Site visit to kick-off the South African mRNA vaccine Technology Transfer hub

6-9 September 2021

Note for the Record

Executive Summary

This visit to Pretoria and Cape Town was organized by invitation from the World Health Organization (WHO) and supported by the Department of Science and Innovation of South Africa. It provided opportunities for:

- High level political engagement:
  - Meetings at Department of Science and Innovation and Department of International Relations and Cooperation.
  - Events at French Embassy, EU Embassy, US consulate with ambassadors, ministries, donors, press.
  - Introductory session to the technical meeting
- Visits to the pilot plant at Afrigen and manufacturing plant at Biovac which enabled:
  - Confirmation of fit-for-purpose and appropriate teams in place at facilities
  - Development of the governance structure for the project
  - Engagement with South African Regulatory Authority, SAHPRA
  - Development of 5-year GANTT chart leading to commercialization of the first African COVID-19 vaccine (Q4 2024)
  - Development a 5-year budget of Euros slightly less 100 million, inclusive of the already announced 2-year budget of Euros 40 million

Next steps

- Donor meeting (22 September)
- Call for expression of interest by WHO for manufacturers interested in receiving technology transfer and training at the Hub (end September)

1. Presentation of the mRNA Hub concept and direction

WHO recalled that the mRNA Hub was establish in response of the flagrant inequity of access to COVID-19 vaccines in developing countries and in particular in Africa. The project is therefore addressing this problem by establishing manufacturing capacity using a Technology Transfer hub model to ensure sustainable vaccine security in future pandemics. While there is an intention to also establish Technology Transfer Hubs for other vaccine technologies (e.g. adenovirus vectors, sub-unit vaccines), mRNA was chosen as the priority technology because of the high efficacy of COVID-19 mRNA vaccines and of the versatility of the technology making it potentially more sustainable than some of the other technologies. The South-African Afrigen, Biovac, MRC consortium proposal was selected by WHO following thorough review by the PDVAC Committee of all applications received as a response to the request for expression of interest issued by WHO.

Although there was an initial intention that WHO might support the early establishment of additional mRNA Technology Transfer Hubs, it now appears clearly that Afrigen has the capacity to rapidly establish the technology and to train manufacturers beyond the African continent. The decision was therefore made that the South-African Hub would be a global mRNA vaccine Technology Transfer Hub.

Following due diligence and consideration of the best choice of technology to implement at the mRNA Hub, WHO engaged with the two main manufacturers of successful COVD-19 vaccines (Pfizer/BioNTech and Moderna) to explore their willingness to transfer their technology to the Hub, but to no avail to this date. The consortium will therefore rely on technical support from the best experts (already identified and willing to support) to develop two variations of COVID-19 mRNA vaccines:

- The first one will attempt to replicate the process used by Moderna, for the following reasons:
    - There is ample information of the process and composition used by Moderna in the public domain, including from manufacturers in Thailand and China already in advanced clinical development with vaccines based on this technology
    - Moderna has committed not to enforce any of their IP rights. While there are no blocking patents in Africa on mRNA vaccines, this commitment by Moderna will simplify technology transfer to other regions
    - Emerging data suggests that the Moderna technology might be superior to that used by other manufacturers
- The second candidate, inspired by the technology used by Genova (India) for a candidate vaccine already in clinical development, might have features more suitable for developing countries (superior heat stability, lower costs of goods), but hasn't yet reached proof of principle of its efficacy. Intellectual Property issues related to this particular technology are being sorted out.

The two prototype vaccines will be developed in parallel during the first few months. Evaluation in a mouse immunogenicity model in Q1, 2022, will allow selection of the prototype to be brought to human clinical trials as first priority.

2. High level political engagement during the South-African mission

The technical mission (Annex 1 for the list of participants) organized by WHO and supported by the Department of Science and Innovation of South Africa provided the opportunity to brief and respond to questions from policymakers:

- Meeting in Pretoria with Dr Phil Mjwara, Director General, and Dr Mmboneni Muofhe, Deputy Director General, Science and Innovation, South-Africa (DSI): The delegation presented the current development status of the mRNA Hub and DG, DSI reiterated his strong support for the project
- Meeting in Pretoria with Zane Dangor, Department of International Relations and Cooperation (DIRCO) and co-chair, ACT-A Facilitation Council Vaccine Manufacturing Working Group of Member States: The delegation presented the overall direction of the Hub project and Mr Dangor committed to advocate for the project at the Facilitation Council, national government and possibly UN levels
- The delegation was invited to present the initiative at a meeting organised in Pretoria at the Residence of the EU Ambassador and responded to questions from representatives of EU Member States, the UK and the USA
- The delegation was invited to an information meeting organized by his Excellency Aurélien Lechevallier, the French Ambassador in Pretoria, followed by a reception, which again provided the opportunity to exchange on the concept and the development status of the Hub and to hear about the support from many countries, including France, Germany, the USA as well as the European Commission

- The delegation was also invited by the US Acting-Consul at the US Consulate General Residence in Cape Town, which provided an opportunity to present and discuss the Hub with various US institutions and the Western Cape Minister of Finances
- Finally, the introductory session to the Cape Town technical meetings allowed for expression of support for the South-African mRNA vaccine Technology Transfer Hub from:
    - International partner organizations: WHO – represented by Assistant-Regional Director AFRO (Lindiwe Makubalo), the WHO Representative in South Africa - Owen Kaluwa, and Martin Friede, the WHO-HQ Project lead; African Union and African CDC – represented by Dr Nicaise Ndembi; MPP – represented by the Foundation's Chair (Marie-Paule Kieny) and Executive Director (Charles Gore)
    - The South-African Government (represented by Dr Mmboneni Muofhe, Deputy Director General, DSI) and organisations (SAHPRA – represented by CEO Dr Boitumelo Semete, MRC – represented by Richard Gordon, as well as consortium partners: Dr Morena Makhoana, Biovac CEO, Dr Petro Terreblanche Afrigen CEO, Dr Vikramkumar Naik, CEO of Avacare Healthcare Group, Afrigen's parent company)
    - Technical partners and in particular Dr Raj Long (Bill and Melinda Gates Foundation and project co-lead), and Dr David Kaslow (Chief Scientific Officer, PATH Essential Medicines, USA)
    - Confirmed and potential donors to the project (European Union, France, German KFW and GIZ, USA)

3. Consultation with SAHPRA

Dr Boitumelo Semete, CEO of SAHPRA participated in the technical discussions and in the site visits to Afrigen and Biovac. She confirmed the support of her institution for the end-to-end development of an mRNA COVID-19 vaccine by the consortium. An overall plan to further develop the capacities of SAHPRA, with support from WHO (led by Dr Rogerio Gaspar) including other partners as needed, was discussed.

During this session, WHO announced that it is putting in place a process by which to recommend to all COVID-19 vaccine manufacturers which strain of variant should be used to make such vaccines.

4. Site visits to Afrigen and Biovac facilities

The visit to the Afrigen facility confirmed the features highlighted in the application dossier. The facility is fit for purpose and complying with highest quality standards. Likewise, the team is competent and experienced in many of the domains of expertise needed to manufacture mRNA vaccines, including preparation of lipid emulsions and liposomes (both technologies relevant to mRNA vaccine formulation). Some key processes are already in place to operate under GMP.

Likewise, the visit to the Biovac facility confirmed that the intended production suite was fit for purpose and perfectly aligned with the Hub concept. The current building would be able to produce up to 50 million doses of vaccine annually. Biovac recently signed an agreement with Pfizer to receive technology transfer for the fill & finish part of the Pfizer/BioNTech COVID vaccine, and this was assessed as a likely additional factor of success for the mRNA Hub. Indeed, learning how to conduct the downstream production steps and the QC for another mRNA vaccine will increase the experience of Biovac staff in this domain. Of note is the fact that the Pfizer-Biovac contract does not prevent Biovac participation in the Hub.

To achieve accelerated technology transfer, manufacturing and commercialization the teams identified the need for an integrated project management between the two entities and early alignment on equipment procurement.

5. GANTT chart and main milestones for the project

The Afrigen and Biovac teams, supported by experts, developed an integrated GANTT chart for the project. This GANTT chart incorporates all foreseen activities allowing Afrigen to develop a robust mRNA vaccine production process, which will be transferred to Biovac. The main milestones are presented below:

15 Oct 2021	Afrigen procurement of essential equipment starts
01 Feb 2022	Procurement of equipment starts at Biovac
01 March 2022	Start of mouse down-selection studies (for 2 months)
01 May 2022	Start of efficacy study in hamster (for 2 months)
01 May 2022	Start of preparation of GMP grade material
01 Sept 2022	Regulatory filing for Phase 1 trial
01 Oct 2022	Enrolment of first Phase 1 volunteers
01 Apr 2023	Start of Phase 1/2 clinical trial (dose finding, elderly, HIV+)
01 Oct 2023	Decision on Phase 3 schedule
01 Dec 2023	Start of Phase 3
01 June 2024	Preliminary results of Phase 3
01 Sept 2024	Approval of the vaccine in South-Africa
Q4, 2024	Start of commercialization
2024 to 2026	Transfer of technology to further recipients in Africa and beyond

PATH (Seattle, USA) will provide product development support to the project and will be setting up meetings with the Afrigen/Biovac teams to refine the GANTT chart, incorporate target product profiles, and assist with the establishment of an integrated project management system.

6. 5-year budget for the project

A budget of Euro 40 million for the first 24 months had already been announced. The technical mission allowed confirmation of this envelope and assessment of the 5-year financial needs, as described below.

- Afrigen budget

CAPEX	Euros 5 million, including €1 million for a lyophilizer
OPEX	Euros 32.5 million, including 7% overheads
Total budget	**Euros 37.5 million**

OPEX includes facility running costs (€12 million), staffing (€12.4 million) GLP tox (€600,000), Phase 1 (€200,000), Phase 1/2 (€600,000), staff training (€300,000), consultancies (€1 million) and technology transfer to Biovac (€4 million)

Of the CAPEX €5 million, €560,000 is needed in Oct 2021, €830,000 in November 2021 and €1 million in Q1, 2022 in order not to delay procurement of essential pieces of equipment.

- Biovac budget

CAPEX	Euros 10.5 million, including €5 million for a lyophilizer
OPEX	Euros 5.9 million, including reproductive tox studies and 7% overheads
Phase 3 trial	Euros 15 million
Total budget	**Euros 31.4 million**

It is expected that funding for Biovac will be made of grants and loans from development banks. Attention will need to be brought to de-risking the investment for Biovac, as was the case for most manufacturers of COVID-19 vaccines.

- Budget for the research component for 5 years

Total budget **Euros 20 million**

The research investment is indispensable to adapt the mRNA vaccine to delivery in low-income settings and to generate a pipeline (e.g. Rift Valley fever, TB, malaria, HIV, arbovirus diseases vaccines) to ensure the sustainability of mRNA vaccine production in Africa.

Preclinical studies in hamsters and non-human primates as well as regulatory strengthening of SAHPRA will be funded independently.

Thus, the total 5-year budget for the project stands at slightly less than €100 million. Some of this funding may be provided as loans.

7. Governance

A strong governance will be critical to ensure the success of the project and the accountability of all involved. Following extensive discussion, the parties agreed on a governance structure which will be presented to the ACT-A Facilitation Council Vaccine Manufacturing Working Group (see Annex 2).

In brief, the proposal is for a Steering Committee (WHO, DSI, African-CDC, MPP + one independent technical expert with industry experience) which will be responsible for decision-making, informed by two standing advisory committees (a subgroup of the WHO PDVAC committee for scientific/technical matter) and the MPP External Advisory Group (EAG) for licensing and other contractual matters. The Steering Committee will make decisions on, inter alia, the choice of technology to prioritize, the selection of Technology Transfer recipients beyond Biovac, and the allocation of un-earmarked funding. A Funders Forum will be put in place, with MPP as the Secretariat, to ensure funders are kept fully informed of the project and its progress.

Any new knowledge or IP generated in the academic consortium will be made available to the global community through a non-exclusive sub-licensable public-health oriented licence to MPP. The data generated will belong to the consortium, who will commit to provide it to WHO to facilitate further technology transfer. Each party will be accountable to its specific funders.

Consortium agreements will need to be put in place between Afrigen, Biovac and the MRC, as well as between MRC and the other academic institutions. These agreements will clarify the responsibilities of each party and highlight in particular the following arrangements:

Biovac will be the regulatory sponsor and commit to:

- Provide material for clinical trials to MRC
- Produce the vaccine under GMP and apply to WHO Prequalification
- Make its best efforts to maintain the production facility operational between pandemics
- Commit to donate 10% of its real-time vaccine production to an UN agency for distribution in LMICs in case of a pandemic

Afrigen will commit to:

- Provide material for clinical trials to MRC
- Provide Transfer of Technology to Biovac free of charge. Principles for funding of further technology transfers remains to be discussed, based on the nature of the recipient companies (e.g. public or private, low of middle-income countries)

See annex 2 for a diagram of flow of decision making and responsibility.

8. Conclusion and Next Steps

There was consensus that the Hub consortium was fit for purpose and that the project had a high chance of success. Technical partners such as PATH and expert consultants will assist Afrigen in developing the production process, based on extensive information already in the public domain. The main “known unknowns” have already been identified by the consortium and will be subject to immediate attention.

MPP and WHO are organizing a Donor meeting on 22 September to present the overall 5-year budget and gather support from already committed and potential funders.

WHO will issue by end-September 2021 a Call for expression of interest for manufacturers interested in receiving technology transfer and training at the mRNA vaccine Hub, as well as a Call for Expression of Interest to host technology transfer hubs for other technologies.

Annex 1: Participants to the international team:

World Health Organization (WHO)

- Lindiwe Makubalo (Assistant Regional-Director AFRO)
- Martin Friede (Project Lead, WHO Headquarters)
- Owen Kaluwa (WHO Representative in South Africa)
- Moredreck Chibi (AFRO)

Medicines Patent Pool (MPP):

- Marie-Paule Kieny (Chair of the Board)
- Charles Gore (Executive Director)

France

- Sana de Courcelles (Health counsellor, Geneva mission and coordinator, French ACT-A engagement)

European Commission

- Bernd Appelt (DG Development, Team Europe Initiative)

In addition, the technical visits and/or discussions were attended by:

Germany:

Susanne Kieffer (German embassy Pretoria: Head of education and Research)
Silke Stadtmann (KFW)
Claudia Aguirre (GIZ)

Belgium:

Mathis Bogaert: Consul General Capetown.

Annex 2:

Overarching Governance Structure