A case study on the ecosystem for local production of pharmaceuticals, vaccines and biologicals

The Pakistan context
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The Pakistan context
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Preface

The Local Production and Assistance (LPA) Unit in the Regulation and Prequalification Department (RPQ), Access to Medicines and Health Products Division (MHP), World Health Organization (WHO), supports Member States, particularly low- and middle-income countries (LMICs), to strengthen sustainable local production and technology transfer to improve timely, equitable access to quality, safe and effective essential medical products. The LPA Unit provides assistance and support to Member States with an ecosystem-wide and holistic approach, such as fostering global coordination and partnerships, conducting ecosystem assessments for sustainable, quality local production, developing and implementing strategies/roadmaps, providing comprehensive capacity building and technical assistance, including for WHO Prequalification (PQ)/Emergency Use Listing (EUL), facilitating technology transfer (TT) and developing global resources on local production and TT.

A landmark resolution WHA74.6 on strengthening local production of medicines and other health technologies to improve access was adopted in the Seventy-fourth World Health Assembly, signalling globally the important role local production plays in improving access and strengthening health security. Within this mandate, the LPA Unit, developed a series of case studies on the ecosystem for local production of pharmaceuticals, vaccines and biologicals, with a focus on country context in the low- and middle-income countries (LMICs). These case studies add to the existing repository of resources on strengthening local production and technology transfer of health products for countries to leverage upon when countries embark in these areas. The countries in this series are Bangladesh, Kenya, Nigeria, Pakistan, Senegal and Tunisia.

From July to September 2022, a series of interviews and consultative meetings, including a review of available literature, policies and other documents, and administration of a questionnaire, were performed. This case study is intended to report the collated information in areas such as available policies, initiatives, financing, regulatory system, patent protection system, research and development (R&D) work, markets and capacity and preparedness to uptake local production of quality-assured pharmaceuticals, vaccines (including mRNA vaccines), and biologicals. The expectations and needs of these countries were also collected and included in the case study, along with proposed recommendations, for the reader to see various viewpoints towards strengthening sustainable local production and achieving universal health coverage and the Sustainable Development Goals.
Acknowledgement

This case study was developed under the lead and supervision of Jicui Dong, Unit Head of Local Production and Assistance (LPA) Unit, World Health Organization (WHO), with a main contribution by Zafar Mirza, WHO consultant, and technical contribution by David Woo, Technical Officer, and Wee Ling Phua, WHO consultant. Particular appreciation is given to the WHO Country Office of Pakistan for the support in facilitating the local arrangements, with particular thanks to Palitha Gunarathna Mahipala, WHO Representative to Pakistan, Farah Sabih, National Professional Officer, and Alia Zafar, Technical Officer, as well as the WHO Regional Office for Eastern Mediterranean and the Government of Pakistan for their support. A special thanks is given to Yukiko Nakatani, Assistant Director-General, Access to Medicines and Health Products Division, WHO, and Rogério Paulo Pinto de Sá Gaspar, Director, Regulation and Prequalification Department, WHO, for their guidance and support.

We would like to acknowledge those who reviewed this document and sent their comments and suggestions: Aamir Ikram (Executive Director, National Institute of Health - NIH, Pakistan), Asim Rauf (CEO, Drug Regulatory Authority of Pakistan - DRAP, Pakistan) and core teams from their institutes including Sayyad Hussain Khan (Additional Director QMS, Drug Regulatory Authority of Pakistan - DRAP, Pakistan), Obaidullah Malik (Director Pharmacy Services, Drug Regulatory Authority of Pakistan - DRAP, Pakistan), Abdul Mughees Mudassir (Deputy Director to CEO, Drug Regulatory Authority of Pakistan - DRAP, Pakistan), and Asad Ullah (Deputy Director QMS, Drug Regulatory Authority of Pakistan - DRAP, Pakistan). We would also like to thank the external entities and individuals who have contributed to the survey, interviews and/or discussion in the development of this case study.

This case study was developed under the WHO Local Production and Assistance Unit’s mandates to support Member States in strengthening sustainable local production and technology transfer to improve access to safe, effective, quality and affordable medicines and other health technologies with funding from the Governments of China and France.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>BPD</td>
<td>Biological Production Division</td>
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<tr>
<td>BOI</td>
<td>Board of Investment</td>
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<td>CEMB</td>
<td>Center of Excellence in Molecular Biology</td>
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<td>CEPI</td>
<td>Coalition for Epidemic Preparedness Innovations</td>
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<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>CPI</td>
<td>consumer price index</td>
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<td>CTU</td>
<td>Clinical Trials Unit</td>
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<td>DCB</td>
<td>Dow College of Biotechnology</td>
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<td>DESTO</td>
<td>Defense Science and Technology Organization</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DRAP</td>
<td>Drug Regulatory Authority of Pakistan</td>
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<td>DUHS</td>
<td>Dow University of Health Sciences</td>
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<td>EOI</td>
<td>expression of interest</td>
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<td>EPI</td>
<td>expanded programme on immunization</td>
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<td>EUA</td>
<td>emergency use authorization</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GBT</td>
<td>Global benchmarking tool</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>GST</td>
<td>general sales tax</td>
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<td>HEC</td>
<td>Higher Education Commission</td>
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<td>HRI</td>
<td>Health Research Institute</td>
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<td>ICCBS</td>
<td>International Center for Chemical and Biological Sciences</td>
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<td>IPV</td>
<td>inactivated polio vaccine</td>
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<td>IVIG</td>
<td>intravenous immunoglobulin</td>
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<td>LMICs</td>
<td>low- and middle-income countries</td>
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<td>MNHSRC</td>
<td>Ministry of National Health Service, Regulation and Coordination</td>
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<td>MOFA</td>
<td>Ministry of Foreign Affairs</td>
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<td>MOST</td>
<td>Ministry of Science and Technology</td>
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<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<td>MRP</td>
<td>maximum retail price</td>
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<td>NCLB</td>
<td>National Control Laboratory for Biologicals</td>
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<td>NCOC</td>
<td>National Command and Operation Center</td>
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<td>NIBGE</td>
<td>National Institute for Biotechnology and Genetic Engineering</td>
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<td>NIH</td>
<td>National Institute of Health</td>
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<td>NMP</td>
<td>National Medicine Policy</td>
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<td>NUST</td>
<td>National University of Science and Technology</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
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<td>PIC/S</td>
<td>Pharmaceutical Inspection Co-operation Scheme</td>
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<td>PIDM</td>
<td>Programme for International Drug Monitoring</td>
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<td>PSF</td>
<td>Pakistan Science Foundation</td>
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<td>QAU</td>
<td>Quaid-i-Azam University</td>
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<td>QC</td>
<td>quality control</td>
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<td>R&amp;D</td>
<td>research and development</td>
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<td>RDV</td>
<td>remdesivir</td>
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<td>RNA</td>
<td>ribonucleic acid</td>
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<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
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<td>STZA</td>
<td>Special Technology Zones Authority</td>
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<td>UHS</td>
<td>University of Health Sciences</td>
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<td>UNIDO</td>
<td>United Nations Industrial Development Organization</td>
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<td>VBPC</td>
<td>Vaccine and Biological Products Center</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WLA</td>
<td>WHO-Listed Authority</td>
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Executive summary

An overview of the ecosystem for local production of mRNA vaccines in Pakistan

The emergence of mRNA-based vaccines is a turning point in global health – arguably the most important development since the introduction of vaccines 225 years ago. Developed in the wake of COVID-19 pandemic, mRNA technology can be employed to produce other vaccines and therapeutic biologicals.

Despite being the fifth largest domestic market in the world and having a high population growth rate, Pakistan has seriously lagged behind in relation to vaccine production. For example, 90% of all vaccines used in the national immunization programme are imported. There have been many previous attempts to promote the local production of vaccines, but they have not produced positive results. Once again, the COVID-19 pandemic has emphasized the importance of vaccines and stimulated a renewed national interest in strengthening local production to achieve relative self-sufficiency. During the global pandemic, Pakistan successfully conducted its first multi-country Phase III clinical trial for a vaccine (CanSino Bio). On completion of the trial, the National Institute of Health (NIH) of Pakistan co-produced the vaccine through technology transfer from the originator Chinese company.

This development and experience has generated opportunities for more collaborative research and development (R&D) on vaccines, including clinical trials in Pakistan. The National Command and Operation Center (NCOC) – the national nerve centre for managing the successful COVID-19 response including the national vaccine procurement and deployment campaign – has also led discussions for strengthening local production of vaccines. This discourse led to the development of a first official report on challenges and opportunities in indigenous vaccine production, which was thoroughly discussed in NCOC and led to the development of a first national vaccine policy in the country. The Ministry of National Health Service, Regulation and Coordination (MNHSRC), Ministry of Foreign Affairs (MOFA), Ministry of Science and Technology (MOST), the Scientific and Technological Cooperation of the Organization of Islamic Cooperation, the Drug Regulatory Authority of Pakistan (DRAP), NIH and some public sector universities all took part in these discussions. Resulting documents have nevertheless not yet been made public.

Other than a relatively small quantity of locally produced CanSino Bio vaccine (following emergency use approval on completion of Phase III clinical trials), more than 96% of COVID-19 vaccines were imported. Approximately 16% of total vaccines used were mRNA vaccines manufactured by Moderna and Pfizer-BioNTech.

Pakistan’s National Health Vision (2016–2025) highlights the issue of low access to and affordability of essential medicines and vaccines, and identifies the strategic objective of ensuring the basic right of citizens to have access to medical products when needed. In this context, strengthening of DRAP is a strategic priority.

In Pakistan, a certain number of COVID-19 vaccines have been made available for mass immunization following approval by DRAP for accelerated emergency use. Pakistan is currently not producing mRNA vaccines, for COVID-19 or any other diseases. At NIH, the Vaccine and Biological Products Center (VBPC) produces other vaccines including tetanus toxoid, measles vaccine, rabies vaccine, anti-rabies serum, anti-snake serum, typhoid vaccine and freeze-
dried typhoid and cholera vaccines. Due to market requirements and various other factors, NIH is currently only producing vaccines through fill-finish processes and quality release. The Biological Production Division (BPD) also produces allergenic extracts. However, seeing the potential of mRNA vaccine technology, Pakistan applied to the World Health Organization (WHO) to be considered as one of the countries to become a ‘technology transfer hub’ for mRNA vaccine production, and it was included in the list along with four other countries. In the past year, however, there has not been any major transfer of technology on mRNA production in Pakistan through this initiative except training of some staff members from NIH in the Republic of Korea.

Dow College of Biotechnology (DCB) is part of the Dow University of Health Sciences (DUHS), a public sector institution. Researchers there have commenced R&D for mRNA vaccine development, and have succeeded in developing a candidate vaccine design against multivariant SARS-COV-2 virus. this led to scientific papers published in peer-reviewed journals, but due to lack of resources they could not start pre-clinical studies. Although there are other universities in Pakistan with biotechnology education, training and research facilities they have not conducted much work on mRNA technology.

In the private sector, there are less than ten companies – among around 620 pharmaceutical manufacturers – that are involved in vaccine and biological production.

In collaboration with the WHO country office, DRAP convened a series of meetings with potential vaccine manufacturers for a comprehensive indigenous capacity mapping exercise, exploring opportunities related to existing development capacities, current product ranges and support for vaccine-related infrastructure such as storage and transportation.

Like their public sector counterparts, those producing vaccines only do so through fill-finish functions, and none produce vaccine substances by themselves. None are conducting mRNA vaccine R&D or production efforts. Getz Pharma is the only company that did start a collaborative project on mRNA vaccines in collaboration with a Chinese company, but due to problems in clinical trial approval the project was shelved.

Amson Vaccines and Pharma is manufacturing human vaccines and anti-venom sera, but they also import all the vaccine concentrates and do fill-finish production. Amson has also been exporting vaccines such as tetanus toxoid and hepatitis B vaccine to the Philippines for many years. In addition, some of its auto-destruct immunization syringes are WHO-prequalified.

The DRAP has an institutional framework that is aligned with international regulatory frameworks for emergency use authorization (EUL) of new health products, fast-track approvals, clinical trials, pharmacovigilance, monitoring of adverse effects following immunization and therapeutics as part of regulatory preparedness.

Given its large domestic market and a sizeable pharmaceutical sector, its selection among the countries in which WHO plans to facilitate technology transfer for mRNA vaccine production, and the significant political interest in vaccine production in the wake of the COVID-19 experience, Pakistan is well-placed to actively pursue mRNA vaccine production in the country.
1. The ecosystem for local production of mRNA vaccines

1.1 Messenger RNA (mRNA)
Deoxyribonucleic acid (DNA) is the well-known double-stranded helical structure found in the nucleus of a given cell, encoded with a sequence of four nucleotide bases that constitute the genes. Through the process of transcription, an enzyme converts gene segments into messenger ribonucleic acid (mRNA). The single-stranded mRNA is then read by a ribosome in the process of synthesizing specific proteins. In this way, mRNA carries the genetic message from the nucleus to the cytoplasm, hence ‘messenger’. The process that converts DNA to mRNA and subsequently into specific proteins is fundamental to many cellular and bodily processes and functions (1).

1.2 mRNA vaccines
Conventional vaccines prevent infections by introducing surface antigens from the infecting organism (or an attenuated organism) into the body to train the immune system to neutralize future infections. The mRNA vaccine, in contrast, only contains the genetic instructions needed to produce these antigens within a cell. The major obstacle to overcome was to insulate mRNA from contact with abundantly present RNase enzymes, which can rapidly denature mRNA on contact. The solution was a lipid nano-encapsulation to protect the mRNA (2). Final testing demonstrated the safety and efficacy of the mRNA vaccine approach.

1.3 mRNA vaccines: a turning point
In the wake of the coronavirus disease (COVID-19) pandemic, the first approval of an mRNA vaccine by a stringent regulatory authority took place in August 2021 (3). This is regarded a major breakthrough because it has significant implications for the way vaccines and therapeutic biological products will be produced in future. mRNA-based vaccine technology is extremely efficient: It took Moderna only two days to create a candidate vaccine after receiving the genome sequence (4). Because mRNA vaccines carry only the directions for producing antigens – and use the human body itself as a vaccine ‘factory’ – mRNA doses are extremely small (20-100 μg), allowing small-scale manufacturing to provide vaccines to millions. While most of the previous research on mRNA vaccines has been focused on cancer treatment, it can be expanded to include many other classes of diseases.

1.4 Safety and efficacy of mRNA vaccines
With conventional vaccines, the delay from discovery to deployment is a long, complicated and expensive process. Typically taking from 10 to 15 years to complete, the process also involves a long discovery phase – in which a candidate vaccine is designed and preclinical experimentation is done – and then the vaccine enters testing in human subjects during Phase I, II and III clinical trials. Many years are generally required to collect sufficient data to demonstrate vaccine safety and efficacy. However, due to tremendous need and pressure to develop a vaccine against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the long-haul vaccine development
process was reduced to less than one year. That was possible both because some knowledge existed (i.e. through the previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) vaccine development programmes)(5) and because hundreds of thousands of people were getting infected with SARS-CoV-2, enabling collection of sufficient data in a placebo-controlled model (3).

1.5 Accelerated emergency use authorization

Despite many ethical considerations, but due to the public health emergency the COVID-19 pandemic represented, regulatory agencies fast-tracked approval processes. The United States Food and Drug Administration (FDA) issued new guidelines for approval of COVID-19 vaccines (6) that demonstrated the minimum efficacy of 50%, although the results from mRNA surprised everyone with 90%+ efficacy that had never been possible for any vaccine.

1.6 COVID-19 vaccines in Pakistan

One of the key features of the Pakistan national response to the COVID-19 pandemic has been the aggressive procurement and deployment of COVID-19 vaccines. Pakistan has vaccinated around 132 million people above the age of 12 years until September 2022, out of the total population of 236 million for all ages – or an approximate of 80% of the eligible population (7). This remarkable achievement has played an important role in controlling the spread of the disease in Pakistan. With the exception of one vaccine, CanSino, which Pakistan tested and co-produced with China, all other seven vaccines that were used were imported, including mRNA vaccines. Fig. 1 provides details of the vaccine volumes and their relative procurement and use.

Fig. 1. COVID-19 vaccine procurement and use in Pakistan (as of 18 November 2021)

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*The data is from the Covid Management Information System at the Federal Expanded Programme on Immunization (November 2021)*
1.7 mRNA vaccines in Pakistan

Two mRNA vaccines were imported and used in Pakistan. Around 21 million doses of Pfizer-BioNTech vaccine were received, making it the third most commonly used vaccine in the country (following around 82.5 million doses of SinoVac and around 40 million doses of SinoPharm). Only 5.5 million doses of Moderna were imported. mRNA vaccines in Pakistan were procured through COVAX\(^6\) and supplied through the United Nations Children’s Fund (UNICEF).

1.8 National policies related to mRNA vaccines in Pakistan

Pakistan does not have a national policy on vaccines, let alone a specific policy on mRNA vaccine production. However, in the wake of the COVID-19 pandemic, indigenous vaccine production has become an active policy discussion and according to internal documents the National Command and Operation Center (NCOC) – the pivotal and principal body governing the policies and implementation of the national COVID-19 effort of Pakistan – has convened in-depth discussions on this issue. These sessions were chaired by the Federal Minister for Planning, Development, Reforms and Special Initiatives and participants included the Special Assistant to the Prime Minister (SAPM – equivalent to State Minister) on Health and Advisor to the Prime Minister on Commerce and Investment, and NCOC officials.

Reportedly, as a follow-up, a policy document has been prepared by the National Institute of Health (NIH) and submitted to the Federal Ministry of National Health Service, Regulation and Coordination (MNHSRC) but the ministry has not taken it up at the cabinet level. So, the document remains unannounced and is not available publicly.

A consultation was made on the National Medicine Policy (NMP) that covers the supply system and related regulations. A draft was prepared which could not be finalized. As a holistic approach, medicines and vaccines including mRNA vaccines can be covered in this policy. A series of consultations would be needed to finalize the draft NMP in light of key medicines and health technology issues.

1.9 High-level national initiatives and developments on indigenous vaccine production

The COVID-19 pandemic led to a stark realization of how much Pakistan has lagged behind in the domestic production of vaccines, and how dependent the country is on imports. This has led to several initiatives, primarily originating from NCOC, which initially requested NIH leadership to develop a paper on the challenges and opportunities for indigenous vaccine production in Pakistan. NIH produced and presented the paper to the NCOC, which led to a decision to develop the first vaccine policy in the country. The NIH situation analysis document and the vaccine policy document have not yet been made public.

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\(^6\) COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator (see: https://www.who.int/initiatives/act-accelerator).
In addition, the Biological Production Division (BPD) at NIH has been strengthened and a Clinical Trial Unit (CTU) has been established. The Ministry of Foreign Affairs (MOFA) has taken an active role in facilitating foreign collaborations on vaccine production and a number of options have arisen in terms of collaborations for vaccine production. The following paragraphs provide some details of the most important ones.

1.9.1 World Health Organization and Drug Regulatory Authority of Pakistan

Throughout the pandemic, the WHO country office for Pakistan provided technical and instructional support to the Drug Regulatory Authority of Pakistan (DRAP) to help strengthen regulatory preparedness. WHO Pakistan along with DRAP invited potential vaccine manufacturers to submit an expression of interest (EOI) to the Coalition for Epidemic Preparedness Innovations (CEPI). Following discussions and consultations with WHO headquarters and regional office, WHO Pakistan provided the platform for arranging joint consultations of regulators and manufacturers. Two meetings were held in the WHO country office, and one meeting was held at the DRAP office in 2021. The main objective was to advance the agenda of vaccine systems support and to assess opportunities and barriers to indigenous production – with a particular focus on COVID-19 vaccines as well as opportunities for technology transfer. Achieving this objective requires a comprehensive roadmap that synergizes and aligns national efforts, and involves two critical actors: regulators and product developers. A brief situation analysis was developed identifying quality and technical barriers, and highlighting roadmap components:

- WHO supported DRAP regulators in emergency use authorization (EUA) and harmonized procedures for COVID-19 vaccines and therapeutics evaluations, and requisite approvals in the country.
- WHO has been supporting synergies for the country regulatory authority (DRAP) to achieve WHO-Listed Authority (WLA) status, through sharing WHO standards and guidelines and a series of capacity-building opportunities. The WHO country office has technically assisted and coordinated throughout DRAP attaining maturity level 3 through the WHO Global benchmarking tool (GBT). The efforts are sustained and observed assessments are underway.

Pakistan has undergone many reforms and policy changes in the past few years for ensuring the delivery of safe and efficacious medicines and vaccines to its people. In November 2018, the country acquired a full membership status to the WHO Programme for International Drug Monitoring (WHO-PIDM). Under Rule 20 of the Bio-Study Rules (2017 and 2018), the DRAP Division of Pharmacy Services maintains a clinical trial registry for approved clinical trials involving human subjects being conducted in Pakistan. There are 36 approved clinical trials and ongoing studies as of 30 May 2022 (8,9).

1.9.2 Vaccine and Biological Products Center of NIH

The NIH was established in 1965 and its BPD has been involved in vaccine and biological production from the outset. The NIH (Re-organization) Act, 2021 established the Institute as an autonomous body with seven centres: one of which is Vaccine and Biological Products Center (VBPC - formerly known as BPD). As a sole public sector manufacturer, BPD produced bacterial, viral vaccines and therapeutic anti-sera. Research and development (R&D) of vaccines has not been the strength of
the BPD, however, and it has been involved mainly in bulk-buying of concentrates and ‘fill–finish’ vaccines.

There have been many initiatives to strengthen vaccine production at BPD, including a major effort to involve the private sector through public–private partnership in 1993 – but these efforts have not been successful.

1.9.3 Clinical Trial Unit at NIH

The NIH has now established a CTU. Managing a first multi-country clinical trial of CanSino Bio vaccine has built confidence and capacity in the institution, leading to approval of EUA by DRAP, followed by other regulatory authorities. After the successful CanSino Bio vaccine clinical trial, a number of offers have been received by the NIH from other countries, and these are under consideration for clinical trials, which would potentially further enhance the capacity of the unit.

1.9.4 Ministry of Foreign Affairs meeting on vaccine production (I)

Due to the national challenge posed by the COVID-19 pandemic, the whole of the government was affected and there was a concern regarding collectively addressing the problem, now and in the future. The Ministry of Foreign Affairs also acted by convening stakeholders to promote vaccine production. The comparative advantage of the Ministry of Foreign Affairs is its access to diplomatic channels to bilaterally and multilaterally connect with countries who have the vaccine production technology, and that have an interest in supporting and collaborating with other countries. On 8 June 2021, the Ministry of Foreign Affairs held a meeting with major stakeholders for the above purpose and formulated a working group on international cooperation and partnerships in vaccine production. Key recommendations emerged from this meeting:

- There should be one window of facilitation for outside parties interested in vaccine production.
- A ‘Center of Excellence for Vaccine Research & Development’ should be established.
- Joint ventures should be supported by the government for complete and transparent technology transfer for continuous vaccine development.
- NIH will be the hub of all activities related to vaccine technology transfer and diplomatic support to facilitate one window of operation.
- NIH will facilitate linkages between academia, R&D institutions, industry and the private sector.
- The government must extend incentives, such as:
  - Buy-back agreements.
  - Defined methodology for sale and purchase, billing and payments.
  - Assure monthly revenue for operations, maintenance, debt servicing, insurance charges.
  - Fixed payment obligations for purchaser and guaranteed by the Government of Pakistan.
• Funding for research needs to be increased by Higher Education Commission of Pakistan (HEC), Ministry of Science and Technology (MOST), Pakistan Science Foundation (PSF), and the Health Research Institute (HRI).
• Lowering operating cost.
• Price checks.
• Duties and tax rebates for 10 years:
  i. Turn over tax on sales revenue to be exempted.
  ii. Zero rating of withholding tax, excise duty on import of plant, machinery and equipment, tools, and consumables.
  iii. Corporate tax on income, profits and gains from projects should be exempted during a tax holiday period.
  iv. Financial support for technology transfer rights and royalties etc.
  v. Loans on soft terms.
  vi. Incentives for export business.
• Multinational manufacturers should invest via Board of Investment (BOI) or trade cooperation.
• Experts for clinical evaluation, testing of biological products, and good manufacturing practice (GMP) inspections should be included as per WHO criteria.
• Research to identify etiological agents and local strains, wherein indigenous technologies need to be exploited.
• Venture capital fund sponsored by government organizations such as HEC, Ministry of Science and Technology, PSF and private sector, organized by the Federal Chamber of Commerce and Industry.
• Research on animal and human health as well as quality control (QC) should be emphasized.
• DRAP needs to be upgraded from maturity level 2 to maturity level 4 as per WHO regulatory standards.

1.9.5 Ministry of Foreign Affairs Meeting on vaccine production (II)

On 9 August 2021, another meeting was held at the Ministry of Foreign Affairs with all the important stakeholders. Stakeholders’ feedback on their capabilities and capacity had been received since the June 2021 meeting and initial analysis had been completed. The mapping of major stakeholders had also been completed. NIH had developed a project concept (PC-2) on a Centre of Excellence for Vaccine R&D and it had been approved. A province-level directory of virologists, bacteriologists, biotechnologists and biomedical engineers had been initiated. Representatives from the pharmaceutical sector highlighted the lack of GMP facilities as a major hurdle in achieving local vaccine production. Representatives from DRAP informed the meeting that a governance-related upgrading is in process and DRAP has submitted an EOI to WHO for regulatory authority maturity level 3 approval. DRAP also informed participants that they have developed a Drug Substance Manufacturing Policy that has been submitted for approval. Pakistan’s Permanent Representatives to WHO and the World Trade Organization (WTO) in Geneva briefed the participants on ongoing

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6 Ministry of Science and Technology (see: https://most.gov.pk/).
7 Pakistan Science Foundation (see: https://psf.gov.pk/).
8 National Health Research Institute (see: https://www.nih.org.pk/health-research-institute).
developments with regards to support being sought from WHO and intellectual property waiver discussions at WTO. The important action points from the discussion from the second meeting at the Ministry of Foreign Affairs are summarized below:

- In the context of a waiver under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS waiver), it is important for stakeholders to pursue a business case for local vaccine development with the longer time objective of creating exportable surplus. Furthermore, a market-shaping role can be taken by placing orders for vaccines.
- A meeting with senior executives of WHO can be arranged with the possibility of declaring Pakistan a regional hub in the WHO Eastern Mediterranean Region.
- Sustaining the Working Group for actively pursuing international partnerships was regarded as very crucial.

However, no information is available about further meetings and outcomes at the Ministry of Foreign Affairs in this regard.

1.9.6 Expression of interest for establishing mRNA technology hub in Pakistan

In pursuance of the above and in the context of TRIPS waiver⁶ – and in response to a WHO call from interested countries in late 2021 – the Government of Pakistan submitted an EOI to WHO headquarters for establishing an mRNA Vaccine Technology Hub at the NIH and for upgrading of facilities for large-scale indigenous vaccine production to fulfil national demand. WHO received expressions of interest from many countries, but it prioritized “countries that do not have mRNA technology but already have some biomanufacturing infrastructure and capacity”. WHO has established two mRNA technology transfer hubs: in South Africa and the Republic of Korea. On 23 February 2022, WHO, the Republic of Korea and the WHO Academy announced that Bangladesh, Indonesia, Pakistan, Serbia and Viet Nam will be receiving mRNA technology from a new established technology transfer hub in the Republic of Korea. These countries were vetted by a group of experts and proved that they had the capacity to absorb the technology and, with targeted training, move to production stage relatively quickly. Argentina and Brazil had already joined this initiative and were already receiving mRNA-related technology transfer. Since this time, two batches of three professionals each from Pakistan have visited the technology hub in the Republic of Korea and the third batch is expected to visit the South Africa hub in 2023.⁷

1.9.7 COMSTECH meeting on vaccine development

The Federal Minister of Science and Technology chaired an expert level meeting on human vaccine development in Pakistan on 14 July 2021 at the Ministerial Standing Committee on Scientific and Technological Cooperation of the Organization of Islamic Cooperation (COMSTECH). All stakeholders, including from the pharmaceutical industry participated in this meeting. The recommendations from the meeting are as follows:

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⁶ On 17 June 2022, during the 12th WTO Ministerial Conference, a Trade Related Aspects of Intellectual Property Rights (TRIPS) waiver was agreed for COVID-19 vaccines.
⁷ Personal communication with senior officials in NIH, Islamabad.
The Government of Pakistan should facilitate public–private partnership for indigenous development of vaccines/biologicals through steps such as buy-back, import substitution, as well as prompt regulatory approval/facilitation from DRAP.

Concerned industries were asked to prepare a position paper highlighting common issues and problems.

Industries were requested to facilitate the process of vaccine development by a buy-back policy and through increased taxes on imported vaccines.

Industry requested an upgrading of the compliance level for DRAP’s National Control Laboratory for Biologicals (NCLB), as per WHO standards, so that products could be exported to developed countries.

Federal Minister for Science and Technology kindly agreed to support R&D institutions working in the development of vaccines and biologics.

### 1.9.8 Government incentives for manufacturers and investors to promote mRNA vaccine production

Despite recommendations from various official meetings to incentivize manufacturers and investors to vaccine production in general, there are currently no specific related government incentives in place. However, the Federal Government has established a special authority to promote science and technology with in-built incentives.

### 1.9.9 Special Technology Zones Authority Ordinance, 2020

On 3 December 2020, the Government of Pakistan promulgated Special Technology Zones Authority (STZA) Ordinance, 2020. The objective of this law is: “To ensure the development of scientific and technological ecosystem through development of zone to accelerate technology development in the country”. The Prime Minister is the President of the Board of Governors of STZA and its key functions include identification, promotion and facilitation of investment in prioritized technology clusters and establishment of technology zones in the different parts of the country. The Federal Government will provide grants to the STZA from time to time and a STZA Fund will be created. To begin with, five technology zones are being established in Islamabad, Karachi, Haripur, Lahore and Quetta. Incentives for zone developers include: tax exemptions on income attributable in relation to the development and operations of the zones for a period of ten years; exemption from all custom duties and taxes for a period of ten years; exemption from general sales tax (GST) on goods and services. And for enterprises in the zones, an attractive incentive package has been developed by the authority including: exemption from all income taxes (e.g. withholding tax, presumptive tax) for a period of ten years; exemption from all custom duties and taxes for a period of ten years; exemption from property tax for ten years; exemption from GST on goods and services on import of materials for consumption; and tax exemption on dividend income and long-term capital gains from related investments. The STZA aims to provide a one-window facilitation to local and international manufacturers. Biotechnology is included in the scope of STZA and 120 acres of land on the NIH campus will be considered as a Special Technology Zone for biotechnology including vaccine production. However, despite the package of incentives, no major enterprise in vaccine production – including mRNA vaccine production – has been set-up under the auspices of the STZA.1

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1 Based on personal communication.
1.9.10 Investment regime to produce mRNA vaccines

The BOI\(^1\) has its own governance but is also linked with the Ministry of Commerce. The first investment policy in Pakistan was developed in 1997. The BOI was established with broad based responsibilities for promotion of investment in all sectors of the economy, facilitation of local and foreign investors for speedy materialization of their projects, enhancement of Pakistan’s international competitiveness and contribution to economic and social development. The BOI assists manufacturers and current/future investors, as well as facilitating the implementation and operation of their projects. The wide range of services provided by BOI also includes providing information on the opportunities for investment and facilitating manufacturers that may be looking for joint ventures. BOI acts as a focal point of contact for existing and prospective investors, both domestic and foreign, to provide them with all necessary information and assistance in coordination with other government departments/agencies at the federal and provincial level.

Biotechnology and vaccine production – including mRNA vaccine production – are currently not among the priority sectors for investment according to the website of the BOI. Vaccine production is not included in the description of ‘Investment regime’ nor the ‘Investment opportunities’ sections of the website.

The only mention of vaccines is with regard to a joint statement made by the former Prime Minister of Pakistan and the President of China during the former’s visit to China from 3 to 6 February 2022. The last bullet point states:

33. The two sides signed or concluded a number of agreements/MoUs, covering bilateral cooperation in areas of economic and technical, industry, investment, infrastructure, space, vaccine, digitalization, standardization, disaster management, culture, sports and vocational education.

1.9.11 Regulation of mRNA vaccine production in Pakistan

Pakistan is a federation with four large provinces and administrative territories. Some northern areas and capital territory are directly administered by the Federal Government. Health provision in provinces is the responsibility of the provincial governments including the regulation of health services through provincial health care commissions. However, drug regulation continues to be the federal responsibility. The DRAP is the apex regulator of therapeutic goods under DRAP Act 2012 (11). The licensing, registering, advertising, clinical trials, GMP compliance, pharmacovigilance and adverse effects following immunization, and therapeutic goods-related import and export functions are performed by DRAP. Vaccines are also subjected to lot release by the National Control Laboratory for Biologicals (NCLB) under DRAP (11). The NCLB has recently been included as Associate Member of the WHO Global Network of National Control Laboratories for Biologicals. DRAP is mandated to “determining standards for biological manufacturing and also to issue and enforce guidelines, among others, for clinical trials” (11).

\(^1\) Pakistan Board of Investment (see: https://invest.gov.pk/).
Vaccines and other biological preventive or therapeutic products are covered under the broad definition of “drug” although these are not specifically mentioned. However, the DRAP Act elaborately defines “biological drug” in Schedule-1 (Annex 1). In this schedule, three kinds of vaccines are defined, as follows:

- Bacterial vaccines including live, killed whole cell, protein sub-unit, polysaccharide or glyco-conjugate, toxin derivatives, and rDNA biotechnology developed.
- Viral vaccines including live, inactivated, sub-unit, DNA, conjugated.
- Polyvalent combinations of vaccines containing combination of vaccines.

There is no specific mention of mRNA technology-based vaccines in the current regulations. One can assume that the existing regulations for “biological drugs” including vaccines will be applicable to mRNA vaccines as and when these are manufactured in the country. The DRAP Act provides that no human vaccines, blood products (e.g. plasma-derived medicinal products) and anti-sera (e.g. antivenoms and anti-rabies) shall be sold and used until a Lot Release Certificate has been obtained from the Federal Government Analyst of the NCLB, Islamabad.

There are comprehensive regulations for ensuring quality and safety of vaccines. The manufacturing capacities have also been assessed for the purpose of this report. Supply chain and logistics, and immunization programmes are other important elements in assessing the current overall landscape of vaccines in the country.

**Table 1. Summary of vaccine production capacities and other key elements**

<table>
<thead>
<tr>
<th>Focus area</th>
<th>Presence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research and development</td>
<td>Initial stages</td>
<td>• Lack of skilled human resources and technological limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-availability of national level vaccine policy</td>
</tr>
<tr>
<td>Regulations and NRA</td>
<td>Yes</td>
<td>• DRAP Act 2012 and rules framed thereunder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRAP regulates licensing, manufacturing, import and export,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sales, storage, and distribution of therapeutic goods</td>
</tr>
<tr>
<td>Manufacturing capacity</td>
<td>Partial</td>
<td>• Biopharmaceutical manufacturers have capability to perform</td>
</tr>
<tr>
<td></td>
<td></td>
<td>one or two of the final steps of vaccine production</td>
</tr>
<tr>
<td>Supply chain and logistics</td>
<td>Yes</td>
<td>• Public and private entities are involved in maintaining</td>
</tr>
<tr>
<td></td>
<td></td>
<td>supply chain and logistics for vaccines</td>
</tr>
<tr>
<td>Vaccine immunization</td>
<td>Yes</td>
<td>• Expanded Programme on Immunization (EPI) under</td>
</tr>
<tr>
<td>programme</td>
<td></td>
<td>Ministry of National Health Services, Regulation and Coordination</td>
</tr>
</tbody>
</table>

*Note: NRA = national regulatory authority.*

For producing quality vaccines, a legislative and institutional framework is important. Under the DRAP Act 2012, the DRAP has been mandated to ensure access to quality assured, safe and efficacious therapeutic goods through regulation of licensing, manufacturing, quality assurance, market control, clinical studies, laboratory testing, import and export of these goods. The DRAP Act
2012, the Drugs Act 1976 and rules framed under these stipulate conditions on which a drug, vaccine, medical device or health & over-the-counter (non-drug) product can be manufactured and sold in the country.

WHO has identified six critical control functions of a national regulatory system (WHONSQ/96.02 Rev.l)) as necessary for ensuring quality, safety and efficacy. DRAP is performing all of the six functions:
- A published set of requirements for licensing.
- Evaluation of clinical performance.
- A system of lot release.
- Use of laboratory when needed.
- Regular inspections for GMP.
- Surveillance of vaccine field performance.

Assessment and approvals of vaccines, current GMP compliance inspection, import and export, lot release and market control activities are performed by DRAP.

**Table 2. Brief summary of regulatory operations conducted by DRAP**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Status</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>National law exists for all medical products</td>
<td>Yes. The DRAP Act 2012 provides legal mandate to DRAP for regulating licensing, manufacturing, import and export, sale, storage and distribution of therapeutic goods.</td>
<td>Vaccines are defined as biologicals in Pakistan under DRAP Act 2012. Drugs Act 1976 and rules framed thereunder are enforced under DRAP Act 2012. Vaccine manufacturing requirements are given in the law.</td>
</tr>
<tr>
<td>Establishment licensing</td>
<td>Yes. The Division of Drug Licensing performs licensing activities and grants manufacturing licenses.</td>
<td>Drug manufacturing licenses are issued after completion of GMP assessment and other national requirements. These licenses are renewed every five years.</td>
</tr>
<tr>
<td>Assessment of vaccines and approval process</td>
<td>Yes. The Division of Biological Drugs in DRAP is responsible for assessment, evaluation, and registration of biological drugs (includes vaccines).</td>
<td>Vaccines are assessed based on the criteria of quality, safety and efficacy by the DRAP Registration Board. Grant of registration is done after successful submission of application on Common Technical Document (CTD), assessment and evaluation, and consideration by the Registration Board. This registration has a validity of five years.</td>
</tr>
<tr>
<td>Current GMP compliance</td>
<td>Yes. The Division of Quality Assurance &amp; Laboratory Testing (QA&amp;LT) performs GMP inspections.</td>
<td>Schedule B-II of Drugs (L,R&amp;A) 1976 provides basic guidance on GMP. Current GMP guidance from WHO guidelines are followed for inspection.</td>
</tr>
<tr>
<td>Quality testing</td>
<td>Quality control (QC) laboratories of manufacturers perform control testing.</td>
<td>Quality testing for vaccines is mandated to National Control Laboratory for Biologicals (NCLB) in Islamabad, which</td>
</tr>
</tbody>
</table>
Data and carrying “to country. The 1.9. capacity investments significance immunization diseases Because Local detailed f In 2022, detailed f In 1.9. rDNA governments and Pharmacovigilance and surveillance Pharmacovigilance preparedness for collection and assessment of adverse events following immunization (AEFIs) exists. AEFIs are reported using various electronic platforms, which are then assessed by National Committee on AEFIs and DRAP for routine analysis. Risk communication is made through various print and electronic means.

1.9.12 Guidelines for regulatory requirements of biological drugs using recombinant DNA (rDNA) technology

In November 2022, the Drug Registration Board constituted a Committee on Biological Drugs. After detailed deliberations, the Committee gave recommendations to the Drug Registration Board, which adopted these recommendations covering: Biological drugs (concentrated form/ready-to-fill form); Biological drugs (concentrated form/naked vials); Other manufacturing processes. The detailed guidelines are available (12).

1.9.13 National vaccine R&D capacity

Local R&D is critical in the field of biotechnology generally, especially in vaccine production. Because of the importance of vaccines as the most cost-effective public health tools in preventing diseases and the negative consequences of low immunization rates for essential vaccines, governments play a definitive role in vaccine R&D, procurement and deployment. Routine immunization programmes and, more recently, COVID-19 vaccination programmes emphasize the significance of vaccines. More than ever, governments are interested in building their vaccine production capacity and achieve as much self-sufficiency as possible. Governments invest in setting up R&D programmes in national public health organizations as well as incentivizing private sector investments in this area. National R&D capacity in vaccines can be seen in terms of public sector capacity as well as that of vaccine producers in the country.

1.9.14 Vaccine R&D capacity in the public sector – NIH

The NIH, based in Islamabad, is the key public sector institute involved in health research in the country. In August 2021, the government introduced the NIH (Re-organization) Act, 2021 in order “to provide for an autonomous body corporate to manage institutes and centres (in NIH) for carrying out research and for the prevention of the spread of infectious diseases and health emergencies in Pakistan”. The new law reorganized and consolidated seven autonomous institutes and centres within NIH, namely: Center for Disease Control; HRI; National Health Laboratory; Health Data Center; Institute of Nutrition and Health; VBPC; and Center of Environmental and
Occupational Health. VBPC was previously named BPD. The functions of the VBPC include: Production of biological materials and vaccines; organization of training programmes through national diploma and specialized short-term training courses for vaccine and biologicals production; collaboration with national and international research institutes to provide technical input in the areas of vaccine development, and vaccines research; promotion of research activities and development towards improving biological products; up-scaling of technologies and introducing newer vaccines, diagnostics and other biological products (Fig. 2).

VBPC now comprises: Quality Assurance Department; Quality Control Department; Allergy Center; Sera Processing Lab; and Department of Veterinary Farms Management.

1.9.15 First vaccine clinical trial in Pakistan

Pakistan participated in a multi-country Phase III clinical trial in 2020 for a vaccine during the COVID-19 global pandemic (CanSino Bio, a single-dose vaccine developed in China based upon inactivated virus). This was the first ever Phase III clinical trial for a vaccine that took place in Pakistan, which has opened doors for more such clinical research in the country. The same trial also took place in Argentina, Chile, China, Mexico and the Russian Federation. The trial included a transfer of technology agreement between CanSino and NIH (Pakistan) for the phased co-manufacture of the COVID-19 vaccine under the name of ‘PakVac’. Formulation from concentrate, filling and packaging along with strict QC is underway at NIH with production capacity of over 3 million doses per month.¹

Fig. 2. Results of a recent SWOT analysis of the Vaccine and Biological Products Center

1.9.16 Vaccine clinical trials in the pipeline

More countries are now showing interest in conducting clinical trials for biological products in Pakistan. According to an official internal document, at least nine clinical trials have been offered

¹ Internal official document (2021).
to NIH and/or are under process in Pakistan in the past two years, including: two COVID-19 vaccines undergoing animal testing by Defense Science and Technology Organization (DESTO), Pakistan; one COVID-19 vaccine in animal testing by National Institute for Biotechnology and Genetic Engineering (NIBGE), Pakistan; work is underway for a randomized single-blind trial by the CEPI in a collaboration between the Agha Khan University, NIH, Harvard University and Oxford University; a project to test a three-dose COVID-19 vaccine is underway by University of Health Sciences (UHS), Pakistan and Anhui Zhifei Longcom China; a global, multi-centre, randomized, double-blind, placebo-controlled Phase III clinical trial to evaluate the protective efficacy, safety, and immunogenicity of a SARS-CoV-2 mRNA vaccine candidate produced by WALVAX Biotechnology Co Ltd, China; efficacy, immunogenicity and safety of the two-dose inactivated COVID-19 Vaccine (TURKOVAC) versus the two-dose CoronaVac (Sinovac) vaccine in healthy subjects by Koçak Farma İlaç ve Kimya Sanayi A.Ş. Organize Sanayi Bölgesi Fatih Cad, Türkiye; a proposal under consideration for a Phase III clinical trial for a bivalent recombinant SARS-CoV-2 spike protein trimeric vaccine for prevention of COVID-19 caused by variants by Chinese Sinocelitech Group; documentation in progress for a Phase I dose escalation study of orally administered PAX-1 in patients with moderate COVID-19 by Komi Pharm International Australia Pvt Ltd.

It is important for the potential manufacturers to provide evidence of their experience in developing and/or implementing innovations, including those that can potentially accelerate vaccine manufacturing and deployment. However, in the case of the antiviral remdesivir (RDV), the product's developer, Gilead, swiftly took action. Within two weeks of receiving FDA EUA for RDV, they entered into agreements with six manufacturers in developing countries. This was to facilitate the manufacture and supply of RDV to 127 low- and middle-income countries (LMICs). The six licensees initially selected included BF Bio in Lahore, a first for any Pakistani manufacturer to be part of an international supply solution of this nature. BF Bio successfully completed the technology transfer within six weeks, and delivered treatments for over 100 000 patients in 24 countries, including Pharmaceutical Inspection Co-operation Scheme (PIC/S) member countries such as Indonesia and Ukraine. BF Bio made investments in biological manufacturing parts as well as QC equipment to ensure start-up in minimal time contributed to the implementation of innovation.

1.9.17 Vaccine R&D capacity in the public sector (Non-NIH)

In addition to NIH, there are some public sector universities and organizations that are involved in biotechnology research, including those related to vaccines. The most important public sector institutions in this regard are:

- Center of Excellence in Molecular Biology (CEMB)
- Defense Science and Technology Organization (DESTO)
- Dow University of Life Sciences (DUHS)
- National Institute for Biotechnology and Genetic Engineering (NIBGE)
- National University of Science and Technology (NUST)
- Quaid-i-Azam University (QAU)
- International Center for Chemical and Biological Sciences (ICCBS)
- University of Health Sciences (UHS)

The below sections provide brief descriptions of these organizations.
The CEMB\(^1\) is a national centre under the auspices of Punjab University, based in Lahore. The facility has a capacity of analysis of over 2500 DNA samples and synthesis of over 200 primers daily. The Centre is positioned to make key contributions to advancements in molecular biology research. One of its key objectives is teaching and training to generate a workforce specifically trained in molecular biology and recombinant DNA technology. One of the centre’s many achievements is to clone human pharmaceutical protein genes for commercial production. CEMB is a potential collaborator in vaccine research, development and production in Pakistan.

The Defense Science and Technology Organization (DESTO) is a multi-disciplinary programme agency located under the Ministry of Defense Production. It is dedicated to evaluation of science and technology for use by the military. DESTO retains its expertise in a variety of disciplines such as aerodynamics, propulsion, electronics, computer systems, engineering, explosives, metallurgy, chemical and biological defence. Because of the strategic nature of the organization, the projects and research work at DESTO remain under strict restrictions and very few details of the projects are known to the public. Among its various responsibilities is its role as Pakistan’s national centre of expertise in chemical and biological defence. Since 2001, DESTO’s multi-disciplinary infrastructure base is now available to the public sector industry under commercial arrangements. DESTO has been collaborating with NIH.

Dow University of Health Sciences (DUHS) is based in Karachi. For several years it has worked on the production of vaccines and biological products and is currently focused on developing an anti-rabies vaccine, anti-rabies serum or immunoglobulin, anti-snake sera, as well as a mRNA COVID-19 vaccine. Highly qualified vaccinologists are working on developing mRNA vaccines at the Dow College of Biotechnology (DCB), a constituent unit of DUHS. They have designed an mRNA vaccine locally, and a paper in this regard has been published in an international journal, entitled *Design and immunoinformatic assessment of candidate multivariant mRNA vaccine construct against immune escape variants of SARS-CoV-2* (13). Other relevant papers have also been published by the team at DCB (14–17).

Dow College of Biotechnology (DCB) provides an excellent platform to achieve excellence in biotechnology and related fields. Currently, a four-year BS-Biotechnology programme is conducted there with 100 students inducted each year. The BS-Biotechnology course has been extensively designed to produce competent human resources in the field of biotechnology, and to train graduates to apply scientific knowledge to address locally prevalent health, environmental, food and industrial issues. The college faculty is involved in close collaboration with industries for their research and finding relevance to the local needs. This also gives a chance of employability to the young graduates of the college in industries, upon their graduation. Recently, MPhil and PhD biotechnology programmes have been initiated at DUHS. Both of these programmes are conducted with relevant PhD faculty from DCB. The College has two large-size (50L and 500L) fermentation units for any large-scale processing. In addition, the DCB is firmly linked with the sister institute Dow Institute of Life Sciences, which has an industrial scale filling facility. Funding is now awaited for the project. The university has also developed intravenous immunoglobulin (IVIG) from the plasma of recovered COVID-19 patients, for treatment of other COVID-19 patients.

\(^1\) Centre of Excellence in Molecular Biology (see: https://www.cemb.edu.pk/).
DUHS is in the process of developing a vaccine for bovine lumpy skin disease in collaboration with the Sindh Livestock Department. The university has a Dow Institute for Advanced Biological and Animal Research, and it also has a CTU. DUHS is a potential collaborator in vaccine research, development and production in Pakistan.

The National Institute for Biotechnology and Genetic Engineering (NIBGE) was established under the auspices of Pakistan Atomic Energy Commission in 1987. There are five research divisions at NIBGE namely: Agricultural Biotechnology; Health Biotechnology; Industrial Biotechnology; Environmental Biotechnology; and Technical Services divisions. NIBGE is the first institute to develop polymerase chain reaction (PCR)-based tests for various diseases. Biotechnology linked industries have been carefully listed for research endeavours. NIBGE has been contributing to developing trained manpower since its inception. The Department of Biotechnology has established MPhil and PhD degrees in biotechnology in affiliation with Pakistan Institute of Engineering and Applied Sciences, Islamabad. It is also affiliated with International Centre for Genetic Engineering and Biotechnology, in Trieste, Italy. The NIBGE has also been nominated as the Regional Centre of United Nations Industrial Development Organization (UNIDO) in Pakistan. The NIBGE library has been given the status of national library for the biological sciences. The NIBGE has been awarded with the ISO 9001-2000 Certification. The NIBGE is a potential collaborator in vaccine research, development and production in Pakistan.

The National University of Sciences and Technology (NUST) is a premier public sector university with a focus on creativity, innovation and entrepreneurship. Various constituent schools include the Atta-ur-Rehman School of Applied Biosciences (ASAB), which claims to be the country’s largest biotechnology cluster. As a strategic unit located within NUST, ASAB boasts state-of-the-art teaching and research. The school is unique in establishing expertise across a broad range of biotechnology topics, thereby encouraging innovative approaches to teaching and research. Areas of expertise include health care biotechnology, industrial biotechnology and plant biotechnology. The research and training programmes have research collaborations with other institutions in Pakistan and abroad. NUST is a potential collaborator in vaccine research, development and production in Pakistan.

The International Center for Chemical and Biological Sciences (ICCBS)\(^n\) – also known as the Hussain Ebrahim Jamal Research Institute of Chemistry and the Dr Panjwani Center for Molecular Medicine and Drug Research – is a Karachi based federally funded national research institute and national laboratory site managed by the University of Karachi for the HEC of the Government of Pakistan.

Quaid-i-Azam University (QAU)\(^n\) is an Islamabad based federal public sector university. QAU has four faculties and nine other teaching and research institutes, centres and schools including Faculty of Biological Sciences, which work in a number of research areas including medical biotechnology.

\(^n\) International Center for Chemical and Biological Sciences (see: https://www.iccs.edu/).

\(^n\) Quaid-i-Azam University (see: https://qau.edu.pk/).
The University of Health Sciences (UHS)\(^6\) is a Lahore based public sector university. UHS regulates and coordinates the activities of medical education, training and research institutions throughout the Punjab. UHC is a research-intensive university. Currently, extensive on-campus medical research is going on in 183 areas including asthma, diabetes, tuberculosis, typhoid, infertility, environmental pollution, various types of cancer, genetic disorders, consanguinity, DNA analysis, developmental abnormalities, metabolic syndromes, hepatitis B and C, liver and renal disorders. A high-tech resource lab and an experimental research lab (animal house) have been established for research purposes.

In various national-level discussions in the wake of COVID-19 about developing vaccine production sector in the country all the above-mentioned academic institutions expressed their confidence and consent that their organizations were adequately equipped to take on such projects and that they are detailing their employees for training in vaccine production.\(^7\)

**1.9.18 National intellectual property protection system towards producing mRNA vaccines**

The pre-partition intellectual property protection regime of 1911 was replaced by the Patents Ordinance of 2000, which was amended by Patents (Amendment) Ordinance in 2002. This was further amended in 2007 and again in 2010. The patent law in Pakistan is presently governed by the Patents (Amendment) Act, 2010 along with the Patent Rules, 2003. As Pakistan grants patents on a ‘first to file’ basis, it is extremely important that the inventor be the first to apply for the grant of the patent. Any invention that has the following three essential ingredients can be patented:

- **Must be novel.** The inventor must have invented a product/process that is new and such an invention must not have ever been used before.
- **Must involve an inventive step.** This would mean that advancement has been made in the technology of the invention from existing technology that is obvious to a person of ordinary skill in that field.
- **Must be capable of industrial application.** The invention must be industrially applicable. It should possess utility before it is recognized as useful and can be granted a patent.

The non-patentable matter in Pakistan in accordance with the law include things that are discovered (i.e. which exist in nature). Only things that have been invented are patentable. For example, human genes may not be patented even in isolated form. Non-patentable matters in Pakistan include: substances that exist in nature or if they are isolated there from; any invention that causes serious prejudice to human, animal or plant life or health or to the environment; plants and animals other than microorganisms, and biological processes for the production of plants or animals other than non-biological and microbiological processes; diagnostic, therapeutic and surgical methods for the treatment of human beings or animals; mere discovery of any new property or new use for a known product or process. Pakistan law also provides for compulsory licenses in accordance with the TRIPS agreement, along with other public health safeguards (18).

\(^6\) University of Health Sciences, Lahore (see: https://uhs.edu.pk/).

\(^7\) According to internal meeting minutes from various national level meetings.
There are no specific provisions in the patent law of Pakistan with reference to mRNA technology for vaccine production.

**1.9.19 Existing and potential technology transfer activities for mRNA vaccine production**

Pakistan has been selected by WHO – along with Bangladesh, Indonesia, Serbia and Viet Nam – as “countries that do not have mRNA technology but already have some bio-manufacturing infrastructure and capacity”. These five countries were vetted by a group of experts on the basis that they had the capacity to absorb mRNA technology and, with targeted training, move to production stage relatively quickly”. Argentina and Brazil had already joined this initiative and were already receiving mRNA technology transfer. Subsequently, in the case of Pakistan, two batches of three professionals from NIH have visited the technology hub in the Republic of Korea. The Government of the Republic of Korea has offered access to a large facility outside Seoul that is already carrying out bio-manufacturing training for manufacturers based in the country and will now expand its operations to accommodate trainees from other countries (10). The facility will provide technical and hands-on training on operational and GMP requirements. The WHO Academy will work with the Korean Ministry of Health and Welfare to develop a comprehensive curriculum on general bio-manufacturing. A third group of professionals is planned to visit South Africa in 2023. South Africa is the first technology transfer hub that WHO helped establish for providing know-how and technology to other developing countries for mRNA vaccine production. Apart from these trainings in the Republic of Korea, there is no other known transfer of knowledge and technology specifically for mRNA vaccine production in Pakistan.

Technology transfer from product innovators, access to the funding sources for upstream integration, and government support in terms of a buy-back commitment have been identified as potential challenges in the context of Pakistan. To combat these challenges, and for Pakistan to enter the vaccine manufacturing landscape, there is a need for active engagement and support of organizations such as WHO, CEPI, Ministry of Foreign Affairs, Ministry of Science and Technology (MOST), the Planning Commission, and the DRAP.

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9 Based on personal communication with senior NIH officials.
1.10 Summary of national strategy to strengthen local production of mRNA vaccines

1.10.1 National strategy to strengthen local production of mRNA vaccines

Currently there is no formal official national policy or strategy for promoting or strengthening local production of mRNA vaccines. What can be drawn from the foregoing review of high-level meetings, interviews and internal documents in this connection, is:

a. In the midst of the global COVID-19 pandemic, when it was realized at the higher political level that Pakistan’s capacity to produce vaccines in the country is limited, and that Pakistan has seriously lagged behind in vaccine production, the NCOC requested the leadership of NIH to develop and present a document on the existing situation, challenges and opportunities for indigenous production of vaccines. NIH has reportedly developed a draft that, as yet, has not been officially adopted nor made public.  

b. Pakistan’s general interest in vaccine production, and in mRNA vaccine production in particular, can be gauged from the fact that NIH and 2–3 potential vaccine manufacturers expressed interest to WHO to be considered as a technology transfer hub for mRNA vaccine production. Subsequently, Pakistan has been included among the countries to receive WHO support to build national capacity in this area.

c. A series of related, high-level meetings have taken place, during which national situational analysis for vaccine production, including mRNA vaccine production, was considered, current issues were discussed and recommendations were made. The details of these meetings are provided in the foregoing. Other than the minutes of these meetings, however, there is no official, coherent documentation of these discussions and recommendations.

1.10.2 Current and upcoming initiatives

According to available information, activities related to establishing mRNA vaccine production capacity in Pakistan are limited. Three related initiatives can be mentioned that have commenced:

a. As a result of an EOI sent by NIH in 2021, and after due assessment by a technical advisory committee of WHO, Pakistan has been included in a short list of countries flagged as potential technology transfer hubs for mRNA vaccine production. However, until now, there has been only few trainings that have taken place in the Republic of Korea involving relevant NIH staff who have taken part in learning visits in two batches.

b. A team at DCB – a constituent unit of DUHS in Karachi – started working on developing a biosimilar of mRNA vaccine developed by Pfizer and Moderna. Some preliminary work has been carried out to design a vaccine construct that could address escape variants of SARS-CoV-2. The team successfully designed the construct and published their findings in a paper entitled: Design and immunoinformatic assessment of candidate multivariant mRNA vaccine construct against immune escape variants of SARS-CoV-2 (13), but this work could not proceed beyond the design stage due to lack of funds. The team did write proposals to

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1 Based on personal discussions with NIH officials and review of internal documents.
mobilize resources but has not yet been successful. Another constituent unit of the DUHS, Dow Institute of Life Sciences (DILS), has a fill–finish production facility of its own. The thinking was that if the DCB was able to successfully complete the pre-clinical and clinical phases of vaccine development, then the vaccine could be produced in-house at the DILS facility.4

c. Getz Pharma, the largest domestic pharmaceutical company in Pakistan1 and the largest exporter of pharmaceutical products from the country, showed interest in setting up a purpose-built factory for mRNA vaccine production. The company leadership announced the company’s willingness to invest up to US$ 100 million in production of mRNA vaccine, and that it would take up to two years as bioreactors delivery time is not less than one year (19). Getz Pharma also went into a joint venture with a Chinese company (details not revealed) to produce a mRNA biosimilar vaccine in Pakistan. The venture progressed to the stage of conducting Phase III clinical trials in Pakistan, but they reportedly could not obtain bioethical approval from the National Bioethics Committee. Currently, according to information provided, the venture is no longer being pursued and has been shelved for the time-being.4

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4 Based on interviews with the Vice Chancellor of Dow University of Health Sciences and the Principle of Dow College of Biotechnology.
1 Getz Pharma (see: https://getzpharma.com/).
4 Based on interviews with the Executive Staff of Getz Pharma.
2. Local production of pharmaceuticals, particularly other vaccines and biologicals

2.1 The ecosystem for local production of health products

Healthcare knowledge, skills and technologies together equip health professionals with tools for the prevention of diseases and related risk factors, for diagnosis, treatment and rehabilitation. ‘Health technology’ is an umbrella term that is used to cover a vast range of products, with no standard taxonomy. The terms ‘health products’, ‘health technology’ and ‘medical devices’ are often used interchangeably.

2.1.1 The pharmaceutical sector in Pakistan

At the time of its independence in 1947, Pakistan had minimal pharmaceutical manufacturing capacity. Today, Pakistan has over 600 pharmaceutical manufacturing firms with an estimated market size of US$ 3.1 billion and the pharmaceutical industry contributes 1.17% of gross domestic product. In the global context, however, this is not even 0.3% of the global market. The top 100 firms in Pakistan control 95% of domestic market sales. Of those domestic sales, 80% of products are manufactured in Pakistan while 20% are imported. Ninety-five per cent of the raw materials and active pharmaceutical ingredients for manufacturing are imported, mostly from China and India. The industry employs an estimated 150 000 people directly and another 300 000 indirectly. In the past two decades from 1996 to 2018–19, average annual pharmaceutical exports from Pakistan have been US$ 103 million, whereas the average annual imports have been US$ 300 million. Over time, the difference between imports and exports has widened (20). The prices of products are regulated by DRAP, although final approval is granted by the federal cabinet. Maximum retail prices (MRPs) are typically increased in line with the consumer price index (CPI) on an annual basis, nevertheless, marketing authorization holders can also apply under a hardship category for approval of price increases, if the products become financially non-viable for them.

2.1.2 Expanded programme on immunization in Pakistan

The expanded programme on immunization (EPI) in Pakistan was launched in 1978 to protect children by immunizing them against childhood tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus, and measles. Later, with the support of development partners, hepatitis B vaccine, *Haemophilus influenzae* type b (Hib) vaccine and pneumococcal vaccine were introduced in 2002, 2009 and 2012 respectively, and inactivated polio vaccine (IPV) was added in 2015. The current EPI vaccination schedule is presented in Table 3.

The Pakistan EPI vaccinates more than 7 million children each year (21). Nevertheless, the programme struggles to achieve the desired immunization results of 90% national coverage (Fig. 3), typically achieving an average coverage of 76%, albeit with vast provincial disparity. Punjab and Azad Jammu and Kashmir (AJK) have the highest coverage at 90%, Gilgit-Baltistan (GB) at 73%, Islamabad Capital Territory (ICT) at 71%, Khyber Pakhtunkhwa (KP) at 68% and Sindh at 61%. KP
merged districts (KPMD) report 43% coverage, and in Balochistan only 38% of children have been completely vaccinated.

Table 3. Current childhood vaccination schedule in Pakistan

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Age of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood TB</td>
<td>BCG</td>
<td>Soon after birth</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>bOPV, IPV</td>
<td>OPV 0 Soon after birth, OPV1 6th week, OPV2 10th week, OPV3 14th week, IPV 14th week + 9th month</td>
</tr>
<tr>
<td>Diphtheria Pertussis Tetanus Hepatitis B Hib</td>
<td>Pentavalent (DPT+HepB+Hib)</td>
<td>Penta-1 6th week, Penta-2 10th week, Penta-3 14th week</td>
</tr>
<tr>
<td>Pneumonia + Meningitis</td>
<td>Pneumococcal conjugate vaccine (PCV-13)</td>
<td>Pneumo-1 6th week, Pneumo-2 10th week, Pneumo-3 14th week</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Rotavirus vaccine</td>
<td>Rota-1 6th week, Rota-2 10th week</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Typhoid conjugate TCV-5</td>
<td>9 months</td>
</tr>
<tr>
<td>Measles + Rubella</td>
<td>MR-10</td>
<td>MR-1 9th month, MR-2 15th month</td>
</tr>
<tr>
<td>Tetanus + Diphtheria</td>
<td>Td</td>
<td>TT-1 during pregnancy, TT-2 after one month</td>
</tr>
</tbody>
</table>

Fig. 3. Provincial distribution of vaccination coverage, in 2018 and 2020
2.1.3 Vaccine and biological production in Pakistan: Public sector

Despite the high prevalence of infectious diseases in LMICs (i.e. 93% of global burden of such diseases), only 18% of vaccine requirements in these countries are met through local production (21). Similarly, only ten countries produced all the COVID-19 vaccines that were supplied to the whole world during the pandemic. Despite pharmaceutical manufacturing in Pakistan fulfilling around 85% of domestic needs, biomanufacturing in the country is in its initial stages. Only around 10% of required human vaccines are currently manufactured in the country, with the remainder being imported in finished form. Vaccines that are manufactured indigenously are primarily produced through fill–finish processes, where a vaccine concentrate is imported and vials are filled, labelled and packaged locally.

In the public sector, the NIH is the main producer of vaccines. The VBPC could also potentially play a larger role in domestic vaccine production, given its current capacity of producing ten vaccines and other sera (Table 4).

Table 4. Current production capacity of the Pakistan Vaccine and Biological Products Center

<table>
<thead>
<tr>
<th>Product</th>
<th>Specification</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus toxoid</td>
<td>5 ml (10 doses)</td>
<td>Vial (freeze dried)</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>10 doses</td>
<td>Vial</td>
</tr>
<tr>
<td>Cell culture rabies vaccine</td>
<td>Single dose</td>
<td>Vial</td>
</tr>
<tr>
<td>Anti-snake venom</td>
<td>10 ml</td>
<td>Vial</td>
</tr>
<tr>
<td>Anti-rabies serum</td>
<td>10 ml</td>
<td>Vial</td>
</tr>
<tr>
<td>Allergen extracts vaccine</td>
<td>10 ml (one course)</td>
<td>Vial</td>
</tr>
<tr>
<td>Typhoid vaccine</td>
<td>50 ml (multi dose)</td>
<td>Vial</td>
</tr>
<tr>
<td>Typhoid and cholera bivalent vaccine</td>
<td></td>
<td>Vial (freeze dried)</td>
</tr>
</tbody>
</table>

2.1.4 National policies about local production of vaccines and biologicals

There are currently no formal national policies on local production of vaccines and biological products.

2.1.5 Government incentives for local production of vaccines and biologicals

The Government of Pakistan has agreed to incentivize indigenous vaccine manufacturing, and will provide a conducive business environment in the country for investors, including those supporting mRNA vaccine production. The government has established a separate department to promote science and technology with in-built incentives (through STZA Ordinance of 2020). The aim of the STZA is to accelerate technology development in the country through the establishment of technology zones offering various tax exemptions and incentives for developers and enterprises within them. Despite these incentives, as yet no major enterprise in vaccine production has been set up under this authority. The BOI also assists manufacturers and investors who are investing or intend to invest in Pakistan and facilitates the implementation and operation of their projects.
2.1.6 Regulatory system for local production of vaccines and biologicals

Pakistan has comprehensive regulations to ensure the quality and safety of vaccines and biologicals. The DRAP under the DRAP Act 2012 has a mandate for regulatory oversight of both pharmaceutical and biological products. The DRAP regulatory operations include licensing of manufacturers, registration/market authorization, advertising controls, clinical trials, GMP compliance, pharmacovigilance, monitoring of adverse effects following immunization, and import/export functions related to therapeutic goods. However, drug control administration of provincial health departments regulate the sale, storage and distribution of drugs and biologicals in their respective jurisdictions.

Vaccines are also subject to lot release by the NCLB, which is under DRAP and recently became an Associate Member of the WHO’s Global Network of National Control Laboratories for Biologicals. The DRAP Act mandates that the Authority determines standards for biological manufacturing and issues and enforces guidelines for clinical trials.

2.1.7 Existing national research and development capacity for local production of vaccines and biologicals

Given the future potential for targeted treatment options, biologicals are an area of both policy and academic interest. Related research is ongoing in various national institutes, and researchers who have acquired skills from abroad are contributing to the expansion of biotechnology, particularly therapeutics development. Some manufacturers have also been developing capacities to meet national needs, with the manufacturing and regulatory aspects harmonized by DRAP.

A recent NIH exercise in collaboration with the Ministry of Foreign Affairs mapped existing R&D for vaccine and biological production in Pakistan, by both public and private manufacturers. Five areas were assessed using a questionnaire. The results are presented in Tables 5 to 9.

Table 5. Existing vaccine-related research and development activities in national institutions

<table>
<thead>
<tr>
<th>Vaccine manufacturing</th>
<th>Academia</th>
<th>Industries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEMB</td>
<td>NUST</td>
</tr>
<tr>
<td>GMP qualified facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment availability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw material supply</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic manufacturing capabilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioreactors, bioprocessors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation fill to finish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage capacities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: green = available; red = absent; yellow = partial or in pipeline. CEMB = Center of Excellence in Molecular Biology; NUST = National University of Science and Technology; NIBGE = National Institute for Biotechnology and Genetic Engineering; ICCBS = International Center for Chemical and Biological Sciences; GETZ = Getz Pharma; AMSON = Amson Vaccines and Pharma; NIH = National Institute of Health.
Table 6 also highlights how industry has more established GMP-qualified facilities and stronger capacities in relation to equipment, raw materials supply, manufacturing, ultrafiltration, fill–finish and storage capabilities, whereas most academic institutions lack related capacities, except for availability of bioreactors and bio-processors where related industry capacity is limited.

Table 6. Existence of specific research and development capacities in national institutions

<table>
<thead>
<tr>
<th>Molecular design</th>
<th>Academia</th>
<th>Industries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEMB</td>
<td>NUST</td>
</tr>
<tr>
<td>Sequence codon optimization</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Gene synthesis facilities</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Molecular cloning facilities</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Cell culture facilities</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Animal house facilities</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Comp modelling facilities</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Any biological R&amp;D center?</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Protein quality control dept</td>
<td>red</td>
<td>red</td>
</tr>
</tbody>
</table>

Note: green = available; red = absent; yellow = partial or in pipeline. CEMB = Center of Excellence in Molecular Biology; NUST = National University of Science and Technology; NIBGE = National Institute for Biotechnology and Genetic Engineering; ICCBS = International Center for Chemical and Biological Sciences; GETZ = Getz Pharma; AMSON = Amson Vaccines and Pharma; NIH = National Institute of Health.

Table 7. Strength of specific human resource capacities in national institutions

<table>
<thead>
<tr>
<th>Scientists (Post-docs), PhDs, Mphil, MBBS, BS</th>
<th>Academia</th>
<th>Industries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEMB</td>
<td>NUST</td>
</tr>
<tr>
<td>Microbiologist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Molecular medicine specialist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Molecular biologist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Bioinformaticians</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Vaccinologist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Virologist</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Engineers</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Biomedical engineers</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Medics staff</td>
<td>green</td>
<td>green</td>
</tr>
<tr>
<td>Assisting technical staff</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Protein chemist</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Immunologist</td>
<td>red</td>
<td>red</td>
</tr>
<tr>
<td>Clinical trial specialist</td>
<td>red</td>
<td>red</td>
</tr>
</tbody>
</table>

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Academia and industry are both sufficiently empowered with required qualified specialists, although there is a pronounced lack of clinical trial specialists in both sectors.

Table 8. Non-technical deliverable capacities in national institutions

<table>
<thead>
<tr>
<th>Supportive sides</th>
<th>Academia</th>
<th>Industries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEMB</td>
<td>NUST</td>
</tr>
<tr>
<td>Non-technical staff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distributors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transporters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold supply chain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Export license</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Import license</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence center/contract</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Industry-supportive capacities for vaccine production are well in place (e.g. distributors, transporters, cold supply chain, export and import license, bioequivalence centre). On the other hand, academia totally lacks these facilities.

Table 9. Site and hospital facilities linked to national institutions

<table>
<thead>
<tr>
<th>Clinical trials site</th>
<th>Academia</th>
<th>Industries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEMB</td>
<td>NUST</td>
</tr>
<tr>
<td>Affiliated hospitals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Allied Hosp Fsd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. PAEC Hosp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. KRL Hosp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. UHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. IHITC 2. Consortium with public hospitals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical site approval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial phase I, II, III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency cope up facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any PC-1 in progress?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: green = available; red = absent; yellow = partial or in pipeline. CEMB = Center of Excellence in Molecular Biology; NUST = National University of Science and Technology; NIBGE = National Institute for Biotechnology and Genetic Engineering; ICCBS = International Center for Chemical and Biological Sciences; GETZ = Getz Pharma; AMSON = Amson Vaccines and Pharma; NIH = National Institute of Health.

In terms of clinical trial sites, both sectors are limited, with few initiatives taken by the industry.
2.1.8 Intellectual property protection system towards local production of vaccines and biologicals

Intellectual property protection has evolved significantly in Pakistan and the Patents Ordinance of 2000 has been amended several times, most recently by the Patents (Amendment) Act, of 2010. In Pakistan, patents are granted on a ‘first to file’ basis, making it crucial for inventors to be the first to apply for a patent. An invention can be patented if it is novel, involves an inventive step, and is capable of industrial application.

However, certain things are not patentable in Pakistan. These include discoveries (things that exist in nature), inventions that could harm human, animal or plant life or the environment, plants and animals (except micro-organisms).

The patent law in Pakistan aligns with the TRIPS agreement and includes provisions for compulsory licenses and other public health safeguards.

2.1.9 Transfer activities on local production of vaccines and biologicals

Pakistan already possesses some bio-manufacturing infrastructure and capacity, which indicates its ability to absorb the technology and transition to the production stage relatively quickly with targeted training.

The Government of the Republic of Korea has offered a large facility outside of Seoul for bio-manufacturing training. Two groups of professionals from the NIH have visited the technology transfer hub in the Republic of Korea. The facility provides technical training on operational and GMP requirements. The WHO Academy will collaborate with the Republic of Korea Ministry of Health and Welfare to develop a comprehensive bio-manufacturing curriculum.

Additionally, South Africa hosts the first technology transfer hub established by WHO to provide knowledge and technology for mRNA vaccine production to other developing countries.
3. Vaccine manufacturers and supply in Pakistan

3.1 Manufacturing capacity in Pakistan

3.1.1 Public sector vaccine manufacturing

Vaccine manufacturers can be divided into those in the public and private sectors. In the public sector the major manufacturer is the VBPC at NIH, the details of which are already provided. Another public sector vaccine production facility in the Dow Institute of Life Sciences (DILS), which is part of the DUHS. DILS has its own fill–finish facility and is currently involved in anti-rabies vaccine production.

3.1.2 CanSino Bio co-manufacturing at NIH

In the wake of the COVID-19 pandemic, and having conducted the first ever Phase III clinical trials in Pakistan starting in 2020, the BPD also successfully launched co-production of the CanSino vaccine at NIH. It involves mainly a fill–finish function, whereby a vaccine concentrate is received from China, and formulation and packaging steps are done locally. Twenty million doses were produced before production was halted as there was no further need for the vaccine. Through transfer of technology from China the next stage would be to produce the vaccine concentrate.

3.1.3 Private sector vaccine manufacturing

Vaccine R&D and manufacturing in the private sector is very limited in Pakistan. Few manufacturers are involved in vaccine and other biological production, and those are primarily fill–finish functions. Manufacturers involved in vaccine production essentially import vaccine concentrate, fill it in vials, package, store and transport resulting vaccines. Amson Vaccines & Pharma is the largest vaccines manufacturer. Others involved in the production of biological products include Macter International and Ferozsons Laboratories’ joint venture with Bagó Group of Argentina to establish BF Biosciences Ltd. Some manufacturers produce interferon and its pegylated version, including Getz Pharma, Pharmedic Laboratories, Werrick Pharmaceuticals and Hilton Pharma.

Amson Vaccines & Pharma (Pvt) Ltd

Amson is a Rawalpindi-based vaccine and pharmaceutical manufacturer. They are the largest vaccine producers in the country. Amson also produces other pharmaceutical products. They are also the largest auto-destruct syringe production plant in the country, with global exports. In vaccine production they are a well-developed and fully equipped fill–finish production plant. Their vaccine product line is as follows:

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1 Based on discussions with the technical staff of NIH.
2 Pharmedic Laboratories (see: https://pharmedic.com).
3 Werrick Pharmaceuticals (see: https://werrick.com).
4 Hilton Pharma (see: https://hiltonpharma.com).
5 Amson Vaccines & Pharma (see: http://amson.org.pk).
- Tetanus vaccine (Imatet) is available that can help prevent tetanus. There are four kinds of vaccines used today to protect against tetanus, all of which are combined with vaccines for other diseases:
  i. Diphtheria and tetanus (DT) vaccines.
  ii. Diphtheria, tetanus, and pertussis (DTaP) vaccines.
  iii. Tetanus and diphtheria (Td) vaccines.
  iv. Tetanus, diphtheria, and pertussis (Tdap) vaccines.
- Typhoid vaccine (TYPBAR) is a highly purified Vi polysaccharide vaccine. It contains the cell surface VI Polysaccharide extracted from Salmonella typhi Ty2 strain. The vaccine appears as a clear, colourless solution. The vaccine is administered intramuscularly.
- Recombinant hepatitis B vaccine (Amvax-B) contains purified hepatitis B surface antigen obtained by culturing genetically engineered Hansenula polymorpha cells. The surface antigen is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed onto aluminium hydroxide.
- Snake anti-venom, also known as snake venom anti-serum and anti-venom immunoglogulin is a medication made up of antibodies used to treat snake bites by venomous snakes.
- Immune globulin (human).

BF Biosciences Limited
BF Biosciences is a Lahore-based private limited company. It is a subsidiary of Ferozsons Laboratories Limited, a leading manufacturer in Pakistan maintaining exclusive agreements with a number of international partners for distribution, selling and co-manufacturing of pharmaceutical products including in collaboration with the Bagó Group in Argentina, BioGaia of Sweden, Biofreeze of Performance Health Inc., PanTheryx, Boston Scientific and Gilead Sciences, Inc. in the United States of America.
BF Biosciences was established with Bagó Group of Argentina by Ferozsons Laboratories Limited under a joint venture to develop a GMP-compliant biotech facility in Pakistan. The plant was built on a 27-acre site in Lahore, and manufactures biological medicines to treat cancer and hepatitis C for the local and export markets. The joint venture has put Pakistan on the map of countries with biotech manufacturing capacity. The products of BF Biosciences include:

- Erythropoietin
- Filgrastim

During the COVID-19 pandemic, Gilead Sciences USA licensed BF Biosciences to use its technology for production of the antiviral medicine RDV to treat COVID-19. BF Biosciences was among nine global manufacturing partners selected by Gilead Sciences globally to manufacture and supply RDV to 127 LMICs under a technology transfer arrangement. Manufacturing capability includes 700 million doses of vaccines per annum (at 10 doses/vial). Extensive cold chain distribution experience, with cold chain logistics across Pakistan and LMICs in Asia, Africa and Latin America.
BF Biosciences has developed local R&D partnerships with premier academic institutions including Lahore University of Management Sciences, Forman Christian College University (Lahore) and the National Institute of Biologics & Genetic Engineering (NIBGE) (Faisalabad). For contract

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a BF Biosciences (see: https://ferozsons-labs.com/).
manufacturing of RDV, BF Biosciences was involved in the technology transfer and staff training for successful manufacturing of RDV and supply to LMICs.

**Macter International Limited**

Macter International is a large public limited pharmaceutical company in Pakistan.\(^{b}\) It claims to be the largest contract manufacturer in Pakistan, particularly for multinational manufacturers, with one of the most advanced production facilities. They have dedicated facilities for biological production and the manufacturing operations reportedly meet international GMP standards. The biological products manufactured by Macter International include:

- a. Epoetin Alpha (MacEpo): Used for treatment of anaemia due to various conditions.
- b. Etanercept (Momentum injection): Used for arthritic conditions and plaque psoriasis.
- c. Peg-filgrastim (Pegstim injection): Used to reduce infections in people who have certain types of cancer and are receiving chemotherapy medications.
- d. Interferon Alpha 2b (Heberon Alfa R). For hepatitis C.
- e. Antigen Hbs hepatitis B vaccine (Heberbiovac Hb). For prevention from hepatitis B infection.

Macter International also produced the Sputnik COVID-19 vaccine under a contract manufacturing agreement with the Gamaleya Research Institute of Epidemiology and Microbiology in the Russian Federation during the pandemic.

### 3.1.4 WHO prequalification situation

Pakistan is among those countries from which the regulatory staff has taken part in various trainings, dossier assessments and inspections organized by the WHO prequalification programme (\(^{22}\)). According to the programme website, there is only one medicine produced in Pakistan that WHO has prequalified:

- **Tab Levofloxacin** by Remington Pharmaceutical Industries (Pvt) Ltd, 18 Km Multan Road, Lahore, 53800, Pakistan. This is a film-coated tablet, 250mg and it was prequalified on 30 August 2021.

To date, Pakistan has the highest number of WHO prequalified QC laboratories in the Eastern Mediterranean Region. Among the list of WHO prequalified QC laboratories there are five public sector and one private sector laboratories that have been assessed as compliant of WHO standards:

- b. Pakistan Drugs Testing and Research Center. Lahore, Pakistan. The Center was WHO prequalified on 3 July 2019.
- c. Drugs Testing Laboratory, Faisalabad, A block, Near DPS School G.M. Abad, Faisalabad. Pakistan. This lab was WHO prequalified on 16 March 2020.

\(^{b}\) Macter International (see: https://macter.com).
d. Prime Health (Pvt) Ltd., Royal Plaza, Islamabad, Pakistan. Prime Lab was WHO prequalified on 4 June 2020.
e. Drugs Testing Laboratory Rawalpindi, Dhamyal Road, Hayal Sharif, Rawalpindi, Pakistan. Added to the WHO list of prequalified QC laboratories on 8 Nov 2022
f. Drugs Testing Laboratory Lahore, 1 Birdwood Road, Lahore, 54000, Pakistan. Added to the WHO list of prequalified QC laboratories on 14 March 2023.

The following nine immunisation devices produced in Pakistan have been WHO prequalified (23);

a. Auto-disable syringe for fixed dose immunisation, 0.5ml. Apple K1 AD syringe
   • Manufacturer: Amson Vaccines & Pharma Ltd., Islamabad, Pakistan.
   • Prequalified on 2 Nov 2012.
b. Auto-disable syringe for fixed dose immunisation, 0.5ml. Destroject 0.5ml AD (1000) syringe
   • Manufacturer: Amson Vaccines & Pharma Private Ltd., Islamabad, Pakistan.
   • Prequalified on 1 April 2014.
c. Auto-disable syringe for fixed dose immunisation, 0.5ml. Apple K-1 3ring AD syringe
   • Manufacturer: Amson Vaccines & Pharma Private Ltd., Islamabad, Pakistan.
   • Prequalified on 16 July 2019.
d. Hypodermic syringes with reuse prevention feature, RUP syringe 3ml. RG-Non reusable syringe 3ml.
   • Manufacturer: Royal Group/China, Karachi, Pakistan.
   • Prequalified on 21 May 2009.
e. Hypodermic syringes with reuse prevention feature, RUP syringe 5ml. RG-Non reusable syringe 5ml.
   • Manufacturer: Royal Group/China, Karachi, Pakistan.
   • Prequalified on 21 May 2009.
f. Hypodermic syringes with reuse prevention feature, RUP syringe 2ml, Apple K1 RUP 2ml
   • Manufacturer: Amson Vaccines & Pharma Ltd., Islamabad, Pakistan.
   • Prequalified on 2 Nov 2012.
g. Hypodermic syringes with reuse prevention feature, RUP syringe 5ml, Apple K1 RUP 5ml
   • Manufacturer: Amson Vaccines & Pharma Ltd., Islamabad, Pakistan.
   • Prequalified on 2 Nov 2012.
h. Hypodermic syringes with reuse prevention feature, RUP syringe 2ml. RG-Non reusable syringe 2ml.
   • Manufacturer: Royal Group/China, Karachi, Pakistan.
   • Prequalified on 14 August 2018.
i. Hypodermic syringes with reuse prevention feature, RUP syringe 10ml. RG-Non reusable syringe 10ml.
   • Manufacturer: Royal Group/China, Karachi, Pakistan.
   • Prequalified on 14 August 2018.

There is no active pharmaceutical ingredient, vaccine, in-vitro diagnostic or vector control product currently WHO prequalified from Pakistan.
3.1.5 Veterinary vaccine manufacturing

Veterinary vaccines are a strong supporting factor for livestock, particularly for low-income populations in the rural areas. National institutes involved in the production of these vaccines in Pakistan include:

1. Veterinary Research Institute, Lahore.
2. Veterinary Research Institute, Peshawar.
3. Veterinary Research Institute, Quetta.
4. Sindh Poultry Vaccine Center, Karachi.
5. Nuclear Institute of Agricultural Biology, Faisalabad.
6. Poultry Research Institute, Rawalpindi.
7. NIBGE.

All these institutes are public sector organizations. Almost 95% of vaccines for use in large animals are produced locally in these institutes. A limited number of veterinary vaccines are also imported. Only a few private entrepreneurs have started to produce animal vaccines in limited quantities.
3.2 Import and export of vaccines and biologicals

3.2.1 Locally produced vaccines and biologicals procured by international agencies and/or exported to other countries

With the exception of the PacVac vaccine that was produced in Pakistan in collaboration with Chinese company SinoVac, all other vaccines for COVID-19 were imported into Pakistan. As of Nov 2021, only 6 million doses of PakVac vaccine were used, from a total of 166 million doses of all COVID-19 vaccines received in Pakistan. Although PacVac vaccines represent a small proportion of vaccines used during the pandemic, it was nevertheless an important development in the context of Pakistan, and generated significant revenue for the Government of Pakistan.

In the case of vaccines used in the Pakistan EPI programme, more than 90% are imported, with the majority donated through Gavi. With an estimated 7 million children added to the population every year in Pakistan, the need for vaccines increases continually.

Currently, Pakistan is paying a total of US$ 28.99 million annually to purchase typhoid, rotavirus, pneumococcal conjugate vaccine (PCV) and pentavalent vaccines, with the remainder being compensated through Gavi during its ‘accelerated transition phase’. As Pakistan improves its economic situation, it will have to pay significantly more, reaching up to US$ 79.40 million in 2024–2025 (Fig. 4).

Fig. 4. Annual cost of EPI vaccines in Pakistan, 2020 to 2025

Presently the Government of Pakistan is purchasing traditional vaccines such as oral polio vaccine, measles, BCG (tuberculosis), tetanus-diphtheria, whereas Gavi is supporting with 70:30 ratios for pentavalent, PCV, rotavirus and typhoid conjugate vaccines; IPV supply is 100% from Gavi. Annually, around PKR 7 billion (approximately US$25 million as of end-2023) is spent by the GoP. Once Gavi withdraws support to Pakistan, domestic expenditure will increase from PKR 28 billion (approximately US$ 100 million) for the past five years to PKR 60 billion (approximately US$ 213
million) for the next five years, and then around PKR 100 billion (approximately US$ 355 million) for the years 2025–30.\textsuperscript{cc}

3.2.2 Which countries might potential mRNA vaccine producers export to?

When Pakistan starts producing mRNA vaccines, its supply could be taken up by international organizations and special initiatives such as Gavi, UNICEF, WHO and COVAX (in the case of mRNA vaccine for COVID-19). Apart from such procurement channels, Pakistan producers (public and private sector organizations) could also export their products regionally and bilaterally to countries in the South Asian region. India is a major regional supplier with a strong economy of scale advantage. Competing on cost with vaccines made by Pakistani producers would be a major challenge, at least in the short to medium term.

Another region of interest for vaccine exports would be the Eastern Mediterranean Region, where currently only Egypt, Iran (Islamic Republic of) and Tunisia have vaccine production facilities, and these are currently insufficient to meet the needs of the region’s approximately 450 million population. Pakistan can also explore vaccine markets for exports to Central Asian states and African countries.

Notwithstanding the potential foreign markets for vaccines produced in Pakistan, price and quality would be major considerations.

3.2.3 Local market for vaccines

The ability to produce vaccines domestically is important, especially from a health security perspective. The COVID-19 pandemic has further highlighted this reality, and there is an urgent need to build local capacity for vaccine production. Pakistan has successfully demonstrated the ability to conduct high-quality clinical trials and co-production of vaccines, there is a need to strive for the production of various vaccines and at a larger scale within the country.

Pakistan has the fifth largest population in the world, at approximately 220 million people. This also makes it the fifth-largest domestic market. With one of the highest population growth rates in Asia (2.4%), around 7 million children are born each year in the country. The need for essential vaccines that are included in the EPI programme is huge and growing. With such a big internal market, the case for local vaccine production is strong.

\textsuperscript{cc} From internal official documents.
References

15. Hussain M, Jabeen N, Amanullah A, Baig AA, Aziz B, Shabbir S et al. Molecular docking between human TMPRSS2 and SARS-CoV-2 spike protein: conformation and


Annexes
Annex 1. Drug regulatory Authority of Pakistan (DRAP) Act, 2012

SCHEDULE-I
[See Section 2 (v, xii, xviii, xix, & xxviii)]

1. BIOLOGICALS includes,

(1) Biological drugs produced by biological systems and which require standardization by biological assays according to the relevant and updated recommendations of the World Health Organization published in Technical Report Series and Biological Standardization Report and includes--

(a) blood products including Plasma, Albumin, Clotting Factors, Factors VIII, IX, Mixed Clotting Factors Tractions, Fibrinogens, Immunoglobulins;
(b) immunological products including Antisera, Antitoxins, specific Immunoglobulins;
(c) in vivo diagnostics including Tuberculins, Lepronin, Histoplasmin, Coccidioidin, Allergens, Allergens Extracts, Antibodies conjugated with isotopes for imaging studies;
(d) antigens, cytokines/antibodies/cells injected to elicit a biological response;
(e) vaccines, including:--

(i) bacterial vaccines including live, killed whole cell, protein sub-unit, polysaccharide or glyco-conjugate, toxin derivatives, and rDNA biotechnology developed.
(ii) viral vaccines including live, inactivated, sub-unit, DNA, conjugated;
(iii) polyvalent combinations of vaccines containing combination of vaccines defined in e (i) and d(ii).

(f) toxins and venoms including snake venoms, scorpion venoms etc;
(g) immunostimulants of biological origin including BCG vaccine for immunotherapy;
(h) biotechnology products which are primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology or other processes involving site specific genetic manipulation techniques.
(i) human interferons, natural hormones, recombinant antibodies, monoclonal antibodies and derivatives gene therapy products;

(2) "Biological Drugs (Finished form)", are Biological Drugs that are defined in subsection (1) above and are manufactured, packed by the manufacturer under his responsibility of quality assurance and is further released by the National Control Authority or the National Control Laboratory of the country of origin under the World Health Organization's Lot Release system of evaluation.

(3) "Biological Drugs (Ready-to-fill form)", are Biological Drugs that are defined in subsection (1) above but are manufactured at one site in the form of a "Ready-to-fill Bulk" but are transferred to another site for final filling, labeling, packaging and QC of the finished form. No
registration the anti indication(s) national release form and any of section evaluation.

(4) "Biological Drugs (Concentrated form)", are Biological Drugs that are defined in subsection (1) above that are manufactured at one site but are stored in the form of Concentrated- Bulk of the active ingredient at controlled temperatures. Such Concentrated-Bulk may be transferred to any other site under temperature controlled conditions for further dilution, stabilization, filling and packaging. The diluted and stabilized bulk requires its own set of QC test and the final finished form of such Biological Drugs under go another set of complete QC tests. The final product is released by the Pakistan's NCLB under the WHO's Lot Release system of evaluation.

(5) "Biological Drugs (Naked vials)", are Biologicals Drugs that are defined in subsection (1) above that are manufactured and filled at one site but the final containers are neither labeled nor packed in cartons. These drugs are imported in unlabelled vials and are labelled and packed in carton locally. In such cases at least an identity test is required to confirm the positive identification of the required antigen. The final product is released by the Pakistan's NCLBIs under the WHO's Lot Release system of evaluation.

(6) Originator Biological Drugs means a biological drug which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data:

(a) reference biotherapeutic product (RBP) means an originator biological drug product that was licensed on the basis of a full registration dossier. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards;

(b) biosimilar biological drugs mean Similar Biotherapeutic Product (SBP) which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product;

(c) similarity means absence of a relevant difference in the parameter of interest.

[(7) No human vaccines, blood products (plasma derivatives medicinal products) and anti-sera (antivenoms and anti-rabies) shall be sold and used until a "Lot Release Certificate" from the Federal Government Analyst of the NCLB, Islamabad has been obtained.]

(8) Pharmaceutical dossier includes a set of documents submitted by a Person for the registration of a therapeutic good, containing complete information about:

(a) master formula;
(b) all ingredients both active pharmaceutical ingredients and inactive excipients added with their safety profile data;
(c) complete manufacturing procedure of the drug, biological or medical device;
(d) QC steps and procedures at each level of raw material selection, in-process testing, finished drug testing, and stability testing;
(e) clinical trial data and published reports about the safety and efficacy of the drug;
(f) complete details of manufacturing plant and equipment, QC laboratories and equipment;
(g) ware-houses capacities and facilities; details of human resources
available and the latest cGMP report shall also be part of this document set;
(h) any other information required by the registration board for establishing the safety, efficacy, bioavailability, bioequivalence, or biosimilarity of the drug.
For more information, please contact:

**World Health Organization**
Local Production & Assistance Unit
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Website: https://www.who.int/teams/regulation-prequalification/lpa
www.who.int