Whitepaper

From Bench to Market: Vaccines Technology Transfer

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Inoculating a global population once Covid-19 vaccines were available required the pharmaceutical industry to produce and mobilize an unprecedented number of doses. Success relied on global manufacturing capacity and rapid and efficient technology transfer, which disseminated the knowledge and ability to produce these vaccines.[1]

This whitepaper provides an overview of the technology transfer process and describes how the development and optimization of a platform to manufacture a vaccine for tropical diseases that was subsequently leveraged for SARS-CoV-2 vaccine process development and transferred to Biofarma, a leading vaccine manufacturer in Indonesia.

The Critical Role of Technology Transfer

Technology transfer is a process by which product and process knowledge related to production of a drug or biologic or a platform for production is moved from one facility, scale, or lifecycle phase to another. The information shared between the originating and receiving sites during the transfer forms the basis for the manufacturing process, control strategy and process validation, and supports continual improvement. A successful transfer requires a collaborative effort among cross-functional technology teams representing various site disciplines, and relies on clear and timely communication as a cornerstone for success. Technology transfer is used by biopharmaceutical companies of all sizes and at different clinical phases, and may be necessary at multiple points during the product life cycle **(Figure 1)**. At each stage and scale, there are likely to be changes in equipment, methods, and materials, which may require process optimization, re-development, and training new production teams.

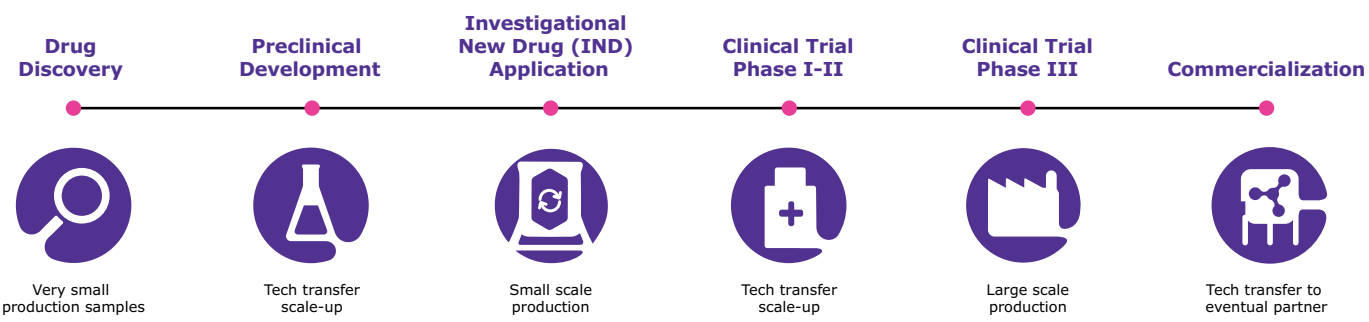


Figure 1. Technology transfer occurs multiple times during the product life cycle, from discovery to commercial production.

The World Health Organization (WHO) has outlined three types of technology transfers **(Figure 2)**.[1] A transfer between two different companies with an originator and receiver is called a **bilateral technology transfer**. The transfer is direct between two or more stakeholders.

A platform approach is one in which distributed stakeholders are consultants, organizations, and experts who come together virtually to establish a production platform which is then transferred to researchers or manufacturers. In the **hub model**, experts come together in the same physical space (e.g. an innovation center) to create a hub and the resulting technology platform is then transferred to manufacturers, often in different countries.

In a typical site-to-site transfer there are many steps, each of which requires detailed planning and precise execution. A cross-functional team is essential for success and includes site management, a steering committee, the tech transfer team and team leaders, and representatives from both the originating and receiving facility.

Best-in-class transfer practices offer the potential to reduce technology transfer timelines from 27-29 months to 8-11 months and include the steps shown in **Figure 3**.[2]

Several regulatory guidelines and other documents discuss aspects related to technology transfers including:

- WHO Technical Report Series, No. 961, 2011 - Annex 7: WHO guidelines on transfer of technology in pharmaceutical manufacturing
- FDA 21 CFR Part 210/211: Good Manufacturing Practice (GMP) guidelines
- EudraLex - Volume 4 - GMP guidelines

During the technology transfer process, it may be necessary to re-validate the process if different equipment is used by the receiving site. Similarly, if the transfer is to a different country, analytical methods may need to be re-validated to comply with local regulations.

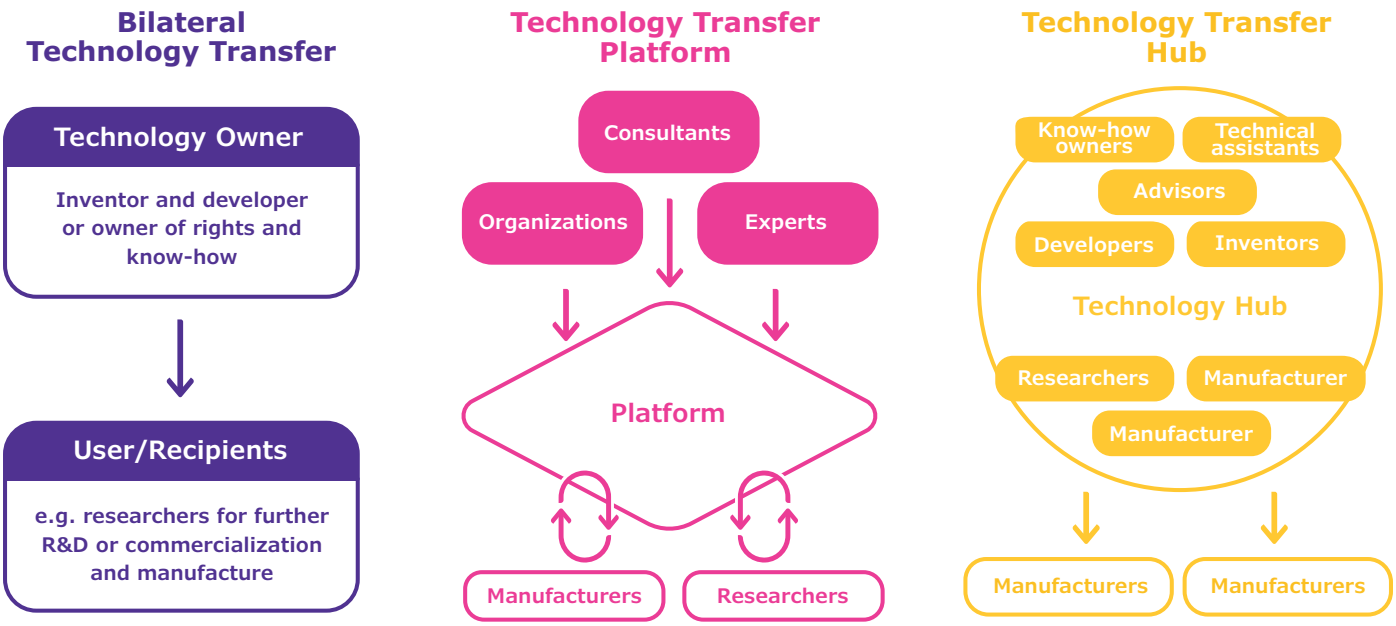


Figure 2. Comparison of a relatively simply bilateral technology transfer process with platform and hub models.[2]

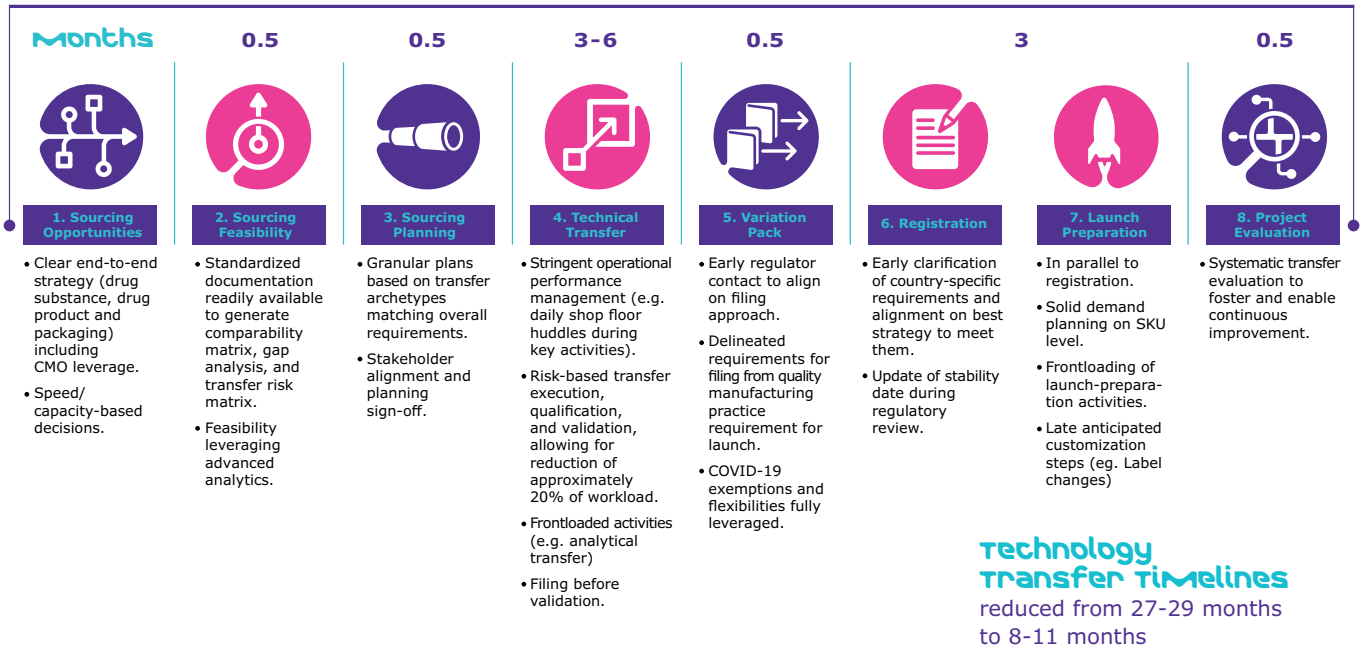


Figure 3.[1] Best-in-class practices to shorten the technology transfer timeline.

Developing a GMP-ready Production Platform for a Schistosomiasis Vaccine and Adapting it for COVID-19 Vaccine Production

The Texas Children's Hospital Center for Vaccine Development (the Center) at Baylor College of Medicine began work in vaccine development in the early 2000s. This academic-based organization embraced a product development partnership (PDP) model that focused on transitioning bench discoveries into products that could enter the critical path of evaluation and technology transfer at the level of production. The team was keen to ensure that their technologies, which were innovative and emergent, could be transferred in a way that was appropriate for the country and the region, and reflected global priorities.

Among the many diseases which the Center focuses upon is schistosomiasis, one of the world's most pervasive parasitic infections. The Center had developed a small-scale process to produce sufficient quantity of a recombinant protein-based vaccine candidate for schistosomiasis for Phase 1 and up to Phase 2 clinical trials.

The *Schistosoma mansoni* Tetraspanin-2 (Sm-TSP-2) surface protein was used as the vaccine antigen. Preclinical studies and early-phase clinical trials have shown positive results that vaccination with this recombinant protein subunit is safe and immunogenic.

To advance from a bench scale process to a commercial-scale cGMP-compliant manufacturing process, the Center's team collaborated with Merck to optimize the purification process. Process steps with low yield were focused on to boost productivity and reduce overall cost. Micro and ultrafiltration steps were combined into a single linked tangential flow filtration (TFF) cascade which led to a significant reduction in cost of goods including a 64% reduction in filtration membrane area, 88% reduction in buffer, and a 38% reduction in labor hours. Yield was improved by 30% which translated into a 36% increase in final product. Details of this optimization can be found in the whitepaper entitled: Neglected Tropical Diseases — Improving the Manufacturing Paradigm for a Novel Recombinant Protein Vaccine.[3]

Development and optimization of the Covid-19 vaccine candidate production process

In 2011 initially to develop a SARS-CoV vaccine prototype and later in 2020, in response to the Covid-19 pandemic, the Center's team quickly leveraged decades of knowledge and adapted their recombinant protein vaccine technology platform to produce a vaccine candidate targeting SARS-CoV-2.[3] The process to develop the vaccine candidate was optimized with Merck prior to creation of a starter kit for technology transfer; for both vaccine candidates (RBD219 and RBD203) shown in **Figures 4**[3,4,5]. Process #2 provided the best combination of yield and purity, and was chosen to be the protocol guidelines in technology transfer cases.

The vaccine production starter kit containing the following components was transferred to geographies with the greatest need:

- **Starter materials:** Engineered, yeast-produced recombinant vaccine antigens; seeds and cell banks fully characterized for ancestral and later strain variants.
- **Recipes:** Process development, formulation, and preclinical testing; scale-up to 10 L production and purification design
- **Assays** for quality and stability: Biochemical/biophysical assays and functional release and stability indicating assays

The optimized process was ultimately transferred to several members of the Developing Countries Vaccine Manufacturing Network (DCVMN), specifically to companies located in India, Indonesia, and Bangladesh.[6]

A. Process development of the COVID-19 vaccine candidates[4]

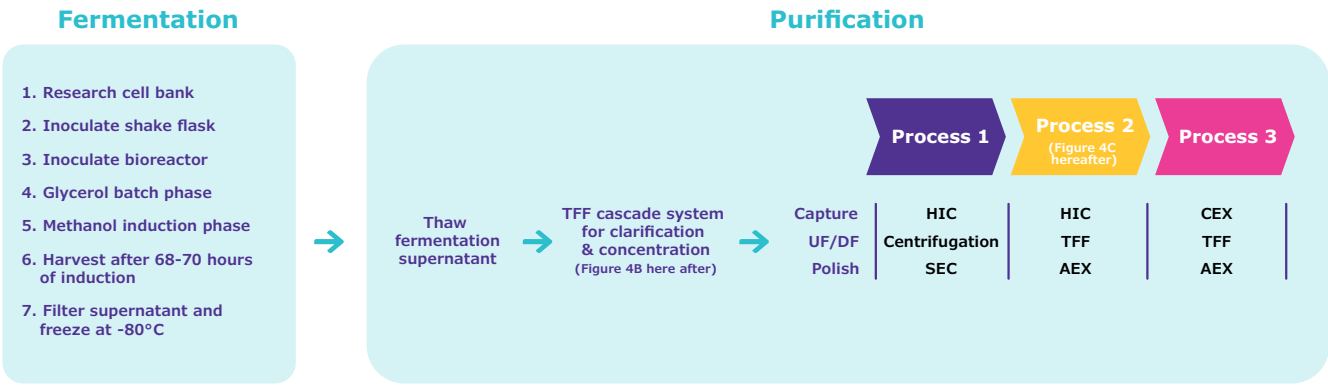


Figure 4A. Process development with various purification scheme tested.[4] Abbreviations: HIC = Hydrophobic Interaction Chromatography - SEC = Size Exclusion Chromatography - TFF: Tangential Flow Filtration - CEX = Cation Exchange Chromatography

B. Cascaded TFF unit operation for process optimization [3]

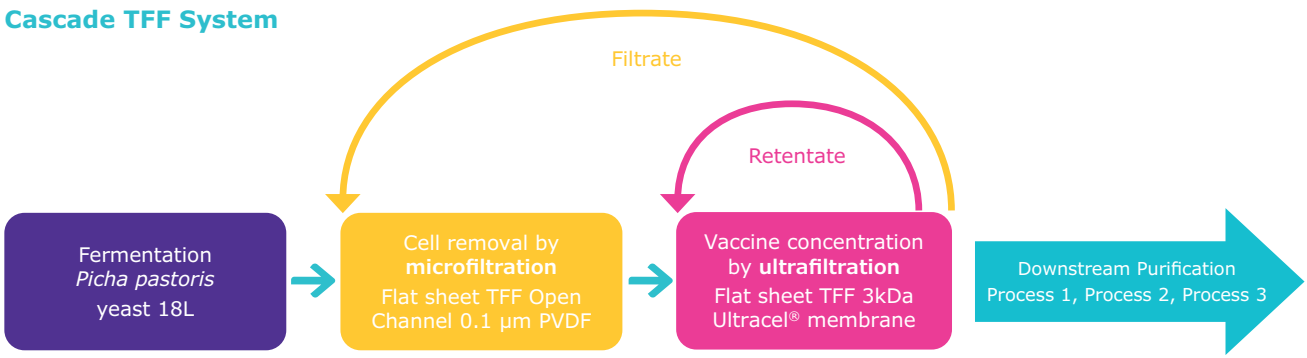
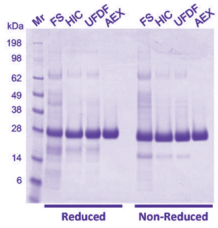


Figure 4B. Post harvest optimization on clarification and concentration using cascaded TFF system[3]

C. Process 2 purification results for yield and purity [4,5]

RBD219

	Yield (mg)	Step Recovery (%)	Overall Recovery (%)	Purity Non-Reduced (%)
Feed Stream	345.0 ± 7.1			77.0 ± 0.4
HIC	154.4 ± 0.0	45 ± 1	45 ± 1	95.2 ± 0.9
UF/DF	173.6 ± 5.7	113 ± 4	50 ± 3	94.6 ± 1.2
AEX	134.9 ± 1.8	78 ± 4	39 ± 0	95.1 ± 0.4



RBD203

	Yield (mg)	Step Recovery (%)	Overall Recovery (%)	Purity Non-Reduced (%)
Feed Stream	492.9 ± 3.0			75.0 ± 0.6
HIC	324.9 ± 3.1	66 ± 0	66 ± 0	95.2 ± 0.9
UF/DF	326.8 ± 4.0	101 ± 2	66 ± 1	94.6 ± 1.2
AEX	270.5 ± 13.2	83 ± 3	55 ± 3	96.4 ± 0.9

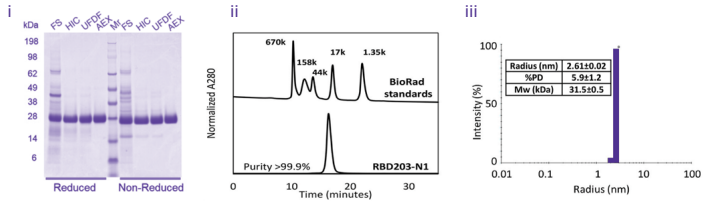


Figure 4C. Process 2 purification results for both COVID-19 vaccine candidates RBD219 and RBD203. Purity assessment of in-process samples analyzed by SDS-PAGE (i), with additional purity and size assessment data for purified RBD203 analyzed with SE-HPLC (ii), and DLS (iii). All results are showing good purification yield and purity.[4,5] Mr = Molecular Weight Marker, FS = Feed Stream, HIC = Hydrophobic Interaction Chromatography, UFDF = Ultrafiltration Diafiltration, AEX = Anion Exchange Chromatography

Production of IndoVac: A Halal-certified COVID-19 Vaccine

Biofarma was one of the companies receiving the technology transfer from the Center and used the Starter Kit (RBD203) and the process to produce IndoVac, a Covid-19 vaccine. While the company and country had access to the Sinovac Covid-19 vaccine, Biofarma understood the urgent need for localized vaccine production in their own facility.

Starting with a working seed stock and process guidelines from the Center, the Biofarma team collaborated with Merck to optimize upstream UF/DF and downstream operations; scale fermentation first to 70 L, and ultimately 1,200 L. The final process is similar to that transferred by the Center **(Figure 5)**.

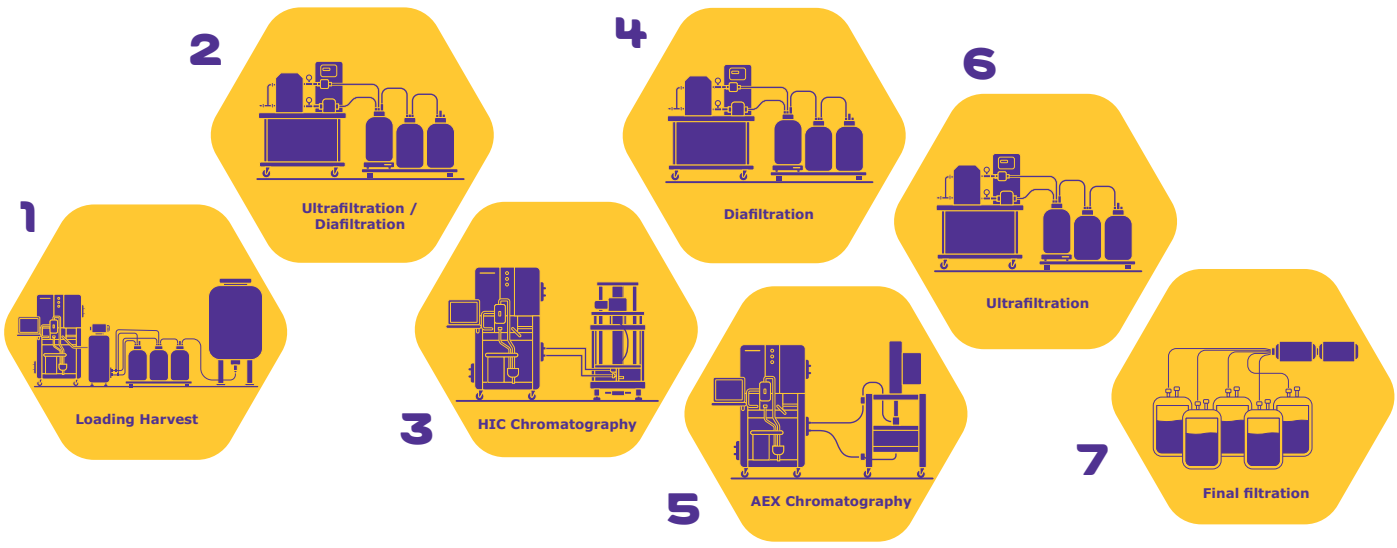


Figure 5. The optimized production process for COVID-19 vaccine IndoVac at Biofarma.
(UF/DF = Ultrafiltration & diafiltration, HIC = Hydrophobic Interaction Chromatography, AEX = Anion Exchange Chromatography)

A critical step in the production of this vaccine in Indonesia, which has the second largest Muslim population in the world, is Halal certification. Halal certification is an independent assessment and determination of a product's compliance with international halal standards. **Figure 6** outlines the process required to secure the certification for IndoVac, which was implemented in parallel with GMP qualification of the existing Biofarma facilities to produce the new vaccine.

In addition to a successful technology transfer, a critical factor that allowed timely production of the Covid-19 vaccine was the ability of Biofarma to produce it in their existing facilities. A campaign production approach was used; this is the manufacture of an uninterrupted sequence of batches of the same product or intermediate in a given time period, followed by strict adherence to accepted control measures before switching to another product. In this scenario, different products are not run at the same time, but may be run on the same equipment. This approach allowed Biofarma to avoid the costly and time-consuming need to build a new production facility.

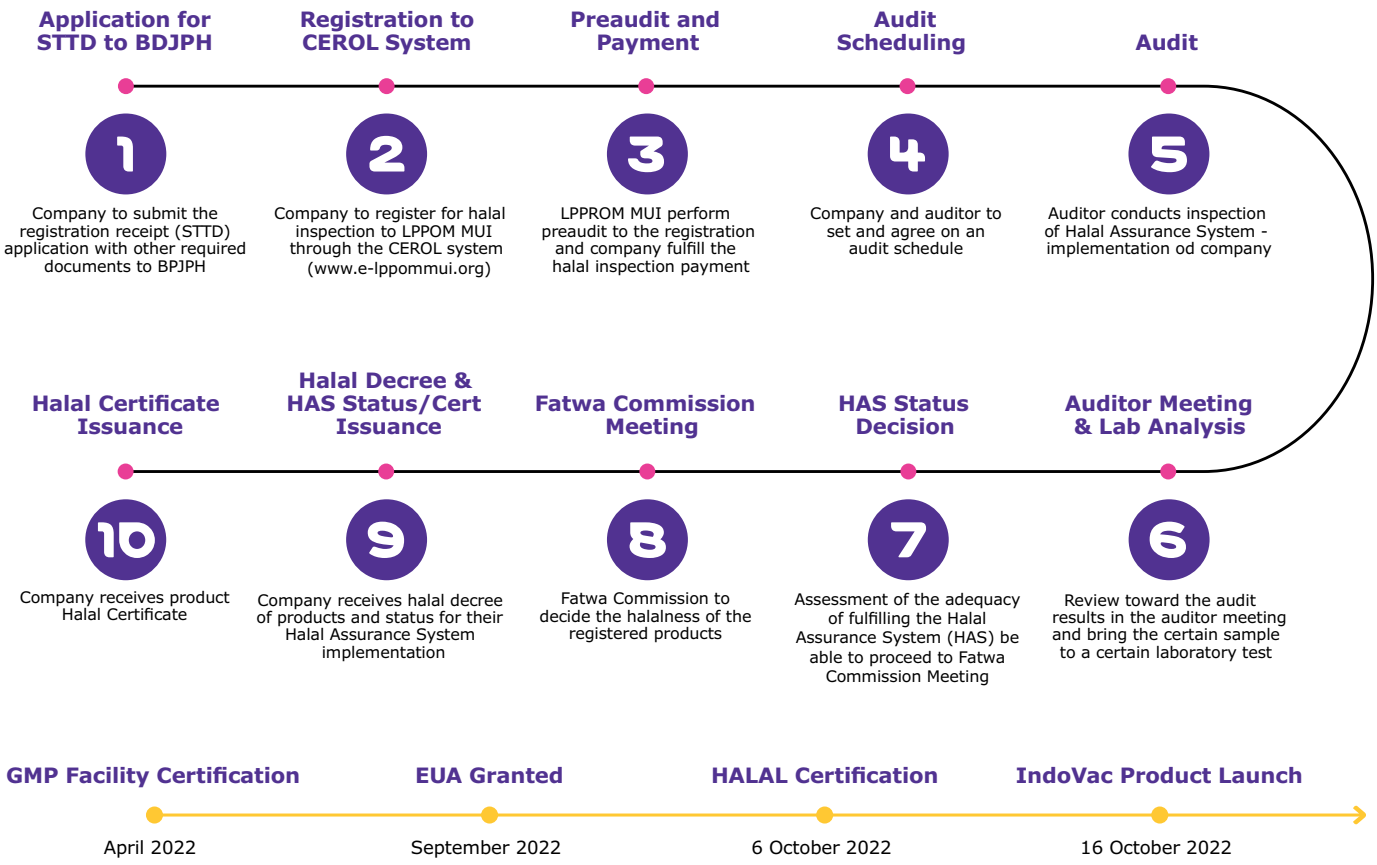


Figure 6. Halal certification process[7] and Biofarma's accomplishments in various certification application milestones.

Conclusion

The global health emergency created by the Covid-19 pandemic brought the necessity of global production capacity to enable mass immunization into sharp focus. Undoubtedly, a new era of vaccine production has been facilitated by countless partnerships and collaborations – such as that described in this whitepaper – which have been enabled by technology transfer. These transfers of technology and know-how were the foundation for unprecedented harmonization across geographies and opportunities for regionalization of vaccine production. This commitment to cooperate translated into an accelerated response to SARS-CoV-2 and helped protect the health of people around the world.

Authors

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Dr. Ravi Ganapathy has more than 30 years of professional work experience in biotech and more so in the vaccine industry. He has hands-on experience in development, manufacturing of recombinant (bacterial/yeast-derived), bacterial, and viral vaccines. Having led R&D, production, and quality assurance teams, he has an extensive understanding of manufacturing and R&D-related quality & regulatory requirements for the commercialization and lifecycle management of biotech products, especially vaccines, and the related GLP & GMP documentation. He serves as the Director–CMC R&D at Hilleman Laboratories Singapore Pte. Ltd. ravi.ganapathy@hilleman-labs.org

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Dea Marsendah is a vaccine practitioner, biotech enthusiast, and life science professional. She has 14 years of experience in vaccine manufacturing which has given her a wealth of knowledge and deep understanding in the field of vaccine production, particularly Hib and Typhoid vaccines. Most recently, she has been involved in Covid-19 scale-up vaccine manufacturing. Dea has a master's degree in biotechnology from the Bandung Institute of Technology, and also an MBA from Tanri Abeng University in Indonesia. She has spoken at some significant international conferences on bioprocesses and biopharmaceuticals, and serves as the Head of Development Management at Biofarma, Indonesia. dea.marsendah@biofarma.co.id

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