

Step 1. Assess Current Vaccine Manufacturing Capabilities

This step requires a thorough assessment of the current state of vaccine manufacturing readiness. The perspectives of both the manufacturing facility and the country (or region) that it plans to supply are important inputs to this process. The assessment should include a review of:

- The potential uses of existing facilities and current equipment available to the manufacturing entity, as well as the potential for retrofitting or expansion, in order to reduce the time to implementation of new activities.
- The current level of expertise and capabilities including staff qualifications, GMP certifications and experience in manufacturing other vaccines, all of which are critical for the success of a new manufacturing operation;
- Existing partnerships with other entities in the vaccine space, at the organizational or country level. Multiple partnerships are needed to support the successful development and manufacturing of a vaccine. These may include alliances with non-profit or multilateral organizations as well as agreements for the licensing, manufacture and/or supply of other products.
- The new manufacturing initiative's ability to access the raw materials and packaging supplies needed for vaccine manufacturing taking into account the location of suppliers, potential import/export restrictions and known challenges with constricted supply chains.
- The availability of existing funding and potential for securing additional funding to support building the capacity and capabilities needed for the success of a New Manufacturing Initiative.
- The level of health systems support available in the country or region, including the capacity of a local regulatory authority to make inspections and license products, distribution and cold chain networks, and local capacity for managing vaccination

campaigns. Local health systems support is an important consideration for assessing the regulatory pathway for licensure of a product in a facility as well as likely distribution channels for the vaccines that the facility produces.

Step 2. Identify Target Outcomes

Having reviewed their current capabilities, new manufacturing initiatives should proceed to the development of a well-defined set of goals. This step is essential to be able to assess the gap between existing and required resources, such as manufacturing and production equipment, and trained personnel to plan, upgrade and operate the facilities.

A basic consideration for all potential projects is "what are you going to make", for example, an mRNA vaccine, recombinant protein vaccine or a subunit vaccine. This question goes beyond deciding to manufacture a COVID-19 vaccine to considering the underlying technology platform that will be used to manufacture the vaccine and the profile of the resulting product. For example, the requirements of controlled storage temperatures have been particularly problematic for some types of COVID-19 vaccines. It has been reported that 44 of the African Union's 55 member states do not have sufficient refrigerators, freezers and other cold-storage infrastructure for distribution of the Pfizer-BioNTech mRNA vaccine.

Consideration of the technology that a new manufacturing initiative wants to use relates to a question of the broader range of vaccines, other than those against COVID-19, that they might plan to develop or manufacture in the longer term. The selection of a platform technology to be used in a facility is a key factor in determining the mix of products that it might be able to produce. This decision also requires an assessment of the current landscape and needs of the country or region that the initiative plans to supply from short to long term. Looking to the African continent, Partnerships for African Vaccine Manufacturing's (PAVM) goal of manufacturing 60% of Africa's vaccine supply on the continent by 2040 will mean that there should be a need (and buyers) for routine childhood vaccines as well as vaccines to respond to disease outbreaks, for example Ebola (or Disease X). PAVM's Framework for Action identifies a critical need for vaccines against 22 diseases. Use of platform-based manufacturing provides a greater opportunity for producing vaccines against multiple diseases, potentially at a lower-cost in the long term. New manufacturing initiatives will need to understand and plan their role in supplying their selected vaccine(s) in their chosen markets in the context of broader regional vaccine plans, policies and politics.

A further assessment to be made by new manufacturing initiatives is of the different stages of the manufacturing process they could undertake and determine the approach that will best fulfill their goals, as well as regional and national needs. In some cases, the desired outcome may be performing the final manufacturing stage of fill/finish (i.e., taking bulk vaccine drug substance supplied by a third party and filling it in the final container along with labeling, packaging and final inspection). Other initiatives may set a goal targeting the more complex process of producing vaccine drug substance, and others still may be aiming to develop novel vaccines instead of, or in addition to, manufacturing vaccines developed by third parties.

Step 3. Identify Essential Resources and Conduct a Gap Analysis

The next step in the planning process is for new manufacturing initiatives to perform a detailed evaluation of the essential resources needed to achieve their target outcomes (see Figure 2) and where there are gaps in their current capabilities. This step is key to ensuring that the facility will have a critical mass of the following items:

- Enough people with the necessary training and expertise for manufacturing the target vaccine(s) for the facility;
- A quality management plan for manufacturing to a standard that will satisfy the requirements of regulatory authorities;
- Qualified and available facilities that can accommodate all necessary equipment and maintain compliance with stringent biosafety requirements;
- Sufficient and sustainable sources of funding from grants, loans and advance purchase commitments;
- The partnerships and agreements needed to secure access to key manufacturing inputs (e.g., raw materials, intellectual property); and/or
- A regulatory strategy including engagement with the relevant regulatory authorities for the site inspections, product licensures, and batch releases required for the finished vaccine to be approved for use in the target market(s).

Step 4. Develop and Implement Capacity Building Plans

This step is essential in order to ensure that the facility has a detailed plan for the activities needed to produce a vaccine. Figure 1 below provides an overview of the critical resources needed for fill-finish operations and drug substance manufacturing, as well as building vaccine development capabilities; these are described in more detail in the next section of this document.

Figure 1: Essential resources for vaccine manufacturing

Part II: Essential Resources for Vaccine Development & Manufacturing

Facility and Equipment

A vaccine manufacturing facility requires land and buildings with reliable access to utilities such as water and electricity. Implementing a drug substance manufacturing process requires isolated areas, or 'suites', that are compliant with current Good Manufacturing Practices ("cGMP" i.e. meeting regulatory requirements for the methods, facilities, and controls used in manufacturing, processing, and packing), clean rooms and containment rooms for cell culture production, vaccine production and purification. Each drug substance manufactured generally requires its own isolated area, therefore a single facility is likely to need several suites in order to maximize its opportunities to partner with multiple developers. A fill-finish facility that focuses on the final stages of vaccine manufacturing requires areas for buffer preparation, vaccine formulation, aseptic filling into final containers, and packaging, labeling and quality control. The demands on facility space will further multiply for a new manufacturing initiative that plans to take on the full lifecycle development of a novel vaccine candidate as additional development and manufacturing suites will be needed to enable work on multiple candidates.

The facility must also be fitted with multiple and diverse pieces of capital equipment depending on the type(s) of vaccine that will be produced and the manufacturing activities to be performed. The equipment requirements range from specialized assembly line equipment for fill-finish activities to bioreactors, filtration pumps and chromatography equipment for upstream and downstream drug substance manufacturing. Each vaccine produced at a manufacturing facility must have its own specialized and dedicated equipment, therefore the equipment requirements grow as the facility's activities expand.

Key Considerations

- Specialist contracting: The process for building and equipping a manufacturing facility is complex and requires specialist expertise. This starts with the conceptual and detailed design which is usually contracted to an expert consulting organization, followed by engagement of an engineering firm to manage the implementation of the detailed design. An additional engineering firm is often used to validate the successful implementation of the build and operability of the equipment. Further contracts will also usually be needed with firms that can carry out construction, electrical work, equipment installation, and other specialist activities, including ongoing maintenance.

- Logistics: The specialist nature of vaccine manufacturing equipment means that there is a small number of suppliers and a potential for long lead times for delivery of the equipment. For an initiative looking to build manufacturing capacity in Africa, it is likely that equipment will have to be imported from the U.S. or Europe, and therefore import/export clearance and shipping arrangements need to be incorporated into planned construction timelines. Where there is a need to import high-cost capital equipment, new manufacturing initiatives should also consider their exposure to foreign exchange risk and ensure they have adequate funds available in the right currency to make any advance payments required by the equipment supplier.

- Flexibility: Manufacturing facilities come with high fixed costs, therefore it is important that a new manufacturing initiative considers the space required for its planned production volume. Too much space could result in an unsustainable level of overhead costs, but too little could mean lost opportunities for new partnerships or additional production volume (and therefore lost revenue).

  This consideration may be particularly important for new manufacturing initiatives planning to start their operations with fill-finish activities and expand to drug substance manufacturing operations further down the line - they will need sufficient space for expansion whilst not incurring the costs to maintain unused capacity. Innovative new facility designs, such as the modular approach being applied by Institut Pasteur de Dakar's MADIBA project can be considered as a way to address this challenge.

Raw Materials

Vaccine manufacturing requires consistent supplies of a substantial number of raw materials. For a new manufacturing initiative conducting fill/finish activities, there are critical raw materials, in addition to the drug substance to be filled, which include glass vials (or an alternative form of final container for the vaccine), and packaging materials such as stoppers, seals and labels.

The number of materials required for drug substance production or development of a new vaccine candidate expands rapidly. For example, the manufacturing process for the Pfizer/BioNTech vaccine requires a total of 280 materials sourced from 86 suppliers. As with the materials required for fill/finish operations, the raw materials required are subject to constricted supply chains. Examples of critical materials[1] for drug substance manufacturing include cellular material, bioreactor bags, filters, adjuvants, lipids, preservatives and excipients. Raw materials sourcing for developing a new vaccine candidate becomes even more complex due to the different variations of materials that are combined in early experiments in order to eventually create a stable and effective candidate.

Key Considerations

- Supply chain management: All manufacturing organizations need to ensure that they have supply contracts in place with third parties for each of the raw materials that it needs for its operations. Each component will need to be sourced from a reliable vendor with established quality management systems and incorporated into the manufacturer's procurement management systems for order, delivery and cost tracking. New manufacturing initiatives also need to consider the full complexities of the supply chain, including obtaining cross-border supplies and the need to manage associated customs, shipping and warehousing arrangements.

  The volume of raw materials purchased also has an impact on cost and risk. Ordering in larger volume from a single supplier can reduce cost but increase risk exposure to supply interruptions, whereas spreading the supply risk over multiple vendors is likely to result in smaller order volumes at an increased cost.

- Proprietary materials: A number of the raw materials used in manufacturing certain vaccines, for example lipid nanoparticles (LNPs) for mRNA vaccines and adjuvants for other vaccine types, are specific to a particular vaccine or type of vaccine. These materials have their own inputs, adding a further "mini supply chain" to the already complex picture. Further, LNPs and adjuvants may be proprietary to a developer or a third party, therefore potentially requiring a license for use in a final product as well as contracted supply volumes.

[1] Also see New COVID Vaccines Need Absurd Amounts of Material and Labor and Landscape of Current COVID-19 Supply Chain and Manufacturing Capacity, Potential Challenges, Initial Responses, and Possible "Solution Space" - a Discussion Document

- Opportunities for local supply chains: During the COVID-19 pandemic, there have been shortages of such materials across the supply chain which have had a negative impact on companies' ability to rapidly expand vaccine production. Some governments, for example the U.S. government, used policy initiatives in order to increase the timely availability of inputs for manufacturing vaccines for the U.S. market. In particular, use of the Defense Production Act to prioritize the supply of raw materials to U.S. vaccine developers may have helped to improve the availability of materials for one market, but reportedly had a detrimental effect on the efforts of manufacturers in other countries. While there are ongoing efforts to guard against nationalistic approaches such as those used by the U.S. government, the risk of supply restrictions for future health emergencies will remain. A coordinated approach to the vaccine supply chain across Africa, taking a "whole of Africa approach", is an opportunity to improve supply chain resilience as well as having the potential to decrease raw materials costs.

  The need for such an "integrated ecosystem approach" is highlighted as part of the Partnerships for African Vaccine Manufacturing (PAVM) Framework for Action to be able to meet the goal of manufacturing 60% of Africa's vaccine supply on the continent by 2040. This effort will require collaboration, coordination and sustained funding across multiple countries and companies to ensure a detailed understanding of supply chain needs and capabilities, which may evolve over time, as well as a reduction in barriers to intra-continental trade.

Human Resources

It is critical that any new manufacturing initiative planning recruits and retains a broad range of skilled personnel. Some of the major business areas requiring highly trained people are:

- Vaccine manufacturing - including individuals responsible for the oversight and coordination of vaccine manufacturing as well as a technical team able to undertake technology transfer activities and operate the facility and equipment to produce the final vaccine product in accordance with the required specifications.
- Procurement - including individuals responsible for managing material supplies requirements and designing and implementing a procurement and inventory management system
- Clinical development - including individuals responsible for designing and implementing a strategy for the clinical trials needed both to demonstrate vaccine safety and efficacy, and to obtain regulatory approvals.
- Quality management - including individuals responsible for incorporating quality requirements into the planning process and the implementation and monitoring of quality management systems.A larger quality assurance and quality control team will be needed as an initiative expands into drug substance manufacturing and vaccine development.

- Regulatory affairs - including individuals responsible for engagement with regulatory authorities. A Qualified Person may also be needed to review the complete vaccine manufacturing process documentation for compliance with cGMP, the predetermined product specifications and regulatory requirements.
- Business and commercial operations - including strategic advisors to assist with sustainability planning and outreach to investors and funders as well as business development, contract negotiation, sales, marketing, analytics and finance personnel

Key Considerations

- Resource availability: The COVID-19 pandemic has highlighted the limited global pool of vaccine manufacturing personnel. Even well-established vaccine manufacturers found their resources stretched. For example, Pfizer reported relying on two staff members for technology transfer activities. Similarly, one of Moderna's major manufacturing partners, Lonza, reported that manufacturing was being delayed due to a shortage of skilled local workers in Switzerland. This challenge is greater in lower-income countries where manufacturers are likely to need to fill some roles with expatriate staff at higher salaries.

- Opportunities to develop local resources: The PAVM Framework for Action provides analysis of the significant scale-up of personnel required on the African continent to meet the goal of manufacturing 60% of Africa's vaccine supply on the continent by 2040. The Framework includes a plan to create regional "Capability and Capacity Centers" to both develop and retain local talent in Africa as well as recruiting experienced staff from the diaspora. The WHO is also establishing technology transfer and training hubs in Africa, South America and Asia in order to provide lower-income countries with the training and know-how needed to manufacture vaccines. Both new and existing manufacturing organizations will need to engage with these efforts in order to contribute to the sharing of existing knowledge as well as finding training opportunities.

Access to Patents & Proprietary Information

Many vaccines are protected by patents, which may cover the complete vaccine, or specific vaccine components, such as LNPs and adjuvants. However, vaccine developers do not file patents in all countries, as can be seen from the VaxPal database for COVID-19 vaccines published by the Medicines Patent Pool. For example, there are notably few pending patent applications or granted patents in African countries, with the main exception being South Africa.

Before beginning manufacturing operations for a particular vaccine, New Manufacturing Initiatives will need to determine whether any specific patents might present a business risk (that is, patent infringement liability) in the country where their products would be manufactured or sold. Evaluating patent risk is a standard business assessment routinely undertaken by pharmaceutical enterprises, including generic product manufacturers, particularly in high income countries and in a few middle income countries (such as India). Evaluating the relevance

and availability of patent rights is similar to the kind of assessment that must be made regarding the availability of components of the vaccine itself.

Notably, in some instances, even the limited number of applicable patents may not be enforced by the patent owner. For example, with regard to mRNA vaccines, Moderna recently stated that it will never enforce its COVID-19 patents for vaccines manufactured solely for use in the 92 LMICs covered by the Gavi COVAX Advanced Market Commitment. Other potentially relevant patents might be waived pursuant to ongoing negotiations by the World Trade Organization under the TRIPS Agreement.

Aside from patent rights, having access to proprietary information (such as manufacturing know-how, standard operating procedures (SOPs), production management software systems and regulatory documentation) is almost always essential for a new vaccine production facility in any country in order to achieve efficient and cost-effective manufacturing. Assessing the need for such resources and identifying sources from which to obtain them is part of the initial strategic planning and gap analysis process.

New manufacturing initiatives that want to manufacture a vaccine developed by a third party (whether fill-finish, drug substance manufacturing, or both) usually obtain access to relevant proprietary information and patent rights if needed, through a partnership with an existing vaccine developer. Such a partnership may be in the form of acting as a Contract Development and Manufacturing Organization (CDMO) on behalf of the developer, or under a license agreement.

Under a CDMO agreement, a manufacturer that is the recipient of a technology transfer is usually paid to produce the drug substance or to fill and finish a vaccine for the developer, whereas a license agreement is more likely to allow the recipient to manufacture the vaccine as its own product which it would then sell to its own customers, while also taking on more of the financial risk in return for a greater portion of the revenue.

A technology transfer for fill-finish operations should include the know-how for the final stages of manufacturing, as well as access to trained staff and their expertise to establish the necessary processes at the recipient's facility. For drug substance manufacturing, the transfer should include manufacturing know-how, access to trained staff, detailed specifications for the raw materials required, testing protocols, production data and clinical data. Typically, access to improvements in the technology would also be transferred over time to obtain the benefits of efficiency.

In contrast, when a new manufacturing initiative intends to develop its own vaccine candidate independently, it will not have access to the information and rights afforded by a partnership with an existing developer. Accordingly, there will be a heightened need to determine the risk of infringing any patents, and new manufacturing initiatives will need to have built up their own know-how, SOPs and other proprietary information. Where new manufacturing initiatives determine that there is a patent infringement risk, access to the relevant rights and proprietary information could potentially come from pooled licensing mechanisms such as the COVID-19 Technology Access Pool although only if such initiatives receive sufficient contributions from

patent holders. Alternatively, a license from the patent owner to use those patent rights may be available through a license agreement, or there may be ways to modify a product to avoid infringement.

Key Considerations

- Building partnerships: To secure a partnership with a vaccine developer, whether acting as a CDMO or obtaining protected information through a licensing arrangement, a new manufacturing entity first needs to ensure that it has developed a credible business plan and quality management system, in order to convince the developer that the facility is capable of meeting both quality and timeline requirements. Following this, new manufacturing initiatives can conduct an outreach program to identify potential interested parties. This program might involve connections and matchmaking via global health funders (e.g., CEPI), existing partners, and organizations such as GAVI. Manufacturers need to secure a portfolio of partnerships and products to ensure that they have a sustainable source of revenue, although this must be balanced carefully against the available capacity of the facility, particularly during the initial set-up and technology transfer stage for a new vaccine, which is usually highly resource intensive.

  For a new manufacturing enterprise, beginning a partnership as a fill-finish manufacturer can provide a foundation for building trust with a particular vaccine developer and establishing a wider reputation as a reliable business partner. Using this approach, a new manufacturing initiative can build on its initial fill-finish operations and add drug substance manufacturing capabilities so that it is able to conduct the end-to-end manufacturing process. The experience and know-how obtained through manufacturing vaccines for other developers will also be valuable if the initiative aims to develop its own vaccine candidates in the long run.

- Agreement terms and their impact on target outcomes: The negotiation of terms for licensing or CDMO agreements with vaccine developers need to be considered in the context of the manufacturer's strategy for achieving its target outcomes. Some of the key questions for new manufacturing initiatives receiving a technology transfer to consider are:
  - *Who decides where the product can be sold?* As discussed above, under a CDMO arrangement, the vaccine developer will be responsible for determining the final customer for the finished vaccine product. This may not contribute to increasing the availability of vaccines in Africa. For example, Aspen Pharmacare in South Africa produced COVID-19 vaccines under a contract arrangement with J&J which resulted in prioritization of deliveries to Europe ahead of African countries. However, this partnership could still have contributed to short-term goals of building experience and trust, as well as generating revenue. Further, J&J has now agreed to a fill-finish licensing deal with Aspen, which allows Aspen to determine the price and distribution of the final product.

- *What factors will impact the price of the finished vaccine?* As well as deciding where the product will be sold, it is more likely that a vaccine developer will have control over the final price of the finished vaccine under a CDMO arrangement than under a licensing agreement. However, under a license agreement, new manufacturing initiatives intending to supply lower-income markets will need to ensure that the payments required in exchange for the license grant (and the drug substance in the case of a fill-finish license) will not impact their ability to offer the final product an affordable price for the final product. The payments that might have to be made, and factored into the total cost of goods for the vaccine, could include an upfront "technology access" license fee, milestone payments and/or royalties calculated as a percentage of sales revenue. Manufacturers might consider whether they can negotiate lower royalty rates for sales to the lowest-income countries or to public sector purchases, to help to support a lower pricing strategy. Some license agreements have also allowed for royalty-free sales during the COVID-19 pandemic.
- *Is there a detailed technology transfer plan?* New manufacturing initiatives should verify that the technology transfer terms of an agreement contain sufficient details of the obligations of both parties to ensure the success of the transfer. An example of a detailed technology transfer provision might include the designation of technology transfer leads from each party, access to sufficiently qualified personnel, provision of technical assistance after completion of the transfer, and a set of success criteria to be fulfilled.

Quality Management

Another critical component of vaccine manufacturing that is not well known outside of the biopharmaceutical industry itself is that of quality management. This requires the implementation of stringent controls over factors such as purity and sterility throughout the manufacturing process to ensure the safety and effectiveness of the finished vaccines. As explained in an International Federation of Pharmaceutical Manufacturers & Associations (IPFMA) statement on the challenges to expanding COVID-19 vaccine manufacturing, "70% of vaccine manufacturing is about quality control and quality assurance".

In order to produce a vaccine meeting the required quality standards, all manufacturers must ensure that the entire process takes place under cGMP conditions. To achieve this, new manufacturing initiatives will need to implement well planned and robust quality systems supported by the right processes, procedures and documentation, as well as facilities and trained personnel. This includes having facilities with sufficient testing capacity to generate the required quality and manufacturing data packages. Further, many of the raw materials used in manufacturing a vaccine must pass their own quality checks.

The quality control measures developed by manufacturing organizations are subject to oversight from regulatory authorities who review quality management documentation and data at multiple checkpoints throughout the vaccine development and manufacturing process. Therefore, a key consideration for new manufacturing initiatives is the need for engagement with regulatory authorities through multiple steps in the quality management process including manufacturing site inspections to validate cGMP production of the vaccine candidate and lot release testing. Release testing involves collecting and testing samples of the vaccine in specialized centers and is likely to occur frequently at the beginning of manufacturing for a new vaccine and reduce over time.

Key considerations

- Establishing a reputation: For a new manufacturing initiative, building a reputation for reliably producing high-quality products necessarily takes time. As highlighted in PAVM's Framework for Action, both potential vaccine development partners and procurement decision-makers may have concerns about a lack of quality management experience, particularly from facilities in countries that are not well-known for vaccine manufacturing and may not have well-resourced national regulatory authorities (NRAs).

Regulatory Strategy

As well as working with regulatory authorities as part of the quality management process, new manufacturing initiatives need to ensure that they have a clear strategy for achieving licensure from regulatory authorities. Key steps in the overall vaccine approval process include:

- The conduct of clinical trials that will be required if an organization develops its own vaccine candidate, or if a vaccine product that is licensed from a developer under a partnering arrangement undergoes a change in manufacturing process. These clinical trials must generate sufficient data to demonstrate the safety and efficacy of the vaccine.
- Applications for authorization to introduce a new product usually in the form of a Biologics License Application or equivalent depending on the regulatory authority. During a pandemic or other public health emergency, manufacturers might first apply for approval for emergency use, such as an Emergency Use Authorization in the US, or WHO Emergency Use Listing in order to expedite the availability of the vaccine. These emergency approvals are converted into full licenses over time with more supportive data, as has been the case with some COVID-19 vaccines.
- A committee review of the data by the relevant authority to make a licensure decision for the vaccine candidate.

When working as a manufacturer in a partnership with the third party vaccine developer, there must be a clear definition of the roles and responsibilities of each party in the regulatory approval process. Under a licensing agreement, such as that between AstraZeneca and Fiocruz,

the manufacturer seeking the license is typically responsible for securing local regulatory approval in the markets for which the license is granted with the cooperation of the partner. However, in the case of the licensing agreement between Novavax and Serum Institute of India, Novavax initially sought regulatory approvals for its vaccine with data generated by the Serum Institute after manufacturing challenges at Novavax's other sites.

Key considerations

- Coordinating with multiple regulatory authorities: A vaccine needs to be approved by the relevant regulatory authority for each market (typically a single country, although there is a centralized procedure in the European Union) in which the manufacturer intends to sell the product. New manufacturing initiatives therefore need to have sufficient regulatory affairs personnel to understand and manage the requirements and sequencing of multiple authorities. If a manufacturer plans to obtain purchase commitments in advance from a procurement agency, such as GAVI, then it may also need to obtain approval from a WHO-listed Stringent Regulatory Authority, as well as the local NRAs.

  There are ongoing initiatives to harmonize regulatory requirements, including the WHO's plan to transition from a list of Stringent Regulatory Authorities to WHO Listed Authorities ("WLAs") which may open up opportunities to a broader range of NRAs. Additionally, the establishment of the Africa Medicines Agency should provide a harmonized approvals process across much of the African continent. However, such efforts will take time to come into effect. In the meantime new manufacturing initiatives will need to plan for engagement with existing, more fragmented structures, as well as monitoring changes to future requirements and planning for transition to new approval processes.

- Opportunities for capacity strengthening: The WHO has estimated that only 7% of African countries have a moderate level of capacity for medicines regulation. Significant investment and training for NRAs is needed in order to support PAVM's goal of manufacturing 60% of its vaccine needs on the continent by 2040, and for African NRAs to be in a position to apply for WLA status. There are several initiatives currently aimed at improving the capacity and capabilities of African NRAs. These initiatives will require sufficient funding from higher-income country governments, global health funders and/or development banks and would potentially also benefit from other in-kind knowledge-sharing and resource support from the global community.

Funding & Sustainability Planning

The start-up funds required to begin manufacturing a new vaccine will vary depending on a number of factors including the technology platform that will be used for manufacturing, the type of manufacturing activities to be performed, and whether there is an existing facility that can be retrofitted. One study has estimated the cost of starting up mRNA vaccine production at

an existing site and manufacturing 100 million vaccine doses at $127 million to $270 million. The cost reported for the Institut Pasteur de Dakar's new drug substance and fill-finish manufacturing facility is up to $222 million. Adding additional suites to an existing manufacturing facility to expand the number of vaccines being produced could cost $50 million to $500 million.

The total costs for developing a new vaccine candidate, starting from the stage of initial identification through to licensure and scale-up of manufacturing for commercial production, can be in the region of $1 billion. However, these costs would be spread over a number of years.

There are a number of routes that a new manufacturing initiative could take in order to obtain start-up funding for building a facility or scaling up existing manufacturing capacity. Examples of potential funding arrangements include:

- Upfront grant funding (direct cost reimbursements) which might be available from some non-profit funders and governments. Examples of this approach include the funding that the Coalition for Epidemic Preparedness (CEPI) has provided for the development and manufacturing of COVID-19 vaccines as well as vaccines against other diseases that have epidemic potential.
- Funding, either on a grant or loan basis, from development finance institutions (DFIs), such as that provided by the International Finance Corporation to Institut Pasteur de Dakar to fund part of the total cost of its new manufacturing facilities.
- Global impact investments from both privately and publicly managed funds. These investors aim to make a measurable social or environmental impact with their funds, as well as receiving a financial return.
- Traditional commercial loans, which are likely to require a higher return on investment and a lower risk profile than other funding options and therefore may be more suitable once a manufacturing organization is more established.

As well as funding from grants, loans and other investments, new manufacturing initiatives need to consider the different opportunities to develop a sustainable business model with various streams of short and long term revenue to maintain their operations. While it may be several years before a manufacturing facility is ready to make sales of finished vaccines, the planning process for revenue generation must begin well in advance. The different options for obtaining purchase commitments include:

- Working under contract as a CDMO for a vaccine developer which has the advantage of not needing to make agreements with the final purchasers for the vaccines, as this task is performed by the developer. A strategy of starting with fill-finish activities as a CDMO and later expanding to manufacturing of drug substance as a CDMO, then transitioning to licensing agreements could be an effective approach for initial revenue generation. This would also give a manufacturer time to build experience and trust with established partners, as well as the credibility that can help to attract additional funding sources and customers.
- Negotiating advance purchase agreements (APAs) with governments or multilateral procurement agencies such as Gavi for vaccine candidates that have not yet been

approved for use. This was a common COVID-19 purchasing strategy for many governments, particularly in higher-income countries as well as COVAX, and has previously been employed by Gavi for pneumococcal vaccines. The purpose of an APA is to incentivize innovation, increase the speed of vaccine development and encourage investment in early and large scale manufacturing. Often this type of agreement will be more suitable for an organization developing a novel vaccine candidate than one manufacturing a vaccine under license from a developer, however some manufacturers did negotiate APAs as part of the COVID-19 response certain groups, such as the agreement between the Serum Institute of India and GAVI.

- Securing high-volume guaranteed offtake agreements (i.e. advance commitments to purchase approved vaccines) from governments or procurement agencies. This high-volume purchase model has traditionally been used by Gavi, and it is unlikely that the governments of individual countries will be able to support the high-volume commitments that new manufacturers in Africa will need for a sustainable business model. However, a pooled procurement initiative such as the African Vaccine Acquisition Task Team (AVATT) could potentially provide guaranteed offtakes both for COVID-19 and other vaccines.

Key considerations

- Attracting investors: Any investor needs to be convinced of the potential for success of the activities that they are funding. This is particularly true of investments for the development of new vaccine candidates, as the average probability of success for producing a safe and effective product and achieving licensure is less than 10%. Different types of investors also have different objectives for their investment. For instance, non-profit organizations want to ensure that their grant funds have an impact on affordable access to vaccines, whereas commercial investors are seeking a return on their investment.

  It is therefore important to demonstrate a balanced approach to potential investors, showing an ability to secure customers and generate profits through sales made at an affordable but sustainable price. Some investors may also be concerned about the possibility of future patent infringement claims, such as those recently made in relation to Moderna's COVID-19 vaccine, which could reduce the value of their investment. New manufacturing initiatives will therefore also need to show that they have the freedom to market a product without undue risk of infringing third party patent rights.

- Pricing: New manufacturing initiatives will need to contend with the broader competitive environment, particularly when it comes to bidding in open public tenders. At least initially, new organizations may struggle to compete with established, large-scale manufacturers from countries such as India and China, which have built economies of scale over time as well as having government support that allows them to operate at low-profit margins.

Procurement decision-makers, whether governments or procurement agencies such as GAVI or AVATT, will need to recognize that the "premium" on the prices charged by new manufacturers in Africa is the price to pay for health security. Additionally, new facilities will need early stage support which may also come in the form of market exclusivity for the first locally produced version of a vaccine, direct subsidies, tax credits or other production-related support.

A government ownership model is also a possible approach for being able to sustain lower profits and therefore charge lower prices. For example, Biovac, a manufacturing partner in the WHO technology transfer hub in South Africa, is a public-private partnership with 47.5% government ownership.

- Agreement terms: All funding arrangements also require the negotiation of an agreement that sets out the terms of the grant funding or investment. There are likely to be substantial differences between the conditions attached to a grant from a non-profit organization, financing from a DFI or a more traditional commercial loan. New manufacturing initiatives will need to implement processes to track and manage the obligations in each investment agreement. These might include:
    - Providing regular progress reports and/or notifying investors of the achievement of certain milestones;
    - Complying with financial terms such as making loan repayments or providing accounts of the actual funds spent, as well as ensuring the segregation and separate accounting of funds received from different parties;
    - Maintaining compliance with the warranties & representations made in the agreement; and
    - Managing intellectual property protection requirements such as making patent applications.

Time

The time required to bring a manufacturing facility to a state of operating readiness varies depending on a number of factors, the most essential being whether there is an existing facility and team with experience in vaccine manufacturing. If starting from scratch ("green field"), then the process from design to completion of a new fill-finish and drug substance manufacturing facility could take approximately five years. This time period takes into account the basic infrastructure required for the site including clearance, utilities and digging foundations.

Progression from the start of operations to fully licensed vaccine production depends on the technology transfer process, quality testing and regulatory approvals. According to statements made by Pfizer, transferring the knowledge of filling and capping vials, even with an established partner, typically takes about 18 months and involves 10 stages. Each stage of the technology transfer process consists of hundreds of steps, with the potential for extended time frames if something goes wrong with any of various steps. The timeframe could be extended to up to 30

months for drug substance manufacturing, and for initiatives planning to develop novel vaccine candidates the time from initial research to licensure of the vaccine can be between five to 18 years.

Fundraising also varies in time to completion and new manufacturing initiatives will need to ensure that they manage their cash flow requirements accordingly. It may be possible to secure smaller funds within a few months, and organizations such as CEPI work with faster funding timelines for pandemic response, but investors making larger funding commitments can be expected to take a longer period of time to make funds available. This timeline takes into account initial engagement with investors, the due diligence process, and the negotiation of agreement terms. Securing the funding from a government agency or DFI could help to shorten timelines for meeting total investment goals as support from a recognized institution could help to attract other investors.

Key considerations

- Reduced time to facility construction: The standard "green field" build timeline can be reduced through innovative new approaches such as the modular containers being used by Institut Pasteur de Dakar's MADIBA project. These modules can be designed offsite then shipped to manufacturing location and placed in an open warehouse-type structure within a year. This approach allows for site clearance and warehouse construction to run in parallel with the offsite construction of the container, and potentially enables a facility to be built, equipped and running test fill-finish batches within 18 months. This timeline assumes that staff recruitment, build out of a supply chain for raw materials, implementation of a quality management system and the identification of partnerships with vaccine developers takes place during the facility construction phase.

- Reduced time to complete tech transfer: The technology transfer timelines achieved during the COVID-19 pandemic were significantly faster than those typical for vaccine manufacturing. While these rapid timelines may not be sustainable in non-pandemic response scenarios, when individual technology transfers are managed amongst multiple other priorities, there may be some best practices that can be applied to streamline the business-as-usual transfer process. Key to maximizing opportunities for rapid technology transfer will be close collaboration and cooperation between the parties, experienced personnel at both the donor and recipient sites, and a clear understanding of the regulatory requirements.

- Reduced vaccine development and approval timelines: As with technology transfer, the COVID-19 pandemic showed that rapid development of vaccine candidates through to emergency use approvals is possible. However, this was facilitated by a number of factors driven by the pandemic context including unprecedented levels of funding, increased willingness to collaborate between established vaccine developers and manufacturers, and flexibilities to regulatory approaches.

Enabling efficient paths for new vaccine development in Africa requires additional ecosystem considerations. As noted in the PAVM Framework for Action it is “currently not possible to move a vaccine concept from research through to clinical trials entirely on the African continent”. Expertise is currently fragmented across Africa and lacking in coordination, and there are infrastructure gaps including sufficient capacity for cGMP batch manufacturing for clinical trials and for animal studies. Based on PAVM’s implementation plan, it will take until at least 2025 for an enhanced and better coordinated ecosystem to be available to support faster development timelines.

Conclusions

Developing sustainable solutions for equitable and timely access to vaccines whether for COVID-19, other diseases or future pandemics, will require a complex decision-making process, extensive planning and creative use of partnerships to obtain necessary materials, experienced advice and other essential resources. It is incumbent on new facilities in every country to go through the analytical and strategic planning steps described in this paper and determine their own optimum path forward based on current requirements and projected future scenarios.

However, to achieve the goal of reduced reliance on imported vaccines across the African continent, new manufacturing initiatives cannot act in isolation. There is a clear need for coordination and cooperation at an organizational, country and regional level in order to ensure the most effective use of facilities, scarce materials and a skilled regional workforce to manufacture a range of vaccines that are available and affordable when they are needed.

As illustrated in Figure 2 below, partnerships with raw materials suppliers, vaccine developers, funders and investors, as well as purchasers of the final vaccine, will be key to the success of new vaccine manufacturing initiatives. These partnerships must be supported by multiple agreements with terms that enable all of the parties to meet their goals.

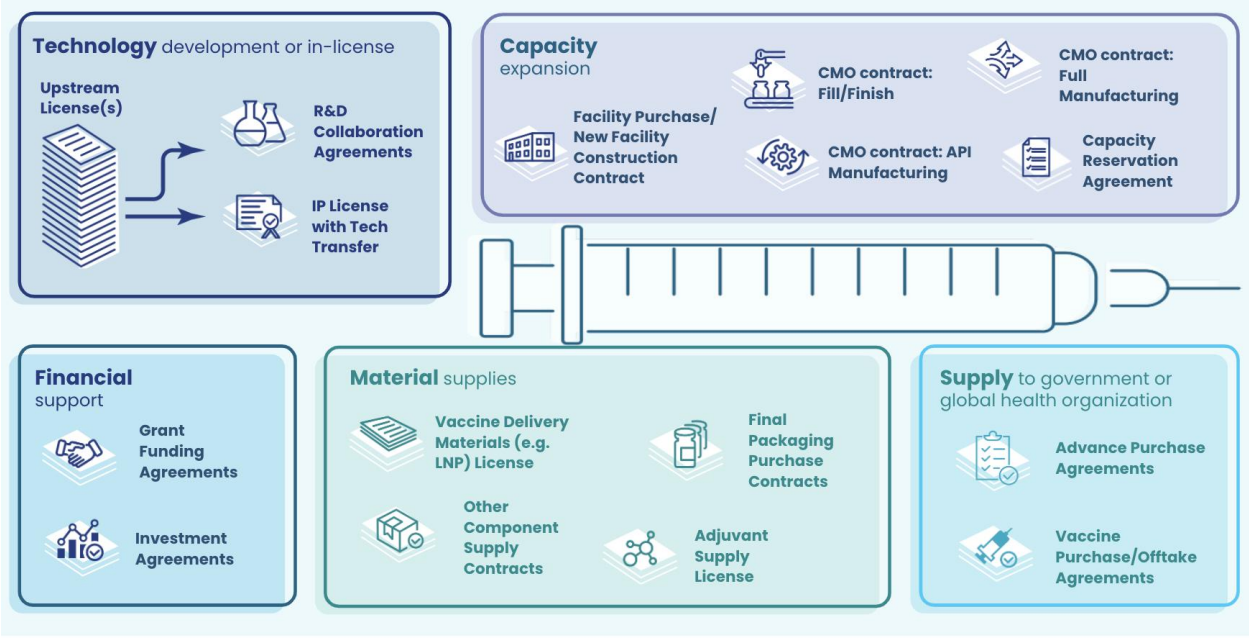

Figure 2: Critical agreements for vaccine development & manufacturing

Other factors that will be critical for the success of efforts to expand sustainable manufacturing capacity in Africa include:

- The availability of funding from public and private institutions to support a sufficient number of facilities, even with some operating at a financial loss for an extended period of time, both during and after the COVID-19 pandemic;

- The willingness of government purchasers and procurement agencies to purchase vaccines manufactured in Africa, even if they are initially more expensive than those available from international competitors;
- The contribution of expertise and funding from national and global actors such as research and academic institutions, vaccine developers and manufacturers, and DFIs to support efforts to build and retain skilled local workforces across Africa; and
- The development of a stronger and more harmonized regulatory system across Africa to enable vaccine manufacturers to engage with an efficient regulatory approvals process as well as achieving the standards required for WHO pre-qualification.

Increasing regional manufacturing capacity seems an obvious solution to the twin problems of an insufficient volume of vaccines and delayed access. However, the success of initiatives already underway in Africa and elsewhere, and the others that will follow, will depend on the alignment of local needs, regional governance, financing, public-private partnerships, global policy and health systems for many years to come. The process for determining the best path forward for an individual new manufacturing initiative is not straightforward. Such a decision must be taken within the context of its current operational capabilities alongside other local, regional and continental factors. The successes and learnings of the initiatives that have already started on this journey will be instructive for others considering embarking on their own paths forward.

Appendix 1: Illustrative Agreements

The examples set out below provide additional details of the types of terms that might be included in some of the types of agreement shown in Figure 2. This analysis is based on publicly available copies of agreements published either under government public disclosure requirements or in company SEC filings. The agreements below are illustrative examples only and have not been selected as representative of 'best practice' or 'standard' agreements. Additional analysis of agreements related to COVID-19 vaccines and other medical products can be found in the GHIAA MAPGuide®.

AstraZeneca - Fiocruz Licensing Agreement

Bio-Manguinhos/Fiocruz ("Fiocruz") is a Brazilian state-owned vaccine manufacturer. Prior to the COVID-19 pandemic, Fiocruz was already an established manufacturer, producing a number of vaccines including yellow fever, polio, meningitis A and C, MMR, monovalent Hib and Hib+DTP, primarily for the Brazilian public health service. Fiocruz also had experience of working in partnerships with big pharma.

In September 2020, Fiocruz signed a "Technological Order Agreement" with AstraZeneca to enable the manufacture of 100.4 million finished vaccine doses for use by the Brazilian public market. The technology transfer to enable Fiocruz to produce the vaccine took place in two stages. First AstraZeneca supplied the drug substance to Fiocruz and transferred the technology required for fill-finish of the vaccine. After the completion of this initial transfer, AstraZeneca transferred the technology necessary for manufacturing the drug substance. This second phase was governed under an additional "Technology Transfer Agreement" which was signed in June 2021.

The license granted under the first agreement is a free, non-exclusive license to import the drug substance for the production of AstraZeneca's ChAdOxnCoV-19 vaccine, and to use it for the manufacture and commercialization of finished vaccines. AstraZeneca also committed to inform Fiocruz of any relevant patent applications that it submits in Brazil and to grant licenses to any such patents. The license grant under the Technology Transfer Agreement is extended to an exclusive license (for the Brazilian public market) to use licensed know-how to develop, make, use, import and sell the finished vaccine, including production of the drug substance. Fiocruz is not permitted to grant sublicenses, and AstraZeneca retains a right to revoke the license exclusivity in the case of severe quality or regulatory issues.

The license grants do not include future developments for new antigens created by AstraZeneca, but Fiocruz has the right of first refusal for licensing negotiations for use in the Brazilian public market. Any improvements made to the vaccine product will be owned by the party that makes them, including that Fiocruz will own any improvements that it makes to the manufacturing process. AstraZeneca and Fiocruz will automatically grant each other licenses to any improvements but the party receiving the license must bear any costs related to the implementation of the improvement at their facility.

The initial Technological Order Agreement sets out technology transfer obligations for both parties, including for Fiocruz to be "operationally and technically capable" of receiving the transfer and for AstraZeneca to use "all commercially reasonable efforts" to undertake the transfer. The Technology Transfer Agreement includes a separate technology transfer work plan as well as requirements for AstraZeneca to transfer the starting materials that Fiocruz needed for beginning drug substance manufacturing as well as transferring manufacturing and release testing processes.

The Technology Transfer Agreement states that Fiocruz is responsible for all regulatory activities and will use its best efforts to obtain regulatory approvals in accordance with a plan agreed with AstraZeneca and managed through a joint steering committee. AstraZeneca will provide support for regulatory submissions, including transferring the know-how required for regulatory activities.

In March 2021, Fiocruz announced that it had received registration from the Brazilian Health Regulatory Agency for the vaccines manufactured under the Technological Order Agreement (i.e. fill-finish manufacturing). This was followed in August 2021 by an announcement that it had delivered 76.4 million vaccine doses to the Brazilian National Immunization Program and had begun manufacturing of the first batches of drug substance. In January 2022, seven months after signature of the Technology Transfer Agreement, Fiocruz received regulatory approval to produce and distribute finished vaccines using the drug substance manufactured by Fiocruz.

Moderna - Lonza CDMO Agreement

At the start of the COVID-19 pandemic, Moderna, unlike many of its competitors, did not have a manufacturing network. It has since built a network of contract manufacturers, and this started with a "Global Long Term Agreement" ("Global Agreement") with Lonza, which became effective in May 2020. Despite being the world's largest CDMO by sales revenue in 2020, Lonza had to expand its manufacturing capacity in order to fulfill Moderna's requirements. This expansion included three new production lines in Switzerland, costing $80 million each, as well as new production lines in New Hampshire which were partially funded by the U.S. government.

The exact activities to be performed are detailed in separate Statements of Work ("SOW") which also set out the pricing schedule for Lonza's services. The financial terms of the Global Agreement include a requirement for Lonza to work continuously to "improve and reduce" direct materials and labor costs, as well as indirect production expenses. Any cost improvements that Lonza achieves may then be taken into account in the form of a reduced price charged to Moderna. Lonza is required to have a business continuity plan to ensure that it can continue uninterrupted supplies to Moderna despite the COVID-19 pandemic. However, Lonza will not be responsible for delays due to raw material shortages outside of its control.

In addition to SOWs, there is also a separate Quality Agreement which sets out the quality requirements for manufacturing in accordance with guidance from relevant regulatory authorities. The Global Agreement states that Moderna will own all regulatory approvals and related documentation, but that Lonza will provide assistance for the preparation of regulatory

filings. Lonza must also notify Moderna of any inspections by regulatory authorities and permit Moderna personnel to be onsite during any inspections.

Moderna and Lonza both grant non-exclusive, fully paid-up licenses under the agreement. Moderna grants Lonza a license under its technology and know-how in order for Lonza to perform manufacturing and process development activities, and Lonza grants Moderna a license (and right to sublicense) under its technology to use, sell, import and export the vaccines that Lonza produces. Moderna and Lonza each own any improvements that are developed as part of the activities under the agreement, and grant relevant licenses to the other party.

It has been reported that the technology transfer process from Moderna to Lonza took approximately six months. The technology transfer requirements in the agreement include transfer of materials and equipment from Moderna to Lonza, as well as "Know-How, documentation, specifications, SOPs, analytical methods and process validation documents." Lonza is responsible for producing a defined set of "Project Documentation" which will include all of the records to demonstrate that the vaccine was manufactured in accordance with the Quality Agreement. The agreement also specifies that Lonza's own operating documents and SOPs will not be provided in a technology transfer to Moderna or any other party.

Gavi - Novavax Advance Purchase Agreement

In May 2021, Gavi entered into an Advance Purchase Agreement with Novavax for the supply of approximately 350 million vaccine doses to participants in the COVAX Facility. The purpose of the agreement is to provide demand certainty for Novavax and secure doses on behalf of COVAX participants. Novavax will enter into separate supply agreements with the relevant COVAX participants based on dose allocations made by Gavi. Novavax must comply with a delivery schedule set out in the APA, as well as a requirement to prioritize COVAX doses.

In addition, the terms of the APA acknowledge that the Serum Institute of India ("SII") will be the primary source of Novavax vaccine to low- and middle-income countries, under the SII brand name "Covovax." The parties expect that Novavax and SII, collectively, will supply 1,092,000,000 vaccine doses. However, if SII is unable to meet its obligations, which are detailed in a separate agreement with Gavi, then Novavax must make efforts to make up the difference in total supply volume.

The financial terms of the APA include an advance payment from Gavi to Novavax based on a fixed amount per dose. This payment is split into two installments, with the second part paid upon receipt of WHO Emergency Use Listing for the Novavax vaccine, which was achieved in December 2021. Novavax will then reduce the purchase price charged to COVAX participants by an amount equal to the advance payment per dose. The purchase price that Novavax will charge is tiered depending on the income level of the recipient country. The tiers are divided into high income, upper-middle income and the COVAX AMC92.

This APA also facilitates Novavax's fulfillment of its obligation in a funding agreement with CEPI to supply its vaccine to a then-unnamed "Global Allocation Body" for distribution to Lower- and Middle-income Countries (LMICs) and other nations.

Appendix 2: Case Studies

Serum Institute of India

The Serum Institute of India ("SII") is a large-scale immuno-biologics manufacturer based in India, which is classified as a lower-middle income country by the World Bank. SII is a private, family-owned business with a philanthropic aim of providing vaccines at affordable prices. SII's current status as producer of over 60% of the world's vaccines has been built up over more than 50 years, starting with a tetanus anti-toxin in 1967.

Some important steps in SII's journey include:

- Entry into the international market in 2010 with MenAfriVac® through the Meningitis Vaccine Project. This project was a collaboration between PATH and WHO, funded by a 10-year grant from the Bill and Melinda Gates Foundation. PATH forged a number of partnerships during the life of the project, and this critically included SII which was able to manufacture the vaccine at an affordable price for use in Africa.
- The acquisition of Bilthoven Biologicals in the Netherlands in 2012, which enabled SII to add a polio vaccine to it's portfolio;
- The launch in October 2017 of the thermostable rotavirus vaccine RotaSIIL®, developed in collaboration with the U.S. National Institutes of Health, as well as the Rabishield® monoclonal antibody, developed in collaboration with the University of Massachusetts Medical School.
- The acquisition of Praha Vaccines in 2017 which provided SII with additional BSL3 and cGMP compliant manufacturing facilities.
- Launch of the PNEUMOSIL® vaccine in December 2020 against pneumococcal pneumonia following a decade-long collaboration with PATH and the Bill & Melinda Gates foundation.

SII's experience of partnering with international organizations and proven ability to produce high quality vaccines at scale put it in a strong position to manufacture COVID-19 vaccines. The underlying wealth of SII's owners also enabled them to make an initial decision to begin manufacturing AstraZeneca vaccines at-risk, without relying on government support.

Notably however, rather than try to develop its own COVID-19 vaccine, it looked for partners to work with. SII recognized the importance of having a portfolio of potential vaccines to manufacture, and entered into a number of partnerships including those with AstraZeneca and Novavax that have resulted in vaccines with WHO Emergency Use Listing, as well as approvals from other NRAs. These vaccines are approved under the SII brand names of Covishield (AstraZeneca formulation) and COVOVAX (Novavax formulation). According to the COVAX COVID-19 market dashboard[2], SII has entered into agreements to supply 1 billion doses of the COVOVAX vaccine and 550 million doses of the Covishield vaccine to COVAX. It has also committed to domestic supplies of almost 1.9 billion doses of the AstraZeneca vaccine.

[2] As at April 12, 2022

Despite the organization's 40 years of experience, SII's efforts to manufacture and supply COVID-19 vaccines have not come without challenges. First, in January 2021, a fire at one of SII's facilities resulted in delays of committed deliveries. Then, in February 2021, SII announced that it had been directed to put India's needs ahead of exports in the face of soaring COVID-19 infection rates in India. This prioritization of domestic supplies forced COVAX to notify its participants of delivery delays and pushed AstraZeneca to serve SII with a legal notice over the delays.

Institut Pasteur de Dakar: MADIBA Project

Institut Pasteur de Dakar ("IPD") is a vaccine manufacturer based in Senegal, which is classified as a lower-middle income country by the World Bank. IPD has been producing yellow fever vaccines for 80 years and is currently the only vaccine manufacturer in Africa that is prequalified by WHO to produce vaccines. The "Manufacturing in Africa for Disease Immunization and Building Autonomy" (MADIBA) project hosted at IPD aims to build a facility capable of producing 300 million COVID-19 vaccine doses per year. IPD aims to be producing 25 million doses by the end of 2022, which, if achieved, will be less than 18 months after the beginning of construction of the facility.

The project is a collaboration between IPD, the Senegalese government, Univercells, MedInstill and KeyPlants. IPD also plans to partner with one or more licensed COVID-19 vaccine manufacturers to add drug substance and fill-finish manufacturing capacity to their network. The contributions from the collaboration partners include:

- A Univercells subsidiary, Unizima, which specializes in setting up and operating local production facilities, will initially conduct feasibility studies and conceptual design as well as providing project management services. This will later be followed by technology transfer and operational support.
- MedIntill has provided a license to use its INTACT™ pouches which are a more cost effective final container than traditional glass vials and therefore more suitable for use in low resource settings.
- KeyPlants is providing expertise in modular solutions and offsite manufacturing for a new facility which will be constructed on land adjacent to IPD's existing yellow fever vaccine facility. The "portable and prefabricated" facility design will enable construction to be completed in less than a year, and its multi-suite capabilities will enable flexibility beyond the production of COVID-19 vaccines.

In addition, CEPI and IPD announced a broad reaching Memorandum of Understanding in January 2022 under which CEPI will provide strategic and technical support for the advancement of the MADIBA project. CEPI will also provide advice on the use of the INTACT™ pouches which were developed with CEPI funding.

In March 2022, it was announced that IPD had secured an investment package for up to $222 million through a mixture of grant, public and private financing. IPD's fundraising efforts were supported by a mandate letter from the International Finance Corporation (IFC - a member of

the World Bank Group). The financing announcement in March 2022 followed an initial $14 million in grant funding in July 2021 from the IFC, the Agence française de développement (AFD), the U.S. International Development Finance Corporation (DFC), the European Commission and the European Investment Bank. Additional support has been provided by the Team Europe initiative including:

- A €20 million grant from the German development bank (Kreditanstalt für Wiederaufbau);
- €1.8 million in financing packages from the Agence Française de Développement (AFD);
- Project structuring support from the AFD Group to assist with obtaining larger scale product financing; and
- Structuring initiatives support from Belgium to produce vaccines and pharmaceuticals, such as the Pharmapolis pharma hub.

This broad base of both financial and manufacturing production support and partnerships is indicative of the resources required to properly build near term capabilities whilst also establishing a foundation that enables longer term growth and sustainability.

Authors

Bridie Telford is a Development Director at the Global Healthcare Innovation Alliance Accelerator (GHIAA).

Thomas Johnston (TJ) is an independent strategic planning and business development consultant to the biotech industry and advisor to GHIAA.

Reid Adler (RA) is a co-managing partner at the Capital Technology Law Group.

Julia Barnes-Weise (JBW) is the Executive Director of GHIAA.

About GHIAA

GHIAA is dedicated to improving the health of the world's communities through accelerated formation of alliances which increase access to medical products. Our goals are to accelerate alliance formation by:

- Promoting transparency of global health agreements and providing tools to enable stakeholders to navigate and interpret key provisions;
- Developing educational resources to facilitate the translation of global health policies into actionable agreement provisions; and
- Engaging in collaborative efforts and open dialogue with academic, governmental, business, and nonprofit organizations to resolve the issues addressed in global health agreements.

Find out more: https://ghiaa.org/mapguide-home/

Acknowledgements

The authors would like to thank GHIAA team members Britnae Purdy and Laura Hoemeke for document formatting and communications support, and Angela Nannini and Fassino/Design for developing the graphics for Figure 1 & Figure 2.

Disclosures

GHIAA's work on this article was supported by a grant from the New Venture Fund. The funder did not have any role in the preparation, review, or decision to publish this document.

TJ is currently a consultant to CEPI and Institut Pasteur Dakar.

JBW is currently a consultant to CEPI.

RA is a consultant to Institut Pasteur Dakar. During the initial development of this paper, he was a consultant to CEPI.

The opinions expressed in this paper are those of the authors and not necessarily those of any of their clients.

Copyright information