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

The Bangladesh context
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A case study on the ecosystem for local production of pharmaceuticals, vaccines, and biologicals: the Bangladesh context

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Photo credits: © WHO/Fabeha Monir. Dr Islam on duty in the dengue ward at Dhaka Medical Hospital on 24 September 2023.
## Contents

Preface .............................................................................................................................................. v
Acknowledgements ............................................................................................................................ vii
Abbreviations ...................................................................................................................................... viii
Executive summary ............................................................................................................................ xi

Part 1 – Overview of the ecosystem for local production of mRNA vaccines .................................. 1

1.1 Section 1 ......................................................................................................................................... 3

1.1.1 Section summary ......................................................................................................................... 3

1.2 Section 2 ......................................................................................................................................... 5

1.2.1 National policies that promote or hinder local mRNA vaccine production ................................. 5

1.2.2 Incentives from government and/or other sectors to promote and sustain mRNA vaccine production .................................................................................................................. 6

1.2.3 Financing mechanisms in Bangladesh for manufacturers to produce mRNA vaccines .......... 8

1.2.4 Regulatory system (regulations, standards and requirements) for mRNA vaccines ............ 9

1.2.5 Existing R&D capability and capacity of manufacturers in Bangladesh ................................... 13

1.2.6 Patent protection system and barriers related to patents/intellectual property rights relating to mRNA vaccine production .................................................................................. 15

1.2.7 Existing and potential technology transfer activities regarding mRNA vaccine production ................................................................................................................................. 18

1.2.8 Analysis of bottlenecks and challenges facing local mRNA vaccine production .................. 19

1.3 Section 3 ......................................................................................................................................... 20

1.3.1 The national strategy, roadmap and/or action plan to strengthen local production of mRNA vaccines ....................................................................................................................... 20

1.3.2 Government initiatives for local production of mRNA vaccine ............................................... 22

1.3.3 Objectives and expectations of Bangladesh regarding the mRNA technology transfer hub ................................................................................................................................. 22

Part 2 – Ecosystem for pharmaceuticals, especially other vaccines and biologicals ................... 28

2.1 Section 1 ......................................................................................................................................... 32

2.1.1 Section summary ......................................................................................................................... 32

2.2 Section 2 ......................................................................................................................................... 36

2.2.1 Different government ministry and agency policies which promote or hinder the production of local vaccines and biologicals ........................................................................ 36

2.2.2 Incentives from government and/or other sectors for manufacturers and investors to promote and sustain the production of vaccines and biologicals ................................................................. 37

2.2.3 Financing conditions and mechanisms in Bangladesh for manufacturers to produce vaccines and biologicals .................................................................................................................. 39
2.2.4 Regulatory system (regulations, standards and requirements) for vaccines and biologicals ......................................................... 39
2.2.5 Existing R&D capability and capacity of each manufacturer in the country, particularly for production of vaccines and biologicals .......................................................... 41
2.2.6 Patent system and possible intellectual property rights barriers towards local production, particularly for vaccines and biologicals .......................................................... 41
2.2.7 Analysis of bottlenecks and challenges for local production of vaccines and biologicals .................................................................. 42

References .............................................................................................................................................................................................................. 44

List of figures

Figure 1. History of mRNA vaccine development ................................................................................................................................. 4
Figure 2. Immunization coverage in Bangladesh (year 2001-2019) ........................................................................................................ 30
Figure 3. Export statistics of last five fiscal years (Directorate General of Drug Administration Annual Report 2021-2022) ........................................................................................................ 33
Figure 4. The Directorate General of Drug Administration organizational chart (Directorate General of Drug Administration website) .................................................................................................. 40

List of tables

Table 1. Immunization coverage in Bangladesh ........................................................................................................................................ 31
Table 2. Export statistics of last five fiscal years (Directorate General of Drug Administration Annual Report 2021-2022) ........................................................................................................ 32
Table 3. Income Tax Ordinance 1984, section 46BB, newly established (between 1 July 2019 and 30 June 2024) - Rate of exemption for a 5-years period* ........................................................................................................ 38
Table 4. Income Tax Ordinance 1984, section 46BB, newly established (between 1 July 2019 and 30 June 2024) - Rate of exemption for a 10-years period# ........................................................................ 38
Preface

The Local Production and Assistance (LPA) Unit in the Regulation and Prequalification Department (RPQ), Access to Medicines and Health Products Division (MHP), 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 & 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. 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 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.
Acknowledgements

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 Tareq Al Mahmud, 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 Bangladesh for the support in facilitating the local arrangements, with particular thanks to Bardan Jung Rana, WHO Representative to Bangladesh, Paritosh Chakma, National Consultant, Essential Drugs and Medicines (EDM), as well as the WHO Regional Office for South-East Asia and the Government of Bangladesh 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.

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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.
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADB</td>
<td>Asian Development Bank</td>
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<tr>
<td>AIT</td>
<td>advance income tax</td>
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<td>API</td>
<td>active pharmaceutical ingredient</td>
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<tr>
<td>BCG</td>
<td>bacillus Calmette-Guérin (vaccine)</td>
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<tr>
<td>BIDA</td>
<td>Bangladesh Investment Development Authority</td>
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<td>BMDC</td>
<td>Bangladesh Medical and Dental Council</td>
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<td>CDRI</td>
<td>Central Drug Research Institute</td>
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<tr>
<td>CGEc</td>
<td>capillary gel electrophoresis</td>
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<td>CIP</td>
<td>WHO Coalition of Interested Parties</td>
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<tr>
<td>CMA</td>
<td>conditional marketing authorization</td>
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<td>CMC</td>
<td>chemistry, manufacturing and controls</td>
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<td>CMSD</td>
<td>Central Medical Store Depot</td>
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<td>COA</td>
<td>certificate of analysis</td>
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<tr>
<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>COVAX</td>
<td>COVID-19 Vaccines Global Access</td>
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<td>CRO</td>
<td>clinical research organization</td>
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<td>C-TAP</td>
<td>COVID-19 Technology Access Pool</td>
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<td>CTD</td>
<td>common technical document</td>
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<td>DC</td>
<td>developing country</td>
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<tr>
<td>DFID</td>
<td>United Kingdom Department for International Development</td>
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<td>DGDA</td>
<td>Directorate General of Drug Administration</td>
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<td>DGHS</td>
<td>Directorate General of Health Services</td>
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<tr>
<td>DPDT</td>
<td>Department of Patents, Designs and Trademarks</td>
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<tr>
<td>EDCL</td>
<td>Essential Drugs Company Limited</td>
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<td>EDM</td>
<td>Essential Drugs and Medicines</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EPI</td>
<td>Expanded Programme for Immunization</td>
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<td>ESP</td>
<td>Essential Service Package</td>
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<td>EUA</td>
<td>Emergency Use Authorization</td>
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<td>EUL</td>
<td>Emergency Use Listing</td>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>FDI</td>
<td>foreign direct investment</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<td>FVC</td>
<td>full vaccination coverage</td>
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<td>Gavi</td>
<td>Gavi, The Vaccine Alliance</td>
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<td>Acronym</td>
<td>Description</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
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<td>GHS</td>
<td>global health security</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<tr>
<td>GSPA-PHI</td>
<td>global strategy and plan of action on public health, innovation and intellectual property</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>IEDCR</td>
<td>Institute of Epidemiology, Disease Control and Research</td>
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<td>IP</td>
<td>intellectual property</td>
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<td>IPR</td>
<td>intellectual property rights</td>
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<td>IPV</td>
<td>inactivated poliomyelitis vaccine</td>
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<td>ISO</td>
<td>International Organization for Standardization</td>
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<tr>
<td>LDC</td>
<td>least developed country</td>
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<td>LMIC</td>
<td>low- and middle-income country</td>
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<td>LNP</td>
<td>lipid nanoparticles</td>
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<td>LPA</td>
<td>Local Production and Assistance</td>
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<td>MA</td>
<td>marketing authorization</td>
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<td>MCB</td>
<td>master cell bank</td>
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<td>MCH</td>
<td>maternal and child health</td>
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<td>MoHFW</td>
<td>Ministry of Health and Family Welfare</td>
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<td>MPP</td>
<td>Medicines Patent Pool</td>
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<td>MRC</td>
<td>Medical Research Council (Bangladesh)</td>
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<td>mRNA</td>
<td>messenger ribonucleic acid</td>
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<td>NCL</td>
<td>National Control Laboratory</td>
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<td>NDP</td>
<td>National Drug Policy</td>
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<td>NFA</td>
<td>National Finance Act</td>
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<td>NIPER</td>
<td>National Institute of Pharmaceutical Education and Research</td>
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<td>NOC</td>
<td>no objection certificate</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<tr>
<td>OOP</td>
<td>out-of-pocket</td>
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<tr>
<td>ORF</td>
<td>open reading frame</td>
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<tr>
<td>QMS</td>
<td>quality management system</td>
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<tr>
<td>PCB</td>
<td>Pharmacy Council of Bangladesh</td>
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<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PHEC</td>
<td>Public Health Emergency Committee</td>
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<td>PIL</td>
<td>patient information leaflet</td>
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<tr>
<td>PQM+</td>
<td>Promoting the Quality of Medicines Plus Program</td>
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<td>PQS</td>
<td>performance, quality and safety</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<td>RMP</td>
<td>risk management plan</td>
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<tr>
<td>RT-qPCR</td>
<td>Quantitative reverse transcription polymerase chain reaction</td>
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<td>SAMRC</td>
<td>South African Medical Research Council</td>
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<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
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<td>SDG</td>
<td>sustainable development goal</td>
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<td>SII</td>
<td>Serum Institute of India</td>
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<tr>
<td>SmPC</td>
<td>summary of product characteristics</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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<tr>
<td>SRA</td>
<td>stringent regulatory authority</td>
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<td>SROs</td>
<td>Statutory Regulatory Orders</td>
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<td>TRIPS</td>
<td>trade-related aspects of intellectual property rights</td>
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<td>UHC</td>
<td>universal health coverage</td>
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<tr>
<td>UK</td>
<td>United Kingdom of Great Britain and Northern Ireland</td>
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<td>UN</td>
<td>United Nations</td>
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<td>UNICEF</td>
<td>United Nations Children's Fund</td>
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<td>UNOPS</td>
<td>United Nations Office for Project Services</td>
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<td>USA</td>
<td>United States of America</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>USP</td>
<td>United States Pharmacopeia</td>
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<tr>
<td>UTR</td>
<td>untranslated region</td>
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<tr>
<td>VAT</td>
<td>value-added tax</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WHO-GBT</td>
<td>World Health Organization global benchmarking tool</td>
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<td>WHO-PQ</td>
<td>World Health Organization prequalification of medical products</td>
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<td>WIPO</td>
<td>World Intellectual Property Organization</td>
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<td>WLA</td>
<td>WHO-listed authority</td>
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<tr>
<td>WTO</td>
<td>World Trade Organization</td>
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<td>WTO-DSB</td>
<td>World Trade Organization-Dispute Settlement Body</td>
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Executive summary

This document describes the landscape of vaccine access and the evolving messenger ribonucleic acid (mRNA) vaccine ecosystem in Bangladesh. Recognizing that universal, equitable immunization against preventable diseases is a key factor towards achieving Sustainable Development Goal (SDG) 14, the WHO Vaccine Ecosystem Initiative envisions improved global vaccine accessibility. In Bangladesh, stakeholders such as the Directorate General of Drug Administration (DGDA), Directorate General of Health Services (DGHS) and private entities contribute to vaccine promotion.

This report traces the history of mRNA vaccines, emphasizing their pivotal role in combating the coronavirus 2019 (COVID-19) pandemic. The first mRNA vaccines in Bangladesh, which were authorized for emergency use in 2021, include Spikevax® by Moderna and Comirnaty® by Pfizer/BioNTech. These vaccines are distributed through the COVID-19 Vaccines Global Access (COVAX) platform, with 190 million doses delivered in Bangladesh.

Despite the success of mRNA vaccines, the report identifies challenges within Bangladesh’s vaccine ecosystem. These include a lack of government policy to support mRNA vaccine research, development, and manufacturing, regulatory shortcomings, market uncertainties, political influences and technological barriers. The report advocates for a comprehensive approach to address these issues, emphasizing the need for research-driven companies, a robust regulatory system and public awareness to strengthen the vaccine ecosystem.

The report’s objectives include evaluating existing strategies and policies, identifying legal and regulatory frameworks, understanding the current vaccine supply system and exploring government policies to foster vaccine manufacturing and distribution. The report also addresses challenges in capacity-building for research and development and proposes a model strategy for local mRNA vaccine production. Additionally, it examines the prospects of technology transfer and outlines potential strategies to transform and bolster the vaccine ecosystem in Bangladesh.

In conclusion, the report underscores the significance of collaborative efforts among stakeholders, evidence-based insights and dynamic leadership to achieve universal vaccine coverage. Bangladesh can enhance its vaccine ecosystem by addressing challenges and implementing transformative strategies, ultimately contributing to global health security.

Since 1982, Bangladesh’s pharmaceutical industry has undergone a remarkable transformation, meeting 98% of the country’s medical product demand through local production. The sector has experienced substantial growth, with the current market size exceeding US$ 3 billion and projected to surpass US$ 6 billion by 2025. The pharmaceutical industry has contributed significantly to gross domestic product (GDP), registering an annual growth rate of 16.7% from 2015 to 2019.

With 271 manufacturers of allopathic medicines, 205 of Ayurvedic medicines, 271 of Unani medicines, 32 of herbal medicines and 79 of homeopathic medicines, Bangladesh has demonstrated substantial progress in providing access to quality medical products. Despite this, out-of-pocket (OOP) expenditure for health care remains high at 67%, with 69.4% of total health expenditure allocated to medical products.
The Bangladeshi drug market is characterized by the dominance of branded off-patent generic drugs which account for 80% of locally produced medicines, with patented drugs making up the remaining 20%. The top ten producers command nearly 70% of the domestic market. These manufacturers produce many medicines, including finished formulations, vaccines, biologicals and high-tech products like insulin, hormones and anti-cancer medicines. The industry’s production facilities cover various dosage forms, from tablets and capsules to injections, inhalers and specialized drug delivery products.

Despite self-sufficiency in many areas, Bangladesh relies on imports for vaccines, biologicals and medical devices. On the other hand, the country has become a significant exporter of generic medicines to 162 countries, a market share which is continually increasing in value.

This comprehensive overview highlights Bangladesh’s pharmaceutical success story, emphasizing its achievements in meeting local medical product demand, its contribution to the economy and its expanding global market presence. The challenges of high out-of-pocket health expenditures and import dependence on specific medical products underscore the need for ongoing strategic initiatives to achieve universal health coverage and sustainable growth in the pharmaceutical sector.
Part 1 – Overview of the ecosystem for local production of mRNA vaccines

Background
In 1796, the first vaccine to prevent smallpox was developed by Edward Jenner. As a result of his invention and its development, smallpox was eliminated by massive vaccination, and finally declared eradicated by WHO in 1980 (1). To date, 28 diseases (excluding COVID-19) are considered preventable by vaccine. Vaccine development, deployment, supply chain and overall adoption make up what is known as the “vaccine ecosystem”. This ecosystem also encompasses factors such as the supply chain, immunization, surveillance, system strengthening, and public awareness and understanding (2). A sustainable vaccine ecosystem can promote equitable access to public health protection and foster global health security (3). WHO has therefore made diagnosing and treating loopholes in the ecosystem for vaccine development and deployment a priority.

In Bangladesh, the national medical products regulatory authority, the Directorate General of Drug Administration (DGDA) is the sole institution responsible for medical products of therapeutic value, i.e. all products containing active pharmaceutical ingredients (API) or finished pharmaceutical products (FPP) supplied as medicines, vaccines, biologicals, medical devices, in vitro diagnostics, etc. The Directorate General of Drug Administration carries out its regulatory functions under a legal and regulatory framework established by the Ministry of Health and Family Welfare (MoHFW)/4).

Bangladesh is now expanding into vaccine development, manufacturing, distribution and control. At present, three existing private vaccine manufacturers and another new private vaccine manufacturer are developing their products in Bangladesh. The Government of Bangladesh is also working to set up state-owned vaccine manufacturing facilities at the Gopalganj plant of the Essential Drugs Company Limited.

Incepta Vaccine Limited, one of the three existing private manufacturers, produces a total of 10 vaccines against hepatitis A and B, rabies, tetanus, influenza, meningococcus, cholera, human papilloma vaccine, typhoid, mumps and measles, four of which are produced from master seed and six from ready-to-fill bulk. The second firm, Healthcare Pharmaceuticals, prepares one vaccine from ready-to-fill bulk, and the third, Popular Pharmaceuticals Limited, prepares four vaccines, all from ready-to-fill bulk. Its vaccines are hepatitis B, rabies, tetanus and human papilloma vaccine (4).

Hitherto no pharmaceutical company in Bangladesh has manufactured indigenous vaccines or mRNA vaccines. A new biotech company, Globe Biotech Limited, is the first company in the country to develop an indigenous vaccine and pioneer mRNA vaccine development. Incepta Vaccine Limited is a partner of the mRNA technology transfer hub and also intends to start local production of mRNA vaccines in Bangladesh (5).

The history of the mRNA vaccine (figure 1) goes back to 1960 when mRNA was first discovered. In 2012, following some dramatic developments, the first mRNA vaccine incorporating a lipid nanoparticle (LNP) carrier was used in mice; in 2015 LNP-mRNA vaccine was administered in a clinical trial in humans. During the public health emergency of the COVID-19 pandemic, demand for vaccines increased manifold and the first LNP vaccine was authorized in 2020 under WHO’s Emergency Use Listing (EUL) and subsequently obtained Emergency Use Authorization (EUA) from the National Regulatory Authority (NRA)/6).
To date only one mRNA vaccine, Pfizer-BioNTech’s LNP-mRNA, has received full marketing authorization in Bangladesh. During the COVID-19 pandemic, nine candidate vaccines received EUA in Bangladesh, two of which are mRNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Messenger RNA vaccine technology is a promising method for providing a sustainable immune defence: it enables dendritic cells to take up mRNA fragments into their internal machinery, thereby producing viral antigens which stimulate the normal adaptive immune system process. As Bangladesh is a low- and middle-income country (LMIC) of growing potential, it may take the opportunity to manufacture mRNA vaccines locally through its connections with the mRNA technology transfer hub(6).

Introduction
In Bangladesh, almost all types of vaccines are in use, and most are imported. The Directorate General of Drug Administration has yet to achieve WHO maturity level 3 according to the last formal assessment conducted by the Organization on 12–23 September 2021, using WHO’s global benchmarking tool (WHO-GBT)(7). Furthermore, the national control laboratory is not fully able to conduct vaccine lot release. At present, only Incepta Vaccines Limited and Popular Pharmaceuticals Limited(8) are producing vaccines either from ready-to-fill bulk or from seed. However, an indigenous vaccine is under development by a Bangladeshi manufacturer.

During the COVID-19 pandemic, Globe Biotech Limited became the first company to develop a new mRNA vaccine Bancovid®, the first D614G-variant mRNA-based vaccine candidate against SARS-CoV-2; and subsequently renamed it Bangavax®. The company developed the vaccine for preclinical trial as a mRNA-lipid nanoparticle (LNP) vaccine for the D614G spike protein variant(9). Although Globe Biotech Limited is not on WHO’s mRNA technology transfer recipients list, Incepta Vaccine Limited is listed(5). The latter has the capacity to conduct mRNA vaccine research and development (R&D), manufacture, distribution and control(10).

A sustainable vaccine ecosystem is essential for preparedness and response to any pandemic emergency. To be sustainable, the vaccine ecosystem should be designed to resemble a natural ecosystem as closely as possible.

The vaccine ecosystem has three components:

- promoting the vaccine market through R&D incentives and procurement models to nurture innovation;
- strengthening the supply chain system through equitable access to guarantee continuous manufacturing and distribution; and
- fostering compliance and reliance on vaccines through reliable policy decisions.

Messenger RNA vaccine technology is a sustainable immunization technology which produces essential, targeted antibody proteins by triggering mRNA and genetic code interaction inside body cells(6). This system has the potential to allow routine, ongoing and sustainable immunization against vaccine-preventable diseases. It is high time for the Bangladeshi government to take the required policy decision and strategize an action plan to promote research, development, manufacturing, distribution and control of local mRNA vaccine production by technology transfer(11,12). As a LMIC, Bangladesh may also benefit from participation in a solidarity trial of newly developed mRNA vaccines the aim of which is to promote access and enable better public health protection against diseases that can be prevented by immunization(2,13).
Study objective
This overview study of the ecosystem for mRNA vaccine development, production and supply had several objectives.

- To gain insight into the existing strategy, policy and action to promote access to mRNA vaccine in Bangladesh.
- To identify the regulatory, market-based and industrial frameworks underpinning the vaccine ecosystem in Bangladesh.
- To identify the existing vaccine and pharmaceutical supply system in Bangladesh.
- To identify government policy and strategy (health, industry, trade, financial, R&D) to promote an ecosystem for vaccine manufacturing, distribution and supply to serve public health priority needs.
- To assess needs and identify challenges involved in boosting the R&D capacity in order to develop the production and distribution of new vaccines, biologicals and other health care products.
- To devise a model strategy for local production of mRNA vaccines, and other vaccines, biologicals and pharmaceutical health products.
- To identify and point the way forward for technology transfer.
- To set out potential strategies towards transformations likely to promote the strength of the vaccine ecosystem.

1.1 Section 1
1.1.1 Section summary

Sustainable protection against all against existing and potentially vaccine-preventable diseases by means of immunization is an important step towards achieving universal health coverage and equitable access to quality health services – a milestone of the SDGs(14). WHO’s vaccine ecosystem study initiative envisions a world with better access to vaccines to protect and safeguard the health and well-being of populations of all ages throughout the world(15). A broad and diverse set of stakeholders is necessary to find comprehensive solutions capable of harnessing the full potential of vaccines for the benefit of all(3).

In Bangladesh, several stakeholders play a role in promoting access to vaccines: the Directorate General of Drug Administration, Directorate General of Health Services (DGHS), Expanded Programme for Immunization (EPI), Ministry of Health and Family Welfare and private manufacturers, importers and suppliers.

Messenger RNA is a transient intermediator between genes and proteins in biological systems. Messenger RNA vaccines exploit its ability to function as a message carrier for the translation of specific proteins within body cells by interacting with ribosomes. Messenger RNA was first conceptualized in the 1960s as having the potential to synthesize specific proteins inside the cell ribosome(6). The technology to incorporate mRNA into intracellular liposomes was developed in 1974. In 2015, the first lipopeptide nanoparticle (LNP)-mRNA vaccine was trialled in humans, and in 2020 the first LNP-mRNA vaccine was authorized by the United States Food and Drug Administration (FDA) for Emergency Use Authorization (EUA). One year later, Pfizer-BioNTech’s LNP-mRNA vaccine received full marketing authorization for COVID-19.(2)
The first mRNA vaccine against COVID-19 to receive a EUA in Bangladesh appeared in 2021. The two mRNA vaccines that have now received EUA are Spikevax®, manufactured by Moderna, the USA, and Comirnaty®, manufactured by Pfizer/BioNTech, the USA(16). Both vaccines are supplied under the COVAX platform through an agreed Partnership Framework Agreement (PFA) with Gavi, WHO, UNICEF, World Bank and other donors. In Bangladesh, 190 million dosages of COVID-19 vaccines have been delivered under COVAX(17).

The Bangladeshi government has not yet set out a policy or guidance to promote the research, development, manufacturing and supply of mRNA vaccine. In Bangladesh, the weak vaccine ecosystem is due to a paucity of research-driven companies, a weak vaccine regulatory system, market uncertainties, political influence, a degree of vaccine hesitancy, and technological and programmatic issues. Studies of the mRNA vaccine’s efficiency and potential during the COVID-19 pandemic have demonstrated that it is safer and more effective than other existing vaccine technologies.

Achieving universal coverage for immunization and protection against vaccine-preventable diseases can be successful if there is a massive change in the entire vaccine ecosystem, followed by R&D prior to manufacture and safeguard of mRNA vaccine supply chains. This can strengthen the system by heightening public awareness and generating trust in the value offered by vaccines, as well as enhancing disease surveillance and monitoring to reinforce health emergency preparedness and response. A combination of evidence-based insights, actionable recommendations and cross-sector dialogue can be reinforced by stakeholder networking, collaboration and dynamic, committed leadership(18).
1.2 Section 2
1.2.1 National policies that promote or hinder local mRNA vaccine production

Bangladesh is still developing its manufacturing of vaccine and biosimilar products. Vaccine and biosimilar products are regulated by the Directorate General of Drug Administration, the national regulatory authority for medical products. Directorate General of Drug Administration reviews, approves, inspects and monitors to ensure the quality, safety and efficacy of vaccines intended for use in the country.


The Bangladeshi government has also issued other acts, rules, policies and guidelines in support of vaccination and immunization activity:

- The Vaccination Act (1880)
- National Health Protection Act (2014)
- National Health Policy (2011)
- National Immunization Policy (2013)

The Directorate General of Drug Administration regulates medical products that are defined as drugs according to the Drug Act 1940. In the wording of the Drug Act 1940, section 3(b)(i): “Drug includes all medicines for internal or external use of human beings or animals, and all substances intended to be used for or in the treatment, mitigation, or prevention of diseases in human beings or animals, not being medicines and substances exclusively used or prepared for use in accordance with the Ayurvedic, Unani, Homeopathic or Biochemic system of medicine.” As vaccines are used for disease prevention, they considered a drug and regulated by the Directorate General of Drug Administration (20).

To promote vaccine manufacturing in the country, the Bangladeshi government has developed a policy which is inscribed in the National Drug Policy 2016, Section 4.11(a) regarding technology and knowledge transfer. In this section, it is stated that “with an appropriate assurance of technical knowledge and technology transfer any foreign research-based company/manufacturer/organization is encouraged to manufacture, market, and promote their high-tech medical products including recombinant technology-generated vaccines, biosimilars, hormones, insulins, and anticancer drugs” (21).

Regarding vaccine regulation, Directorate General of Drug Administration applies the following guidelines:

- General Guidelines for Lot Release and Standard Operating Procedures for Production of Vaccines in Bangladesh;
- Guidelines for registration of human vaccines in Bangladesh;
- Guidelines for regulation of biosimilar products; and
A number of standard operating procedures (SOPs), manuals, protocols and checklists exist to enable regulation of vaccines and biological products.

Messenger RNA vaccine is a promising technology whereby genetic materials are used to vector protein information for the in vivo development of required antibodies. The technology is still new in Bangladesh. These vaccines were first introduced in Bangladesh under EUA but have yet to receive full marketing authorization. In Bangladesh, only one pharmaceutical manufacturer, Globe Biotech Limited, has developed a mRNA vaccine; it is currently undergoing clinical trials. This vaccine is therefore the first indigenous vaccine. The Bangladeshi government has yet to develop a specific strategy, roadmap, action plan, policy or guideline to sensitize and promote research, development and manufacturing of mRNA vaccines in Bangladesh.

Manufacturers from 15 countries are part of the WHO mRNA technology transfer hub; Incepta Vaccine Limited connects Bangladesh to the mRNA technology transfer hub as a recipient of mRNA technology.

1.2.2 Incentives from government and/or other sectors to promote and sustain mRNA vaccine production

There is currently insufficient data on research and development (R&D) researchers and expenditure regarding mRNA vaccine development. Since Bangladesh is now graduating from least developed country (LDC) to developing country (DC) status, the Bangladeshi government has strategised many actions to promote R&D in the country, although no special initiative has been taken for mRNA vaccine development, manufacturing or distribution. Given that mRNA vaccine technology is completely novel it lacks the commensurate R&D infrastructure.

The government’s apex investment promotion agency Bangladesh Investment Development Authority (BIDA) offers general incentive systems throughout the fiscal and non-fiscal year to encourage, motivate and facilitate investment for local production. Provision is made for privileges, facilities and incentives including value-added tax (VAT) reduction or exemptions, reduced import taxes on capital machineries and raw materials and lowered corporate income tax. The government also provides export subsidies, banking facilities and other benefits. The National Finance Act (NFA) and individual Statutory Regulatory Orders (SROs) allow annual revision of these incentives. Corporate income tax reduction offers are applied to newly established business facilities based on sector and location for the fiscal period between July 2019 and June 2024. According to Section 46BB of the Income Tax Ordinance (1984), newly established firms working in pharmaceuticals, active pharmaceutical ingredients and radiopharmaceuticals are eligible for income tax reduction or exemption between 1 July 2019 and 30 June 2024. No specific policy exists, however, for incentives, subsidies or tax exemption/reduction for import of raw materials and equipment, or in the R&D, manufacturing, distribution and export sectors.

During the COVID-19 pandemic, a new vaccine and biotech firm Globe Biotech Limited launched a research programme into mRNA vaccines and developed a vaccine for preclinical trials in 2020. The vaccine was listed in the WHO landscape for monitoring progress toward development and manufacturing. It was developed as Bancovid®, the first D614G-variant mRNA-based vaccine candidate to trigger neutralizing antibodies and a balanced cellular immune response against SARS-CoV-2. Bancovid® was the first mRNA vaccine to be researched and developed in Bangladesh, and the country’s first indigenous vaccine.
During this study report, open-ended interviews were held with the key stakeholders: Globe Biotech Limited, Incepta Vaccine Limited, Popular Pharmaceuticals Limited and Healthcare Pharmaceuticals Limited as well as with relevant academicians, experts and researchers on the challenges, needs and the issue of government support for research, development, manufacturing, distribution and control of mRNA vaccines in Bangladesh.

Government now appreciates the need for mRNA vaccines as a sustainable immunization solution. Since mRNA vaccines work to produce targeted antibodies in body cells, they can provide a realistic, successful and workable solution to combat vaccine-preventable diseases, protect public health and aid recovery from pandemics.

The stakeholders urge government support to conduct research and create incentives for the development, production, distribution and control of mRNA vaccines in a timely manner for a sustainable immunization system. Such a strategy ought to trigger impetus for mRNA vaccine R&D.

Before a new mRNA vaccine is developed in Bangladesh, the government should support potential manufacturers connected with the mRNA vaccines technology transfer hub: this is in line with WHO’s initiative, which was announced on 21 June 2021. The key objective of this technology transfer hub is to capacitate low- and middle-income countries (LMIC) to manufacture mRNA vaccines via a center of excellence, training and technical assistance. The hub is Afrigen Biologics and Vaccines, Cape Town, South Africa, a biotechnology company that works through a collaborative network of LMICs.

The vaccine ecosystem can have an impact today and drive sustainable immunization solutions in the future. For a sustainable vaccine ecosystem, the government needs to follow the recommendations below.

- Ensure a return on investment for donors, governments and global stakeholders.
- Guarantee that multiple effective suppliers exist to reduce monopolies and secure supply.
- Set up funding and infrastructure for R&D.
- Demonstrate political will, prioritize vaccines and raise awareness about their importance, demand, needs and supply.
- Strengthen local manufacturers to develop, manufacture and supply of vaccines through knowledge and technology transfer.
- Secure balanced public-private partnership perspectives for global public goods and make a distinction between the roles of each partner.

In Bangladesh, the government has yet to make a policy decision about financial support or provide an incentive for mRNA vaccines. Manufacturers and regulators suggest that, if government set out a strategy and support plan, private investors, entrepreneurs and manufacturers would be more likely to present for mRNA vaccine development, manufacturing and supply. Since mRNA vaccine technology is a sustainable immunization technique for vaccine-preventable diseases, it will bolster successful implementation of the global health security agenda.
1.2.3 Financing mechanisms in Bangladesh for manufacturers to produce mRNA vaccines

Although Bangladesh is in the transition phase from LDC to developing country (DC) status, it still has a lack of financial strength, equipment, technology and competency. Both private manufacturers and government need support to consolidate vaccine lot release and vaccine testing facility. At present, the World Bank is providing financial support through the United Nations Office for Project Services (UNOPS) to strengthen the laboratory testing of vaccines in Bangladesh. Another state-owned pharmaceutical company intends to set up vaccine manufacturing facilities that will need extensive support as an institution potentially able to provide a local supply of vaccines for public health protection. The government has an annual budget for reinforcing the vaccine testing laboratory, but its scope is currently limited to general vaccines and does not extend to mRNA vaccines.

On 22 June 2021, the Asian Development Bank (ADB) approved a loan package of US$ 940 million for the Government of Bangladesh to purchase safe and effective COVID-19 vaccines[24], but the government ultimately declined the loan. The World Bank also approved a loan of US$ 2.7 million for access to safe and effective vaccines to combat COVID-19 by strengthening the Directorate General of Drug Administration and National Control Laboratory (NCL) (17).

From the development sector, WHO Bangladesh and the World Bank through UNOPS, United States Agency for International Development (USAID) and United States Pharmacopeia (USP) are providing support to procure vaccine testing instruments for the national control laboratory. With the direct technical support of USP and WHO, Directorate General of Drug Administration’s physicochemical laboratory in the NCL vaccine wing has received WHO prequalification. The microbiology section of the same laboratory and the vaccine testing laboratory have yet to achieve WHO prequalification: this would enable the country to conduct vaccine lot release at WHO performance, quality and safety (PQS) standards. This support needs to be extended, however, for prospective local production and testing of mRNA vaccine.

To encourage private sector engagement in the research, development, manufacturing and distribution of mRNA vaccine, government should incentivize and extend its financial support. The government needs to stimulate collaboration between the Ministry of Finance, Ministry of Law, National Board of Revenue (NBR), Ministry of Health and Family Welfare, Ministry of Commerce and Industries, Department of Patent, Design and Trademark (DPDT), Bangladesh Trade and Tariff Commission (BTTC), Directorate General of Drug Administration and Directorate General of Health Services (DGHS) for sustainable policy development, especially for VAT reduction and tax exemption for imports related to mRNA vaccine development and manufacturing. The Government of Bangladesh is working to develop this policy.

To collect information and recommendations relating to existing financing mechanisms, incentive systems, tax exemption, financing institutionalization, financing relevant currency rates and transaction channels, requests were forwarded to focus persons in the above departments.

**Expert’s recommendations**

1. Provide subsidies for the import of equipment, machines and technologies to adopt, develop and promote new technology in the country.
2. Engage development partners in a collaborative platform, e.g. Coalition of Interested Parties (CIP), to standardize and develop the system for mRNA vaccines research, development, manufacturing, distribution and supply.

3. Offer financial incentives through government action and/or through a donor-funded project to trigger mRNA vaccine development and manufacturing.

4. Fund scholarships for Bangladeshi researchers to promote R&D.

5. Ensure researchers of benefits on completion of their research.

6. Update academic study curriculums.

7. Set up experience-sharing visits and research collaboration through public-private partnerships.

8. Support Directorate General of Drug Administration to strengthen regulatory capacity towards achieving WHO maturity level 3 so it can test mRNA vaccines and oversee lot release.

9. Facilitation of access to WHO prequalified vaccines through recognition of the responsible NRA’s lot releases to enable local manufacturers to expand the market regionally and attract foreign currency, thereby creating a level playing field for global public health protection and ensuring universal health coverage (UHC), global health security (GHS) and health-related SDGs.

### 1.2.4 Regulatory system (regulations, standards and requirements) for mRNA vaccines

The Directorate General of Drug Administration is the sole authority responsible for regulating all medical products, including biologicals, vaccines, medical devices and in vitro diagnostics. Messenger RNA vaccines are regulated in the same manner as other vaccines (8,25), although Directorate General of Drug Administration has no specific provisions for mRNA vaccines regulation. The Directorate General of Drug Administration provides licences to vaccine manufacturers and importers, as well as registrations and marketing authorizations for mRNA vaccines. At present only two mRNA vaccines are being used in Bangladesh: these are imported and registered as Emergency Use Authorization (EUA) in Bangladesh if they meet the following criteria (26).

The Directorate General of Drug Administration classified vaccine sources into five categories in order to formulate the specific steps involved in the evaluation process:

1. imported COVID-19 finished vaccine;
2. locally manufactured COVID-19 vaccine from imported bulk;
3. locally manufactured COVID-19 vaccine acquired by technology transfer;
4. locally produced COVID-19 vaccine from a master cell bank (MCB) approved in other countries with WHO maturity level 3 in terms of vaccine manufacturing capacity; and
5. indigenous COVID-19 vaccine development and local production.

In the regulatory context, imported/locally manufactured vaccines are eligible for an EUA in Bangladesh if they meet the following criteria:

- All clinical trial phases (preclinical, phase-I, phase-II and phase-III/non-inferiority trial) as appropriate to be determined by Directorate General of Drug Administration should have been
completed for local production. The manufacturer should submit further trial data on a rolling basis, when available.

- Vaccines should have registration/EUA issued by the NRA of the country of origin with satisfactory clinical and preclinical data and complete chemistry, manufacturing and controls (CMC) data evaluated and recommended by Public Health Emergency Committee (PHEC); or have registration/EUA in any of the following seven countries—United States of America, United Kingdom, Switzerland, Germany, France, Australia, Japan—and/or the European Medicines Agency (EMA) or WHO’s EUL.
- An EUA for COVID-19 vaccines is applicable following a ruling by the PHEC or Directorate General of Drug Administration. It depends on the duration of the pandemic (based on WHO declarations), sufficiency of supply versus demand, transition from EUA system to full marketing authorization in other countries, or other guidance from WHO.

The Directorate General of Drug Administration follows two pathways for a vaccine EUA: a reliance and recognition pathway, and a critical review pathway.

**Reliance and recognition pathway (26)**

Regulatory reliance has emerged as an exciting and viable way to avoid duplication of review efforts, ease the burden on underresourced regulatory agencies and still deliver new medicines to patients who need them. The Directorate General of Drug Administration may totally or partially rely upon evaluations performed by another NRA or trusted institution in reaching its own decision, although it remains responsible and accountable for all decisions taken even when it relies on information from other sources.

With increasingly strong collaboration among regulatory agencies, it is becoming possible to build upon existing frameworks and global standards, nurturing trust and sharing resources and experiences, hence the rationale for applying this pathway for imported COVID-19 vaccines that had already received EUA/conditional marketing authorizations (CMA) in any of the seven listed countries (United States, United Kingdom, Switzerland, Germany, France, Australia and Japan) or by the EMA and/or WHO EUL (26). Preclinical and clinical dossiers for imported bulk for fill-finish or for technology transfer are subject to the reliance pathway and the previously listed criteria. The reliance and recognition pathway also requires satisfactory evidence of submission of all documents as required by the Directorate General of Drug Administration.

**Critical review pathway (26)**

The new vaccine or bulk for vaccine or master cell bank for vaccine should go through the critical review pathway, if:

- the imported COVID-19 vaccines are not listed by the previously mentioned regulatory bodies/countries or WHO-EUL;
- local manufacturing takes place with imported bulk;
- local manufacturing occurs via technology transfer (either from bulk or master seed);
- local production involves a master cell bank (MCB) which is approved in other countries with WHO maturity level 3 in terms of vaccine manufacturing capacity; or
- COVID-19 vaccine development and production are indigenous.

The eligibility procedure to obtain an EUA for a mRNA vaccine is the same as that for all other vaccines.
Full registration and marketing authorization of mRNA vaccines

Messenger RNA vaccines are classified as biologics(23). Consequently, adequate control of the starting and raw materials, excipients and the manufacturing processes is required. As with all vaccines, a description of the intended clinical use of the mRNA vaccine should be provided, including the pathogen targeted, target antigen(s) and disease to be prevented(27).

The relevant biological characteristics of the specific mRNA technology used should also be described, such as the ability of the given mRNA to trigger innate immune responses as well as target antigen-specific responses, as well as biostability and other parameters(25).

To justify the vaccine design, all known or available information about the type of immunity considered relevant to the specific pathogen and disease should be provided. This includes the rationale for selecting the target antigen sequence and any coding sequences added to or modified by the target antigen, such as those to ensure that the target antigen folds into a specific conformation(25).

The entire annotated sequence, identifying all open reading frames (ORFs), untranslated regions (UTR) and other sequence elements and justifying their use, should be identified. Justifications should be provided for the use of specific noncoding sequences (e.g. 5' UTR, 3' UTR and poly A signal) and structural elements, such as the chosen 5' cap structure. The complete annotated sequence identifying all ORFs and all other sequence elements, including justifications for their use, should be indicated. Justifications for the use of specific noncoding sequence (e.g. 5' UTR, 3' UTR and poly A signal) and structural elements such as the chosen 5' cap structure should also be provided(9, 25).

Any viral replicase gene encoded in the vaccine construct to allow amplification of the mRNA in human cells after delivery should be described for the mRNA vaccine. The formulation of the drug product and all excipients, including all components used to generate LNPs, should be described. The method of manufacture of LNPs and drug products, including information on critical quality attributes of intermediates and final product, as well as in-process controls and any sterilization procedure, should be described(25).

Registration and marketing authorization procedure for mRNA vaccines(25)

Messenger RNA vaccine is a novel product in Bangladesh and will be developed as indigenous vaccine. Alternatively, the unintroduced mRNA vaccine may be manufactured from ready-to-fill bulk (locally developed). For this type of vaccine the Directorate General of Drug Administration procedure is listed below.

*Note: if the vaccine is novel and has never been registered before in the country, Drug Control Committee (DCC) approval will also be needed.

Step 1: Application for a no objection certificate (NOC) to import or permission to develop host cell/cell line/master cell:
   a) Host cell/cell line/master cell identification and characteristics document.
   b) Certificate of analysis.

Step 2: Application to Directorate General of Drug Administration for the permission to start preclinical study:

For a preclinical study to be conducted inside Bangladesh

2.1 Information about product development
   a) Information about cell bank
   b) Procedure to prepare working cell bank
c) Data generated from development of R&D batch, manufacturing flowchart, cell bank history, preliminary characterization and manufacturing process in brief

d) Analytical specifications

2.2 Information about preclinical study
a) Protocol for preclinical study for local study.

For a preclinical study to be conducted outside Bangladesh

2.3 NOC application to send sample to overseas clinical research organization (CRO)
   a) Description of the test product
   b) Overseas CRO information
   c) Non-commercial invoice.

Step 3: Application to the Directorate General of Drug Administration for research/manufacturing licence to prepare clinical trial batches:
Information about production of a preclinical trial batch
   a) Preclinical batch summary report
   b) Certificate of analysis (COA)
   c) Stability study of at least 3 months of development batch.

Step 4: Application to the Directorate General of Drug Administration for the permission to start clinical trials:
4.1 If clinical trials are to be conducted overseas, application to Directorate General of Drug Administration for NOC to send sample
4.2 If clinical trials are to be conducted in Bangladesh, trial permission and conduct of trial should follow Good Clinical Practice (GCP) guidelines for pharmaceutical product trials in Bangladesh.

Step 5: Application for registration/formulation approval and marketing authorization (MA):
   a) Dossier in common technical document (CTD) format with 5 modules
   b) Sample and lab document submitted to NCL.

Step 6: Price certificate issuance:
After approval of the annexure, the price certificate is issued.

Step 7: MA certificate issuance:
After issuance of the price certificate, the MA certificate is issued.

Step 8: Postmarketing documents:
   a) Real-time stability data over shelf-life
   b) Postmarketing observational study report on reasonable number of subjects within a period of 6 months to 1 year.

Any change should be submitted as per the International Council for Harmonisation (ICH) Q5E guideline.
1.2.5 Existing research and development capability and capacity of manufacturers in Bangladesh

Bangladesh’s National Drug Policy (NDP, 2016) sets out a programme for joint collaborative research and development of drugs including vaccines and biosimilars. In section 4.12(a) of the NDP 2016, it is noted that “Both local and multinational drug and raw material manufacturers are encouraged to establish research and development facilities in Bangladesh. The initiative is taken to reduce imposed duties on imported machineries for such research laboratories. Creating collaborative environment among universities, research institutes and drug manufacturers will be encouraged to conduct basic and applied research jointly on drugs” (21).

In Bangladesh, Globe Biotech Limited was the first company to develop mRNA vaccine as an indigenous vaccine. Globe Biotech Limited is a sister concern of Globe Pharmaceuticals Limited. It was established in 2016 in Bangladesh with the vision of novel biotech drug discoveries (9).

Globe Biotech Limited initially developed mRNA vaccine in Bangladesh under the name Bancovid®, the first D614G-variant mRNA-based vaccine candidate against SARS-CoV-2 to elicit neutralizing antibody and a balanced cellular immune response (9).

Globe Biotech Limited subsequently renamed the vaccine Bangavax® (28). It was submitted for a preclinical trial as a D614G-variant mRNA-LNP vaccine. The country’s Medical Research Council (Bangladesh MRC) approved this vaccine for clinical trial and Globe Biotech Limited is in the process of submitting the clinical trial protocol to the Directorate General of Drug Administration for regulatory approval (29).

Globe Biotech Limited is developing three vaccine candidates as the first indigenous vaccine in Bangladesh (9):

- a mRNA vaccine presented as LNP (lipopeptide nanoparticles)-encapsulated mRNA for SARS-CoV-2, under clinical trial;
- a DNA plasmid vaccine targeting SARS-CoV-2, under clinical trial; and
- an adenovirus type 5 vector (non-replicating viral vector vaccine) targeting SARS-CoV-2, under clinical trial.

At present, two manufacturers in Bangladesh, Globe Biotech Limited and Incepta Vaccine Limited, have R&D capacity for mRNA vaccine development. The Bangladeshi government has also undertaken to boost R&D of vaccine candidates including mRNA vaccine.

During the COVID-19 pandemic in Bangladesh, nine vaccines received emergency use authorization (EUA) (16):

- Covishield® (non-replicating viral vector vaccine: Oxford-AstraZeneca formulation), manufactured by Serum Institute of India (SII);
- Covovax® (protein subunit vaccine: Novavax formulation), manufactured by SII;
- Spikevax® (mRNA vaccine), manufactured by Moderna, the USA;
- Comirnaty® (mRNA vaccine), manufactured by Pfizer/BioNTech, the USA;
- Sputnik V® (non-replicating viral vector vaccine), manufactured by Gamaleya, Russia;
- Jcovden® (non-replicating viral vector vaccine: Janssen formulation), manufactured by Johnson & Johnson, the USA;
- Vaxzevria® (non-replicating viral vector vaccine), manufactured by Oxford-AstraZeneca, United Kingdom;
- Covilo® (inactivated vaccine), manufactured by Sinopharm, China; and
- CoronaVac® (inactivated vaccine), manufactured by Sinovac, China.

Of these nine imported vaccines, two are mRNA vaccines and used for the first time in Bangladesh under an EUA.

**Preparedness for mRNA vaccine testing in Bangladesh**

The vaccine manufacturers Incepta Vaccine Limited and Globe Biotech Limited have research, development, manufacturing and testing facility capacities. Although the regulatory authority Directorate General of Drug Administration has a National Control Laboratory (NCL) with a special vaccine wing, its laboratory testing capacity for mRNA vaccine is still insufficient. WHO and the Promoting the Quality of Medicines Plus (PQM+) program – funded by the World Bank, Asian Development Bank (ADB) and USAID and led by the USP – are providing support to the NCL to strengthen its vaccine testing capacity including testing, quality assurance and NRA lot release of mRNA vaccine.

Laboratory testing capacity for mRNA vaccine is still insufficient, and lacks a proper facility and requisite infrastructure. In terms of quality assurance, the following tests are available for private manufacturers (30):

- **Identity test** with sequence confirmation using sequencing methods (USP reference <1125>, <1126>) and/or RT-qPCR: (USP reference <1126>, <1127>), sequencing by nucleic acid-based techniques: extraction, detection, sequencing, amplification, microarray, genotyping and detection of trace nucleic acids (residual DNA testing).

- **Purity test** with attributes of RNA integrity and product-related impurities, using capillary gel electrophoresis (CGE) methods (USP reference <1053>), agarose gel electrophoresis for nucleic acids (USP reference <1126>), and ion-pair reversed-phase high-performance liquid chromatography (IP-RP-HPLC) (USP reference <621>).

- **Potency test** with quality attributes of antigen expression, using the Western blot method (USP reference <1104>), flow cytometry (USP reference <1027>) and other cell-based assays (USP reference <1032>, <1033>, <1034>).

- **Concentration test** to ensure RNA content, using quantitative reverse transcription polymerase chain reaction (RT-qPCR) methods (USP reference <1127>), fluorescence spectroscopy (USP reference <853>), ultraviolet absorbance (USP reference <857>) and anion exchange chromatography (USP reference <1065>).

- **Particle size test** to confirm nanoparticles using light scattering methods (USP reference <1430.2>, <1430.3>, <1430.5>, <1430.6>).

The Government of Bangladesh is developing a state-owned vaccine manufacturing facility under the name Essential Drugs Company Limited. The government plans to set up a special vaccine manufacturing line for mRNA vaccine, and to manufacture mRNA vaccine by technology transfer.
It is high time for the government of Bangladesh to set aside a budget for procurement of testing equipment and technology for research, development, manufacturing, testing, quality assurance, distribution and supply chain management. The government is currently seeking support from development partners and donor agencies to strengthen the essential mRNA vaccine ecosystem in Bangladesh.

**1.2.6 Patent protection system and barriers related to patents/intellectual property rights relating to mRNA vaccine production in Bangladesh**

Bangladesh is a LDC now graduating towards developing country (DC) status. As a member of the World Trade Organization (WTO), Bangladesh has been benefiting from the trade-related aspects of intellectual property rights (TRIPS) Agreement since its inception as a LDC: these benefits will cease when it becomes a DC. This raises the question of how Bangladesh will cope under the impact of this change(31), and merits discussion. As a LDC member, Bangladesh enjoys various benefits from the TRIPS Agreement while missing out on some other potential measures(32).

Because LDC countries are exempted from applying the TRIPS Agreement’s provisions, LDC countries can copy and produce any patented pharmaceutical and agricultural chemical products without securing permission from the inventors. These provisions are helping billions of people in LDC countries to obtain medicines, fertilizers and pesticides at affordable prices(33).

According to Article 3.1 of the TRIPS Agreement, nationals of other Members shall not be treated less favourably than nationals of a Member. However, Article 4 states that if a Member grants any advantage, favour, privilege or immunity to the nationals of any other country regarding intellectual property, it shall accord them immediately and unconditionally to the nationals of all other members.

Owing to the above provisions, LDC countries cannot grant patents for pharmaceutical and agrichemical inventions. Once a LDC country grants a patent for pharmaceutical and agrichemical inventions, it simultaneously has to grant patents to the companies of developed countries and to take regulatory measures against the unauthorized producers of patented products. In order to keep pharmaceutical and agrichemical prices at an affordable level, LDC countries have therefore been avoiding issuing patents for those products(34).

Bangladesh will officially graduate from LDC to non-LDC in November 2026. Until that date, it can continue to manufacture high-priced patented medicines without acquisition of rights. If there is no waiver or extension of TRIPS, Bangladesh will need to prepare to be a TRIPS-compliant regime. Collaboration between the TRIPS Council, WTO, the Bangladesh mission in Geneva and LDC Group in WTO are essential to safeguard extension of the TRIPS agreement waiver.

The Government of Bangladesh has endorsed and published in its official bulletin the Patents Act 2022. According to Chapter 8, Section 33 of the Patents Act 2022, any innovator, researcher, institution, manufacturer can register a patent locally for their product and technology. Section 36 states that decisions made at the WTO meeting on 30 August 2003, will be integrated in the amendment of the TRIPS Council Agreement (Article 65). When Bangladesh graduates from LDC to developing country in November 2026, the compulsory licensing provision may be imposed(35). Its clauses are generic: all drugs including vaccines, biologicals and mRNA vaccines remain under the same criteria(36).
The Bangladesh Patents Act 2022 has been endorsed by the Legislative and Parliamentary Affairs Division and will mainly be applied and controlled by the Ministry of Law and Legal Affairs, the Ministry of Commerce and the Department for Patents, Designs and Trademarks (DPDT).

Experts in the field have pointed out that the development of local capacity should be boosted by enhanced investment in R&D. It is crucial that a new policy be devised which obliges pharmaceutical manufacturers and companies to invest a specific portion of their profits into R&D. A significant percentage of such investment should be allotted to universities, which in turn should introduce institutional intellectual property (IP) policies in order to increase joint research programmes with industrial entities.

In order to be able to prepare a new medical product, e.g. molecule, vaccine or biological, placement-based goals and plans have to be adopted by the pharmaceutical industry. A policy for government incentives to encourage the development of new drugs may be initiated. Globally accredited drug testing laboratories should be established by the Directorate General of Drug Administration to guarantee drug quality.

There is no currently established patent protection system for medical products in Bangladesh, although after 2026 Bangladesh will inaugurate a patent protection system(37). There is no specific legal provision, regulation, policy and/or guideline to overcome challenges related to research, development, manufacturing, control, distribution and supply of mRNA vaccine.

A breakthrough analysis has been performed to diagnose and detect the impact on domestic industries based on discussions with, and collection of information from experts in the relevant departments of the Government of Bangladesh. This analysis also served to define hindrances and challenges which will need to be overcome when graduating from LDC to developing country (DC) status.

Experts commented that WHO is providing support to build or leverage capacity for local manufacture of vaccines in LDC and DC, and Bangladesh undoubtedly has the capacity while it has remained within the LDC regime until now. But patent protection is not the issue: indeed, there are no patents in developing countries which are likely to block or hinder local production of mRNA vaccines(38). On the other hand, WHO's initiative to promote technology transfer for mRNA vaccine through the COVID-19 Technology Access Pool (C-TAP) and the technology transfer hub are providing support to overcome challenges facing local production of mRNA vaccine in Bangladesh. This opportunity is one of great potential for Bangladesh and the government should make the most of it.

**Analysis of impact on domestic industries and general public health on waiver expiry in 2026**

- Should the waiver period come to an end in 2026 the impact on domestic industries and general public health might not be severe. All common medicines (including antibiotics) are now in the public domain.
- According to the Article 33 of the TRIPS Agreement, patented medical products will remain protected for manufacture as generics in Bangladesh and access will be limited owing to increased costs under compulsory licensing.
- Probably only a few medicines for severe diseases like cancer, viral diseases and other new diseases like COVID-19 pandemic will remain patent-protected after 2026.
- However, a study is required to determine the complete picture. Whatever its findings, it will not change the situation for Bangladeshi nationals compared with nationals in other developing countries since they will also be buying patented medicines at a higher price.
Bangladesh’s intellectual property laws, particularly the Patent and Design Act 1911, should be harmonized with the TRIPS Agreement. Traditional knowledge in Bangladesh could be protected by drawing up a new Traditional Knowledge Act. Moreover, the Trade Secret and Integrated Circuit Layout Design Act may also need to be reconsidered.

The newly enacted Patents Act 2022 may need to be updated in order to address the challenges facing the pharmaceutical sector, especially for biologicals and vaccines, including mRNA vaccines.

### Hindrances and barriers for Bangladesh on graduating from LDC to DC
- Transition periods enjoyed by Bangladesh as a LDC to delay implementation of the TRIPS Agreement have been a defining feature of LDC flexibility in the WTO.
- Access to manufacture and supply of generic medicines.
- Access to production of APIs.
- Manufacturing facilities must be compliant with the defined regulatory authorities.
- Earning of foreign revenue by exporting generic drugs.
- Partnership with international companies.
- Access to essential life-saving medicines.

### Challenges for access to mRNA vaccine on graduating from LDC to DC
- If the TRIPS waiver is not extended, Bangladesh will need to prepare for the TRIPS compliance regime.
- Bangladesh can manufacture high-priced patented medical products including vaccines and biologicals without acquisition of rights until November 2026 when it will graduate from the LDC group.
- The cost of vaccines, especially mRNA vaccine under new technology, will increase due to the proprietary rights costs of mRNA technology, ready-bulk and master seeds.
- All local pharmaceuticals will be affected if the Patents Law does not adopt all TRIPS Agreement safeguards.
- Bangladesh’s graduation will challenge the SDG target 3.8, increase the health risk and raise the price of medicines.
- Discovering new technology-based mRNA vaccines is not just a matter of R&D capabilities: it involves extensive risk-taking, since results are erratic and outcomes highly unpredictable.
- There are insufficient R&D facilities for mRNA vaccines, other vaccines and biologicals.
- There is a lack of standard and qualified CROs for clinical trials and bioequivalence studies.
- There is insufficient expertise for technology transfer and in licensing and out-licensing legal procedures.
- CROs do not support clinical trials for biosimilar and biotech products, which is a barrier for manufacturers seeking to introduce new products.
- No institutions exist as in India (National Institutes of Pharmaceutical Education and Research (NIPER) and Central Drug Research Institute (CDRI)) for mitigation of upcoming challenges.
- An intellectual property rights course is not included in the technical studies curriculum of universities and research institutions.
- Bangladesh is not yet ready to face legal issues in WTO’s Dispute Settlement Body (WTO-DSB).
- There are no competent legal advisors for mitigation of TRIPS Agreement challenges and implementation of the action plan, roadmap, strategic plan and institutional development plan (IDP).

### Recommendations to overcome the challenges
1. Negotiate to extend the LDC waiver in the WTO.
2. Prepare for the post-LDC future of Bangladesh.
3. Initiate preparatory actions to anticipate TRIPS compliance.
4. Develop and implement a national policy for mRNA vaccine development, manufacturing, distribution and control.
5. Amend and apply the Patents Law if no extension is forthcoming.
6. Seize the opportunity: the Bangladesh pharmaceutical sector can gradually evolve to provide low-cost substitute of important potential drugs to other developing and LDC countries.
8. Strengthen R&D for all vaccines including mRNA and other biosimilar products.
9. Amend the Patents Law of April 2022 to include the concerns of the pharmaceutical sector.
10. Close the mailbox Department of Patents, Designs and Trademarks (DPDT) and include compulsory licensing, research exemption and parallel imports in the Patents Law.
11. Increase investment in pharmaceutical R&D, and incentivize innovation activities for vaccines, biologicals, biotech products, biosimilar products and bioequivalence studies.
12. Establish strong research institutions similar to India’s NIPER and CDRI.
13. Introduce a TRIPS-related course in the academic curriculum with reference to mRNA vaccines, biologicals, pharmaceuticals, APIs, medical devices, in vitro diagnostics, etc.

1.2.7 Existing and potential technology transfer activities regarding mRNA vaccine production

The Government of Bangladesh has no special provision or technical policy for promoting local production of mRNA vaccine through technology transfer. The private company Bangladesh Incepta Vaccine Limited initiated its own request to be connected to the hub. The government supported the manufacturer by issuing an official letter setting out its approval and stating that it had no objection with technology transfer and local production of mRNA vaccine in Bangladesh(5).

WHO’s mRNA technology transfer hub is an initiative to empower LMICs and make a greater effort to encourage empowering countries to produce their own mRNA vaccines for public health protection(5). This technology transfer initiative is supported by WHO, the Medicines Patent Pool and Act-Accelerator/COVAX to promote the local production of mRNA vaccine through technology transfer. The hub comprises Afrigen Biologics, the South African Medical Research Council (SAMRC) and Biovac, a South African vaccine producer. Afrigen is mandated to establish a mRNA vaccine production technology transfer hub within a consortium of LMICs: SAMRC provides the R&D and Biovac is the first manufacturing spoke(5, 27).

WHO has selected several beneficiaries in all six WHO regions at an expert group meeting to determine technology transfer recipients for mRNA vaccines. At the European Union-African Union summit in Brussels on 18 February 2022, the WHO Director-General announced that the first six countries to receive technology transfer for local production of mRNA vaccines would be Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia(39).

Fifteen countries are now connected to the technology transfer hub, one of which is Bangladesh. Incepta Vaccines Limited was the beneficiary of this technology transfer opportunity with government authorization, although the government of Bangladesh itself has not initiated any special provision or system to join the hub. Awareness-raising and consultations with potential vaccine manufacturers and research organizations could well encourage them to gain access to this hub.
Mention is also made here of the expert’s opinion: “The Government of Bangladesh should take the initiative to be connected to the technology transfer hub, which would provide the country with a platform for knowledge- and technology-sharing. Bangladesh is moving forward to achieve WHO maturity level 3 and be recognized as a WHO-listed authority (WLA), a status that will enable Bangladesh to conduct independent vaccine lot release. Local manufacturers will also be able to prequalify their vaccines and unlock the global window for worldwide supply. In short, the initiative would be beneficial for local manufacturers, local experts, the government of Bangladesh as well as the country’s economy. Since the list of required materials for local production of mRNA vaccine is long, the hub will enable materials to be supplied from validated sources without wasting time.”

1.2.8 Analysis of bottlenecks and challenges facing local mRNA vaccine production

Bangladesh is still categorized as a LDC although it will soon be a developing country (DC).

Challenges outlined in the study to promote a mRNA vaccine ecosystem in Bangladesh:

- Public misunderstanding about mRNA interference with human body cell DNA.
- Potential conflict of interest between business groups.
- Deficit of political willingness and transparency.
- Sociopolitical influence.
- Regulatory bias towards specific manufacturers.
- Competency gaps in technical human resources.
- Insufficient infrastructure and facilities.
- Weak regulatory system at WHO maturity level 1.
- Lack of up-to-date legal and regulatory provisions.
- Lack of government initiatives to promote R&D.
- Lack of policy for financial incentives to promote a mRNA vaccine ecosystem.
- Lack of central government initiative and support for technology transfer.
- Lack of government initiative to allow vaccine lot release via surrogate NRA until Directorate General of Drug Administration achieves WHO maturity level 3 and/or is WHO pre-qualified.
- Lack of willingness to participate in a solidarity trial due to sociopolitical conflict.
1.3 Section 3

1.3.1 The national strategy, roadmap and/or action plan to strengthen local production of mRNA vaccines

Short-term action plan

- Bangladesh should still negotiate to raise the threshold for graduating from LDC status or to extend the waiver by creating a new category such as “newly graduated countries in transition” so as to achieve SDGs for global health and well-being.
- Bangladesh should also negotiate to sustain the transition period up to 2033 during the graduation process and even after being formally declared DC for well-founded reasons such as the COVID-19 pandemic.
- A specific point to be incorporated in the patents Law for pharmaceuticals: patentability criteria should also include the clause: “Bangladesh shall not grant patent to any pharmaceutical product already registered or marketed in the country before graduation and after being formally declared DC for well-founded reasons such as the COVID-19 pandemic.”
- No secondary patent, no patent term extension. Bangladesh could refer to Section 3d of the Indian Patent Amendment Act 2005 in which it is stated that: “The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant, is not patentable. For the purposes of this clause salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixture of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”
- Bangladesh should provide “process patent” not “product patent”. Bangladesh could use India as an example: it was granted a transition period until 2005 to fully comply with TRIPS.
- TRIPS safeguards such as compulsory licensing, parallel imports, anti-competitive behaviour, research exception, etc., should be included in the revised patents law.
- Bangladesh can adopt measures necessary to protect public health as per Articles 8 and 31 of the TRIPS Agreement. Should an emergency or pandemic arise, the government has the power to decide whether or not to grant a patent for any particular lifesaving medicine.
- Bangladesh may refuse to accept the patent on three grounds relating to public health (Article 27.2, Article 27.3A, Article 27.3B) of the TRIPS Agreement.
- Bangladesh needs to avoid mailbox provision since it may allow multinational companies to obtain patents filed before the patent implementation date in Bangladesh.
- The government may also approach the World Intellectual Property Organization (WIPO), WHO and IP offices of leading developing countries for technical assistance in dealing with a TRIPS-compliant patent regime, particularly pharmaceutical patents.
- Bangladesh should increase the number of patent examiners with expertise in chemistry and pharmacokinetics in order to ensure that frivolous, evergreening patent claims relating to existing drugs are rejected in the light of robust patentability criteria to be applied by the examiners. DPDT should be supported by Directorate General of Drug Administration in this area.
- The registration of new molecules must be facilitated and simplified so that Bangladeshi pharmaceutical industries can register as many molecules as possible before graduation.
- Companies with the facilities to manufacture biosimilar drugs, blood products, plasma substitutes, hormones or monoclonal antibodies should register them before graduation.
- The Directorate General of Drug Administration ought to set up a committee comprising the Directorate General of Drug Administration and Bangladesh Association of Pharmaceuticals
Industries (BAPI) members with a sitting legal advisor and technical consultant in order to ensure the best interests of the country in relation to the pharma sector.

**Long-term action plan**
Considering this paradigm shift, Bangladesh should update its national IP policy which was drafted in 2008.

- **IP policy upgrade**
  - A new policy formulation may be required to encourage pharmaceutical companies to invest profit margins in R&D for a mRNA vaccine.
  - A significant percentage of such investment should be earmarked for universities to promote R&D for a mRNA vaccine.
  - Universities should introduce institutional IP policies to step up collaboration with industrial research entities, especially vaccine manufacturers in Bangladesh or abroad.

- **New mRNA vaccine development**
  In order to acquire the ability to prepare new mRNA vaccines, i.e. new vaccine substances, placement-based goals and plans have to be adopted in the vaccine manufacturing industry.
  - A policy ought to be adopted for government incentives to encourage development of new mRNA vaccines.
  - The Directorate General of Drug Administration’s accredited drug-testing laboratory/National Control Laboratory (NCL) should be strengthened and upgraded to ensure capability for vaccines lot release.

A national health strategy should be established which integrates long-term innovation and access to objectives by encouraging collaboration between universities, industries and government, and public-private partnerships.

- **Intellectual property rights (IPR) education**
  An IPR course should be added to the educational curriculum in various universities and research institutions. All local pharma manufacturers need to be informed about IPR.

- **Contract research organization (CRO)**
  Potential world-class contract research organizations (CRO) should be set up which are able to conduct clinical trials of mRNA vaccines.

- **Research/innovation**
  Research and innovation should be stimulated by productive academic-industry collaboration to develop new technology and products. The government should set up research laboratory facilities in the respective departments of all public universities.

- **Institutional expansion**
  Establish a National Institute of Pharmaceutical Education and Research (NIPER) and Central Drug Research Institute (CDRI), similar to the existing institutes in India, to meet the potential pharmaceutical industry challenges in Bangladesh as a result of its transition from a least developed country (LDC) to developing country status.
1.3.2 Government initiatives for local production of mRNA vaccine

Following the COVID-19 pandemic, the government of Bangladesh became concerned about access to vaccine technology to combat emergency situations. Since 2016, the government has been working to strengthen its national regulatory authority, Directorate General of Drug Administration and national control laboratory to enable vaccine testing and NRA lot release.

The Government of Bangladesh is supporting private manufacturers Incepta Vaccine Limited and Globe Biotech Limited to produce mRNA vaccine locally. It has yet to seize the initiative and encourage production through incentives or tax exemption/reduction schemes for import of long-listed items for mRNA vaccine production.

WHO Bangladesh, World Bank, USAID, USP-led PQM+, Gavi, UNICEF, UNOPS, DFID and other relevant development partners are providing support to the government of Bangladesh for system improvement to allow sustainable access to vaccines. However, no special initiative has been taken to promote research, development, manufacturing and distribution of mRNA vaccines.

The Directorate General of Drug Administration is working to achieve WHO maturity level 3, especially for vaccines, and hopes to become a WHO-listed authority: this would enable the country to conduct vaccine lot release at WHO prequalification of medical products (WHO-PQ) standards. If the Directorate General of Drug Administration and NCL become WHO-prequalified for vaccine testing and lot release, several manufacturers are likely to come forward to manufacture vaccine products including mRNA vaccines. The mRNA technology transfer hub currently offers a great opportunity for Bangladesh to achieve benchmarks in its knowledge, competency, technology and overall capacity for local production of mRNA vaccines.

1.3.3 Objectives and expectations of Bangladesh regarding the mRNA technology transfer hub

Bangladesh is still a LMIC-listed country and lagging in terms of R&D technology for mRNA vaccines. Becoming a spoke of the mRNA technology transfer hub presents a great opportunity for Bangladesh to realise its need to step forward and promote its local production of mRNA vaccine(39). Infrastructure for mRNA vaccine R&D has been scanty until recently. The government is working to start up local vaccine production in its state-owned pharmaceutical Essential Drugs Company Limited (EDCL). Technology transfer is an opportunity that will enable public and private vaccine manufacturers, and research organizations in Bangladesh to develop the research, development, manufacturing and distribution of mRNA vaccines locally.

Objective of connecting to the technology transfer hub(5)

- To receive technical support from WHO on development themes and how to strengthen research, development, manufacturing, distribution, control and regulation of mRNA vaccines.
- To devise a benchmarking system for regulation of mRNA vaccines.
- To standardize the competency of regulators, manufacturers, researchers and academicians regarding mRNA vaccines technology.
- To strengthen research in Bangladesh in collaboration with the South African Medical Research Council (SAMRC), South African hub including Afrigen Biologics, and South African vaccine producer Biovac.
▪ To encourage local manufacturers (public and private), researchers and entrepreneurs to engage in mRNA vaccine production.
▪ To gain access to the hub in order to promote Bangladesh’s overall capacity for local production of mRNA technology given that the field is still unconstrained by intellectual property rights.

**Strategy and plan for local production of mRNA vaccine**
The Government of Bangladesh has yet to initiate a specific plan for research, development and local production of mRNA vaccines. However, Globe Biotech Limited, a vaccine manufacturer, has developed an indigenous mRNA vaccine for COVID-19 which is still under clinical trial. Incepta Vaccine Limited is linked to the technology transfer hub for local production of mRNA vaccine(39).

**How to promote the local production of mRNA vaccine**
There are some crucial measures which Bangladesh can undertake to promote the local production of mRNA vaccines:
▪ the Government of Bangladesh, by offering scholarships and incentives to academicians, CROs, manufacturers, regulators and other relevant interest groups, should encourage the research, development, manufacturing, distribution, control and regulation of mRNA vaccines;
▪ the government should issue incentives and tax exemptions or VAT reductions for import of materials required for the development and manufacture of mRNA vaccine;
▪ government facilities should be developed;
▪ a special budget should be earmarked to support the development and local production of mRNA vaccines;
▪ government initiatives to make Bangladesh a mRNA technology transfer hub spoke;
▪ research collaboration between academia, research organizations and manufacturers should be promoted;
▪ investors should be encouraged by making investments easier and creating business access to mRNA vaccine manufacturing;
▪ CROs should undertake clinical trial initiatives;
▪ the regulatory system should be strengthened and manufacturers encouraged to follow regulatory compliance;
▪ the National Control Laboratory (NCL) and Directorate General of Drug Administration should be upgraded for laboratory testing and vaccine lot release;
▪ competency should be promoted through training, education and experience-sharing visits to the innovator countries in collaboration with the technology transfer hub; and
▪ the government should support the technology transfer agreement to manufacture mRNA vaccine.

**Support required from WHO for local production of mRNA vaccine**
▪ Regulatory system strengthening.
▪ Competency development through local, regional and global training, with workshops and seminars.
▪ Encouragement through advocacy and knowledge-sharing in the global arena.
▪ Equipment support for NCL to strengthen its laboratory testing and lot release.
▪ Communication and system harmonization through regional and global meetings, workshops, seminars, etc.
▪ Technical assistance for strengthening research, development, manufacturing and regulation of mRNA vaccines.
- Gap assessment and system harmonization between existing practice and standard practice for the regulation, control, manufacturing and distribution of mRNA vaccines.
- Technical assistance to strengthen Directorate General of Drug Administration and NCL’s quality management systems (QMS) to ensure the quality, safety and efficacy of mRNA vaccines.
- Technical support for WHO prequalification of mRNA vaccine production in Bangladesh.
- Support to bring the Directorate General of Drug Administration up to WHO maturity level 3 and enable it to become a WLA.
- Information-sharing platform development among mRNA technology transfer hub spoke countries.
- Collaboration to boost financial support from other donors to develop infrastructure and human resource competencies.
- Technical support to develop a strategic and action plan for development, manufacturing, distribution, supply, control and regulation of mRNA vaccines.
- National, regional and global harmonization of support through WHO’s Coalition of Interested Parties (CIP) mechanism.

**Messenger RNA technology transfer hub**

The pharmaceutical sector in Bangladesh is an example of how health and economic development intermix. The Bangladesh pharmaceutical regulatory system is shifting up a gear with dual contributions from improved access to medical products for better health outcomes and economic development owing to a dramatic growth of the local pharmaceutical industry. One of the SDG priorities is access to safe, effective and quality medicines and vaccines for everyone. Access to these essential medicines and vaccines, which should also be affordable, means achieving universal health coverage. Out-of-pocket (OOP) expenditure for health care amounts to 67% of overall health expenditure, of which 69.4% is spent on medicines and medical products.\(^8\)

The Directorate General of Drug Administration’s capacity should be strengthened to protect public health while advancing industrial development in Bangladesh. A strengthened regulatory system can ensure quality, safe and effective medical products by guaranteeing quality standards in pharmaceutical manufacturing.\(^4\) No longer benefiting from the TRIPS Agreement will put a significant negative impact on access to public health protection.

Now that it is moving towards the end of the grace period for LDCs, Bangladesh is preparing the regulatory landscape so that it can deal effectively with the intellectual property requirements which will arise in the near future. For both active pharmaceuticals and finished pharmaceutical properties, Bangladesh is reaching out to local industries and regulators to raise their awareness on the policy and practice implications of TRIP compliance.\(^13\) In collaboration with the WTO and WHO, Bangladesh’s national regulatory authority and Ministry of Commerce are developing a training programme for professionals in the pharmaceutical sector on the implications of international agreements on their work. Greater efforts are needed in medical biotechnology fields, such as stem cell therapy, gene therapy and mRNA vaccine technology, to meet the health needs of the population and ensure access to life-saving therapies which include vaccines, biologics and other immunological products.

Bangladesh would urge WHO and other development partners to step up efforts to promote technology transfer and capacity building for local production. Bangladesh is a country with the potential to manufacture quality medical products at affordable prices and could take on a strong role globally to ensure access to new therapeutic products, especially if supported by the global community to play such a role.\(^39\) Additional technical and financial support is needed to establish strategies and alliances which
encourage innovation and technology transfer to countries with existing local capacity and a political environment conducive to development of the pharmaceutical sector so that they can play an active role in improving access to new health technologies.

The mRNA vaccine technology transfer hub initiative, first announced on 21 June 2021, aims to build capacity in low- and middle-income countries so that they can produce mRNA vaccines via a centre of excellence and training (the mRNA vaccine technology hub)(5).

Resolution WHA 68.18 adopted by the Sixty-eighth World Health Assembly (WHA, 2015) set out the global strategy and plan of action on public health, innovation and intellectual property (GSPA-PHI) as a complementary measure to the Organization’s comprehensive evaluation to ensure access to medical products for all. In May 2008, the GSPA-PHI was subsequently adopted at the WHA to simultaneously stimulate R&D for new products for the treatment, mitigation and prevention of diseases, and ensure implementation of global health security through improved access to health care products(40).

Access to medicines is a big challenge for least developed country (LDC) members which have been benefiting from the transition period under the TRIPS Agreement. The Doha Declaration (2001) pointed out that while the protection of intellectual property is important for the development of new pharmaceutical drugs, concerns about its effect on prices are also legitimate since they have direct consequences for access to medicines in LDCs and developing countries(34).

During the transition phase, LDCs are not expected to enforce the provisions of the TRIPS Agreement, except for Articles 3, 4 and 5, which include provisions on national treatment and most favoured nation treatment. LDCs were granted this degree of flexibility in recognition of their special needs and requirements, their economic, financial and administrative constraints and their need for more time to establish a viable technical base. With regard to pharmaceutical products, LDCs are not obliged to grant patent protection and other applicable provisions under Sections 5 and 7 of Part II of the TRIPS Agreement or to implement the rights provided for in these Sections until or before 1 January 2033.

Bangladesh is now moving forward in terms of clinical trials and in R&D for new medical products and health technologies. Although there have been significant delays in the steps taken to face the challenge, to date a total of 13 contract research organizations (CRO) have been authorized and 32 protocols approved for clinical trial in Bangladesh. Government support and sufficient funding to allow robust research and clinical trials will play a key role in squaring up to the challenge and transforming access to medical products and health technologies.

Only a bilateral technology transfer system exists in Bangladesh. However, as the number of manufacturers increases, a multilateral technology transfer initiative would be a sustainable solution for the country, in which case the government will need to develop a central system for technology transfer.

Technology transfer is one of the major components of the GSPA-PHI: it was boosted during the COVID-19 emergency by the technology transfer initiative for the mRNA vaccine which was supported by WHO, Medicines Patient Pool (MPP) and the Act-Accelerator/COVAX(41).

Thanks to the technology transfer process, the first batch of COVID-19 mRNA vaccines has already been produced. A list of 15 countries has been drawn up with 15 manufacturers/beneficiaries in all regions to receive mRNA vaccine technology transfer(5). WHO will conduct a training programme to boost competency in the beneficiary countries so that they can start producing safe and effective mRNA vaccines.
as soon as possible. Access to mRNA vaccines will promote health security worldwide by preventing vaccine-preventable diseases such as COVID-19.

**Required documents for mRNA vaccine registration through technology transfer**

- Copies of technology transfer agreements between innovator and receiving manufacturer.
- Evidence of transfer of starting materials including cell bank and seeds, manufacturing process, analytical methods.
- Evidence of demonstration of analytical comparability on a commercial scale: “process performance qualification” batches.
- Evidence of comparability of commercial-scale batches with clinical batches to demonstrate safety and efficacy (a comparability study between the tech-transfer plant vaccine and the receiving unit vaccine in a reasonable number of subjects).
- Product performance qualification from two different sites at the sending unit and receiving unit.
- Reference can be made to WHO-TRS 961, Annex 7.
- Research licence (Form 17 of Bengal Drug Rules 1946), if produced from master-cell bank.
- Innovator’s audit report.
- Evidence of EUA issued by the NRA in the country of origin.
- EUA/registration from any of the 7 listed countries (the USA, United Kingdom, Switzerland, Germany, France, Australia and Japan), and EMA or WHO EUA (if applicable).
- Preclinical study report.
- Phase I, phase II, and phase III full study reports.
- Complete dossier in CTD format.
- Applied COVID-19 vaccine risk management plan (RMP) to be submitted by the receiving manufacturer.
- Proper labelling and patient information leaflet (PIL).
- Summary of product characteristics (SmPC).

**The following stakeholders have specific roles to ensure quality access to mRNA vaccines in Bangladesh**

- Government leaders and policy makers.
- Ministry of Health and Family Welfare (MoHFW).
- Directorate General of Health Services (DGHS).
- National Regulatory Authority that is Directorate General of Drug Administration.
- Manufacturers of pharmaceutical products.
- Donors, nongovernmental organizations and international humanitarian programmes.
- Procuring organizations, wholesalers and distributors.
- Dispensers.
- National disease programmes.
- Medicine prescribers.
- Patients, consumers and patient advocacy groups.
- Bangladesh Medical and Dental Council (BMDC).
- Academia, University Grants Commission (UGC) and Pharmacy Council of Bangladesh (PCB).

**Recommendations for strengthening the mRNA vaccine ecosystem**

1. Raise social awareness and counter popular misunderstandings through scientific proofs that mRNA vaccines do not interfere with cell DNA. Cell DNA lies inside the body cell nucleus and is surrounded by a double-layered nuclear membrane, which prevents mRNA from entering the nucleus. Vaccine mRNA therefore cannot enter the nucleus unless degraded to smaller single nucleotides, which are harmless.
2. Promote and monitor regulatory system transparency.
3. Endorse the technology transfer initiative for mRNA vaccine technology.
4. Strengthen the technology access pool system.
5. Develop national legal and regulatory provisions that properly reflect the flexibilities of the TRIPS Agreement, including those addressed in the Doha Declaration on the TRIPS Agreement and Public Health, notably Articles 27, 30 (including the research exception and “Bolar” exemption), 31 and 31bis of the TRIPS Agreement.
6. Develop a new patents act addressing the recommendations mentioned in the GSPA-PHI that will promote R&D for access to new health technologies.
7. Strengthen research collaboration, information sharing and fund raising.
Part 2 – Ecosystem for pharmaceuticals, especially other vaccines and biologicals

Background
Access to safe, effective and quality-assured medical products (including medicines, vaccines, biologicals, medical devices and in vitro diagnostics) for all is one of the major targets to achieve UHC and reach the SDG milestones (United Nations, 2016). Achieving UHC requires access to safe, effective, quality and affordable essential medicines and vaccines. In Bangladesh, out-of-pocket (OOP) spending accounts for 67% of total health expenditure, and the share of OOP spending on medicines and medical products is 69.4%. While 98% of the country’s needs for essential medicines are manufactured locally (Ministry of Health and Family Welfare- Directorate General of Health Services, 2018; Directorate General of Drug Administration, 2017), access and use are limited as evidenced by the cumulative nationwide monthly reported stock-out period, which ranged from zero to over 15 000 days over a review period of 12 months for selected essential medicines (Directorate General of Health Services, 2018). In Bangladesh, data to measure the “proportion of health facilities that have a core set of relevant essential medicines available and affordable on a sustainable basis” have still not been established to address SDG indicator 3.b.3.

Vaccines are life-saving medical products. Over two centuries, vaccines have been crucial in reducing the scourge of diseases like measles and polio, and promoting life expectancy among children and other sections of the population. Vaccines are considered to be one of the most cost-effective ways of advancing global public health. Over the last 40 years, Bangladesh has made significant achievements in immunization and gained many health benefits. The country reached its milestone of eliminating neonatal tetanus in 2008 (and maintains this status), and also received its polio-free certificate in 2014(42). Between 1990 and 2012, mortality has been reduced in children under five years of age by 73%, a statistic that was made possible due to strong leadership and government ownership(42). Bangladesh has a roadmap with established targets and the capacity to provide immunization at 140 000 vaccination points. Progress in immunization is closely monitored, with tracking of disease outbreaks by a well-equipped and established immunization surveillance system that is actively supported by WHO.

Introduction
The pharmaceutical sector in Bangladesh provides an example of how health and economic development intermix. The rationale for strengthening Bangladesh’s pharmaceutical regulatory system is compelling because of the dual contribution a strong local pharmaceutical industry can have in terms of improving health outcomes and economic development. Bangladesh has made remarkable progress in providing immunization coverage for 10 diseases through scheduled routine immunization which targets 3.8 million children and 6 million women every year(42). Expanded Programme for Immunization (EPI) coverage allows approximately 200 000 deaths to be prevented in Bangladesh every year (42), a programme which absorbs US$ 160 million (136 crore Taka) annually. In 2020, the Government of Bangladesh contributed 39% of this sum with 61% provided by support from Gavi, UNICEF, WHO and other relevant partners. As previously noted, Gavi funding support to Bangladesh is being gradually phased out from 2022 to 2026. Every year Bangladesh therefore needs to boost its self-funding coverage by 20–25% to sustain the country’s immunization coverage(42).

The government’s national EPI imports six vaccines from WHO prequalified sources:
- bacillus Calmette–Guérin (BCG) vaccine;
- pentavalent vaccine;
- inactivated poliomyelitis vaccine (IPV);
- pneumococcal conjugate vaccine (PCV);
- measles and rubella vaccine; and
- tetanus toxoid for women within the age group 15–49 years.

The national EPI introduced hepatitis B vaccine in 2003 and *Haemophilus influenzae* type B (as pentavalent vaccine) in 2009; and measles second dose and measles and rubella vaccine in 2012. The Ministry of Health and Family Welfare also introduced pneumococcal vaccine in 2014 for prevention of specific forms of childhood pneumonia and meningitis. It is also planned to add some other life-saving vaccines in coming years for prevention of cervical cancer (caused by human papilloma virus) and rotavirus-induced diarrhoea, typhoid and cholera; as well as hepatitis B (birth dose), inactivated polio vaccine (IPV) and other new and underutilized vaccines.

Bangladesh needs to promote local production of vaccines to allow sustainable immunization coverage. At present there are three manufacturers producing vaccines locally:
- Incepta Vaccine Limited;
- Popular Pharmaceuticals Limited; and
- Healthcare Pharmaceuticals Limited.

Three manufacturers are about to start vaccine manufacturing:
- Globe Biotech Limited;
- Active Fine Chemicals Limited; and
- the state-owned Essential Drug Company Limited.

These Bangladeshi firms manufacture a variety of vaccines including fill-finish vaccines and vaccines from master cells.

At present there are four vaccine importers:
- Sanofi Bangladesh Limited;
- Janata Traders;
- Healthcare Pharmaceuticals Limited; and
- government bodies (Directorate General of Drug Administration, EPI).

In Bangladesh, the Directorate General of Drug Administration is the sole authority responsible for regulating vaccines, biologicals and all other pharmaceuticals. The Directorate General of Drug Administration is committed to safeguarding Bangladeshi citizens from unsafe and infective medical products in health care, including those intended for use in the treatment of emerging infectious diseases (such as COVID-19). The Directorate General of Drug Administration performs nine major functions according to WHO global benchmarking requirements: 1) national regulatory system; 2) registration and market authorization (MA); 3) pharmacovigilance; 4) market surveillance and control; 5) licensing establishment; 6) regulatory inspection; 7) laboratory access and testing; 8) clinical trial oversight; and 9) NRA lot release.

The Directorate General of Drug Administration is solely responsible for establishing the requirements, procedures and timetable for vaccine manufacturers and importers to request authorization for the introduction and use of their products in Bangladesh. The Directorate General of Drug Administration is also required to ensure that vaccines and manufacturing facilities meet established standards, including
manufacturing, quality control and distribution processes, and to oversee their clinical study and improved access.

**Vaccination coverage**

In Bangladesh, immunization coverage is high and static, i.e. it has been sustained at over 80% for more than ten years and 84% of children under 12 months of age are fully immunized as captured until 2019 (42). However, Bangladesh is currently not on track to achieve the health-related SDGs targeting immunization of 95% of children with all required antigens by the year 2030. There is a burning need for Bangladesh to promote efforts to enhance the static coverage of immunization with a global commitment to protect children’s health against preventable diseases. Inequities in immunization are apparent in Bangladesh, although coverage is still relatively good, with the most significant inequities being observed between urban and rural areas. In terms of full vaccination coverage (FVC), there is a persistent 31% gap between the highest-performing district Bhola (96%) and lowest-performing district Khagrachari (65%)(42). Detailed vaccination coverage statistics are presented in Table 1 and Figure 2.

The figures for COVID-19 vaccination coverage to the end of April 2022 were: first dose 75.46%; second dose 68.19%; and third dose 9.10%. The population eligible for COVID-19 vaccination was 119.26 million, corresponding to 70% of the total population of 170.37 million. The various vaccines used were: 17.2% AstraZeneca; 18.1% Pfizer; 45.9% Sinopharm; 4.1% Moderna; 14.6% Sinovac; and 0.1% Johnson & Johnson(43).

**Fig. 2: Immunization coverage in Bangladesh (year 2001-2019)**
Table 1: Immunization coverage in Bangladesh

<table>
<thead>
<tr>
<th>Year</th>
<th>BCG</th>
<th>Penta3</th>
<th>MCV1/MR1</th>
<th>Fully vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>94.00%</td>
<td>64.00%</td>
<td>52.00%</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>95.00%</td>
<td>65.00%</td>
<td>56.00%</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>95.00%</td>
<td>69.00%</td>
<td>63.00%</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>95.00%</td>
<td>77.00%</td>
<td>71.00%</td>
<td>64.00%</td>
</tr>
<tr>
<td>2006</td>
<td>98.00%</td>
<td>84.00%</td>
<td>78.00%</td>
<td>71.00%</td>
</tr>
<tr>
<td>2007</td>
<td>98.20%</td>
<td>86.60%</td>
<td>80.60%</td>
<td>75.00%</td>
</tr>
<tr>
<td>2009</td>
<td>99.00%</td>
<td>85.50%</td>
<td>82.80%</td>
<td>75.00%</td>
</tr>
<tr>
<td>2010</td>
<td>98.60%</td>
<td>88.70%</td>
<td>84.80%</td>
<td>79.40%</td>
</tr>
<tr>
<td>2011</td>
<td>99.00%</td>
<td>89.60%</td>
<td>85.50%</td>
<td>80.20%</td>
</tr>
<tr>
<td>2013</td>
<td>95.10%</td>
<td>92.00%</td>
<td>85.50%</td>
<td>80.70%</td>
</tr>
<tr>
<td>2014</td>
<td>99.20%</td>
<td>93.00%</td>
<td>86.60%</td>
<td>81.60%</td>
</tr>
<tr>
<td>2015</td>
<td>99.30%</td>
<td>93.60%</td>
<td>87.40%</td>
<td>82.50%</td>
</tr>
<tr>
<td>2016</td>
<td>99.50%</td>
<td>90.10%</td>
<td>87.50%</td>
<td>82.30%</td>
</tr>
<tr>
<td>2019</td>
<td>99.70%</td>
<td>93.30%</td>
<td>88.60%</td>
<td>83.90%</td>
</tr>
</tbody>
</table>

BCG: bacillus Calmette-Guérin vaccine
Penta3: pentavalent vaccine three doses
MCV1: measles-containing vaccine first dose
MR1: measles rubella first dose

Vaccine sourcing

For the EPI calendar involving BCG, pentavalent, inactivated poliomyelitis vaccine (IPV), pneumococcal conjugate vaccine (PCV), measles and rubella vaccine and tetanus toxoid, vaccines are imported from WHO prequalified sources. Vaccine procurement is supported by UNICEF, funded by Gavi and technical assistance provided by WHO. In Bangladesh, a total of 55 vaccine formulations are currently being imported and 24 vaccine formulations locally produced. The Bangladeshi firm Incepta Vaccine Limited also manufactures 10 bulk antigens.

In Bangladesh, the 55 vaccines imported from different WHO-prequalified sources and those manufactured in the country are subject to a stringent regulatory authority (SRA). According to the Clause 6.C(1) of the National Drug Policy 2016, any medicine or vaccine to be imported into Bangladesh must be registered in one of seven listed countries (the USA, United Kingdom, Switzerland, Germany, France, Australia, and Japan) and listed as WHO prequalified/emergency use.

For EPI, all vaccines are imported from the following sources which comply with Directorate General of Drug Administration requirements.

For COVID-19 coverage, the Directorate General of Drug Administration accorded EUA to nine vaccines:

- Covishield® (non-replicating viral vector vaccine: Oxford-AstraZeneca formulation), manufactured by Serum Institute of India (SII);
- Covovax® (protein subunit vaccine: Novavax formulation), manufactured by SII;
- Spikevax® (mRNA vaccine), manufactured by Moderna, the USA;
▪ Comirnaty® (mRNA vaccine), manufactured by Pfizer/BioNTech, the USA;
▪ Sputnik V® (non-replicating viral vector vaccine), manufactured by Gamaleya, Russian Federation;
▪ Jcovden® (non-replicating viral vector vaccine), manufactured by Johnson & Johnson, the USA;
▪ Vaxzevria® (non-replicating viral vector vaccine), manufactured by Oxford-AstraZeneca, United Kingdom;
▪ Covilo® (inactivated vaccine), manufactured by Sinopharm, China; and
▪ CoronaVac® (inactivated vaccine), manufactured by Sinovac, China.

Vaccines are imported from the following sources:
▪ Aventis Pasteur SA, France (2 vaccines);
▪ Baxter AG, Austria (1 vaccine);
▪ Berna Biotech, Republic of Korea (2 vaccines);
▪ Chiron Behring Vaccine Pvt. Ltd., India (1 vaccine);
▪ Glaxo Smith Kline Bioglan SA, Belgium (16 vaccines);
▪ GlaxoSmithKline Biologicals, Germany (1 vaccine);
▪ GP Grenzach Produktions Gmbh, Germany (1 vaccine);
▪ Instituto Grifols SA, Spain (1 vaccine);
▪ Wyeth Lederle Vaccine SA, Belgium (1 vaccine);
▪ Medac Gesellschaft für klinische Spezialprparate, Germany (1 vaccine);
▪ Merck Sharp & Dohme Corp., the USA (4 vaccines);
▪ Novartis Vaccines and Diagnostics, Germany and Italy (3 vaccines);
▪ Pasteur Mérieux Serums and Vaccines, France (1 vaccine);
▪ Pfizer manufacturing, Belgium, Ireland and the United Kingdom (3 vaccines);
▪ Sanofi Pasteur SA, France (17 vaccines); and
▪ The Research Foundation for Microbial Disease of Osaka University, Japan (1 vaccine).

2.1 Section 1
2.1.1 Section summary

Bangladesh has made remarkable progress in the last three decades in terms of access to medical products, by strengthening the local production of medicines, vaccines, biologicals and medical devices. Before 1982, access to medical products in Bangladesh was import-dependent but following implementation of the legal provisions of The Drugs (Control) Ordinance, 1982, and the first national drug policy in the same year, its pharmaceutical sector has grown exponentially. Bangladesh is now able to meet 98% of its demand for medicines from local production: only 2% needs to be imported. However, the country is still dependent on the importation of vaccines, biologicals and medical devices. Bangladesh exports generic medicines to 162 countries.

Table 2: Export statistics of last five fiscal years (Directorate General of Drug Administration Annual Report 2021-2022)

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>Total exports (million US$)</th>
<th>No. of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016–2017</td>
<td>90</td>
<td>113</td>
</tr>
<tr>
<td>2017–2018</td>
<td>104</td>
<td>140</td>
</tr>
<tr>
<td>2018–2019</td>
<td>130</td>
<td>146</td>
</tr>
</tbody>
</table>
The local vaccine manufacturer Incepta Vaccine Limited is exporting vaccines in small quantities to six LDC countries where regulations have yet to be standardized: Burundi, Ivory Cost, Nepal, Zimbabwe, Chad and Gabon. The firm is trying to expand in the global market but remains restricted owing to the regulatory status of Bangladesh’s national regulatory authority, the Directorate General of Drug Administration: vaccine lot releases are not performed to WHO-PQ standard. The Directorate General of Drug Administration is also trying to attain WHO maturity level 3 and become a WHO-listed authority (WLA).

In Bangladesh, there are three vaccination schemes: 1) the expanded programme of immunization (EPI); 2) emergency vaccinations, e.g. COVID-19 prevention; and 3) vaccinations of interest (meningococcal, pneumococcal, rotavirus, oral cholera, HPV vaccines, etc.).

The Government of Bangladesh provides 33% of the funding for the routine immunization programme while the other 67% is met by Gavi, UNICEF, WHO and other partners. The government also provides 32% funding for other vaccines. Since Gavi support is shrinking 20% annually to 2026, the sustainability of the vaccine ecosystem will be a challenge in coming years.

Bangladesh is one of the very few least developed countries (LDCs) which was able to take significant advantage of the flexibilities granted to the LDCs under the auspices of the World Trade Organization’s Agreement on Trade-Related Intellectual Property Rights (WTO-TRIPS). These flexibilities are made possible by two waivers: a general waiver from TRIPS compliance requirements, first granted for 11 years in 1995 (until 2006), followed by an extension for 8 years (until 2013), an additional 8 years (until 2021) and through to the last extension in 2021 for 13 years (until 31 July 2034); and a special waiver for the pharmaceutical sector, first granted in 2001 for 15 years (until 2015) and extended in 2015 for a further 17 years (until 1 January 2033).

However, if no specific decision is taken in support of a graduating LDC, this country ceases to benefit from the aforesaid two waivers once it graduates from the LDC group. Since Bangladesh is set to leave this group on 24 November 2026, the country will thus not be eligible for the benefits and flexibilities which it has been enjoying as a LDC beyond this timeline.
An overview of the ecosystem for local production of health products

Bangladesh has drawn up three types of medicines lists: 1) essential medicines list (2016), containing 285 allopathic generics; 2) the Essential Service Package (ESP) medicines list (2018), containing 142 generics; and 3) the primary health care (PHC) medicines list 1993, containing 117 generics. According to the ESP medicines list, the government’s public health care supply is organized in tiers to primary, secondary and tertiary care hospitals: 70% takes place via a central procurement system and 30% via district civil surgeons’ offices. The Essential Drugs Company Limited (EDCL) is a 100% state-owned pharmaceutical manufacturing company which supplies government medicines through the country’s Central Medical Store Depot (CMSD). In 1962, the EDCL, functioning under the then central government, was called the Government Pharmaceuticals Laboratory (GPL); it was subsequently renamed the Pharmaceuticals Production Unit (PPU) in 1979. For public health benefit, and in the interest of smooth organizational governance, it was registered as a Public Limited Company under the 1994 Company Act. The controlling authority of this state-owned company is the Ministry of Health and Family Welfare. In 1983, the company was established as the EDCL: its main objective was to set up a state-of-the-art pharmaceuticals industry and guarantee public access to quality-assured medical products in Bangladesh through the local production of medicines and their supply countrywide for public benefit. In the government sector, EDCL has secured a strong base to sustain its growth, success and reliably serve public health. Central supply via the CMSD and local manufacture by EDCL contribute significantly to reduce out-of-pocket (OOP) expenditure in Bangladesh.

An estimated 270 pharmaceutical companies and more than 160 000 medicine storage units or outlets (warehouses, depots, retail shops, etc.) exist throughout the country and more than 40 000 brand products are available on the market.[44]. Bangladesh imports vaccines for routine child immunization and manufactures hepatitis A and B, rabies, tetanus, influenza, meningococcal, cholera, human papilloma vaccine, typhoid, mumps and measles vaccines. Although the Directorate General of Drug Administration’s NCL has been performing lot release of imported and locally manufactured vaccines since 2011, results from its WHO-GBT assessment indicate that additional work is needed to reach WHO maturity level 3 for lot release for both imported and exported vaccines, the latter of which requires additional capabilities.

As noted, Bangladesh’s pharmaceutical industry has been among the very few in LDCs which has been able to take advantage of the TRIPS flexibilities in a significant way through: 1) waivers from patenting and licensing; 2) flexible production practices and reverse engineering; and 3) policy autonomy providing derogation from TRIPS compliance and TRIPS enforcement requirements. The country’s pharmaceutical industry has developed in two ways: as an import substituting industry catering for about 98.0% of domestic demand (the market is estimated to be worth about US$ 3.5 billion); and as an export-oriented industry, with exports of about US$ 170 million to more than one hundred countries (in 2021–2022). The pharma industry has contributed to the Bangladeshi economy through: 1) providing an opportunity to access essential medicines at affordable prices (thanks to production of generic/patented medicines under a flexible regime); 2) employment creation (the sector employs about 170 000 people, as is one of the very few industries in Bangladesh with a substantial share of white-collar jobs, including many for women); 3) multiplier impacts on the economy through upstream and downstream value- and supply-chain networks; and 4) generating benefits to other low-income countries and LDCs by providing access to low-priced medicine exported from Bangladesh.
However, once Bangladesh graduates from the LDC group in November 2026, it will immediately be subject to TRIPS-regime compliance (although the LDC flexibilities will be in force until January 2033 and July 2034 respectively under the current dispensation) and the country will no longer be eligible for the LDC benefits. The implications will be felt in several ways: 1) a TRIPS-compliant patenting-licensing regime will need to be enforced for Bangladesh’s pharmaceutical sector; 2) domestic industry protection policies will need to be revisited and revised to ensure TRIPS compliance; and 3) export, import, foreign direct investment (FDI) and other policies relating to the pharma sector will have to be TRIPS compliant. A study by the South Centre estimates that the price of insulin in Bangladesh could go up by 11 times compared to the prevailing market price consequent to TRIPS regime enforcement, with significant adverse implications for households concerned (45).

On the other hand, Bangladesh’s LDC graduation bespeaks the country’s significant socioeconomic achievements over the past years. Not many LDCs can claim this distinction. Building on its past track record, Bangladesh has the capacity to strengthen its pharma industry further, to be able to remain competitive in the domestic market while raising its competitiveness in the global pharma market to more than US$ 1 trillion. By strengthening both backward and forward linkages, the sector could potentially be a driver of Bangladesh’s sustainable LDC graduation and accelerated future development.

The Directorate General of Drug Administration is Bangladesh’s NRA, a government organization which operates under the Ministry of Health and Family Welfare. Its director-general also heads the NRA, which is the licensing authority for all drugs and health products (API, medicines and finished goods, medical devices, vaccines, biologicals and in vitro diagnostics). The Directorate General of Drug Administration’s task is to enforce all prevailing drug laws and regulations and supervise all activities related to access to quality-assured safe and effective health care products. It has a number of committees, composed of experts and representatives of different associations, academia, research organizations, etc., who advise the licensing body.

The Directorate General of Drug Administration is responsible for establishing a regulatory pathway to register medical products. One of the major requirements for registration is quality testing of the applied product. Operating a laboratory entails fixed and variable costs associated with labour (e.g. workload by type of staffing), supplies (e.g. reagents, reference standards), infrastructure (e.g. laboratory equipment, physical space) and services (e.g. equipment maintenance and calibration). Laboratories must recover these costs through government funding, charging for tests, or some combination of the two. For the NCL to operate according to international standards (ISO 17025:2017/WHO-PQ) and to sustainably maintain its accreditation and prequalification, the laboratory must regularly review its funding and income.

The Institute of Epidemiology, Disease Control and Research (IEDCR) is an organization under the Ministry of Health and Family Welfare which is mandated to support epidemiological and communicable disease research and testing services. It is the country’s primary source for conducting disease surveillance and outbreak investigations. The IEDCR comprises five separate laboratories and the aim is to have all of them operating at international standards. During the height of the COVID-19 pandemic, IEDCR provided large-scale viral diagnoses which helped to identify focal infections and was critical in containing virus spread and preventing deaths.

The IEDCR collaborates with multilateral funding agencies such as WHO, UNICEF, USAID, etc. on a broad range of issues: for instance, arsenicosis, infectious disease surveillance, reproductive health, HIV/AIDS, malaria, health care management and antimicrobial resistance to protect public health. These collaborations and multiple projects have led to a need to expand its testing facilities.
Bangladesh is a prospective country for manufacturing active pharmaceutical ingredients (API). Currently, Bangladesh imports more than 95 percent of its API from abroad, including public health priority drugs. To promote API manufacturing in Bangladesh, the government has invested more than US$ 32 million to establish a dedicated API manufacturing facility (API Park) at Gazaria, Munshiganj, where 200 acres of land will be allocated to 27 companies to set up API industries in the park. In 2018, the Ministry of Commerce formulated the National Active Pharmaceutical Ingredients (API) and Laboratory Reagents Production and Export Policy to incentivize API production. This policy aims to support local production of API by providing various incentives to manufacturers such as tax exemptions, tax holidays, VAT reduction, cash incentives, etc. The policy also contains provisions to support R&D, manufacturing and supply of API in Bangladesh. After Bangladesh’s TRIPS graduation (2026), the country’s pharmaceutical sector will also face challenges to produce affordable and quality-assured medicines due to the increasing costs of API. The government therefore considers the local manufacturing of API a national priority.

### 2.2 Section 2

#### 2.2.1 Different government ministry and agency policies which promote or hinder the production of local vaccines and biologicals

Bangladesh’s pharmaceutical industry grew remarkably by 17% in the years 2014 to 2020, with 25% export growth year on year. The evidence indicates that from 2015 to 2021, the export growth rate was 15%. The pharmaceutical sector contributes 2% to Bangladesh’s GDP, but the main obstacle to further growth is higher local production costs of about 15%, as compared to India and China, owing to the country’s dependency on imported API for manufacturing pharmaceutical products. In contrast, human resources, technology and infrastructure are around 15% cheaper that in neighbouring countries (India and China).

For better access to medical products including vaccines, the government has launched several policies to promote local production. Policies in support of local production and supply of medical products are: 1) the National Health Policy 2011; 2) the National Immunization Policy 2013; 3) the National Drug Policy 2016; and 4) the National API Policy 2018. There are also several Bangladeshi acts, laws and ordinances that promote or support the local production of pharmaceuticals:

- The Drugs Act, 1940
- The Bengal Drugs Rules, 1946
- The Foreign Private Investment (Promotion and Protection) Act, 1980
- The Drugs (Control) Ordinance, 1982
- The Bangladesh Investment Development Authority Act, 2016

The Government of Bangladesh has run general incentive systems in various fiscal and non-fiscal years to encourage, motivate and facilitate investment for local production. These include privileges, facilities and incentives involving VAT reductions or exemptions, import tax concessions on capital machineries and raw materials, as well as on corporate income taxes. The government also has provisions on export subsidies, banking facilities and other privileges. The National Finance Act and individual statutory regulatory orders (SROs) stipulate that these incentives should be revised annually. Corporate income tax reduction is offered to newly established facilities based on business sector and location, and applicable for the fiscal period July 2019 to June 2024. According to section 46BB of the Income Tax Ordinance (1984), pharmaceuticals, active pharmaceutical ingredients and radiopharmaceuticals are eligible for income tax
reduction or exemption: this applies for newly established firms working in the sector between 1 July 2019 and 30 June 2024. There is no specific policy offering incentives, subsidies, tax exemption or reduction relating to the import of raw materials and equipment, R&D, manufacturing, distribution or export.

2.2.2 Incentives from government and/or other sectors for manufacturers and investors to promote and sustain the production of vaccines and biologicals

The Government of Bangladesh strongly supports the local production of pharmaceuticals, biologicals, vaccines, medical devices and in vitro diagnostics. The government launched its API policy in 2018, aiming to promote investment of US$ 1 billion for local production of API to manufacture medicines, vaccines and biologicals. The goal was to reduce import-dependence to 80% by 2032 for the benefit of local production in order to stimulate access to medical products and generate a sustainable public health ecosystem in Bangladesh to ensure the supply of quality-assured, safe and effective medicines, vaccines, biologicals, medical devices, in vitro diagnostics and other health care and therapeutic products.

To promote local pharmaceutical production, the Government of Bangladesh has several policies in place:

- A 100% tax holiday for producers of five API molecules.
- A 75% tax holiday for producers of three API molecules.
- Producers of APIs and laboratory reagents registered in Bangladesh enjoyed a 100% corporate tax holiday until 2021–2022.
- After this fiscal year, producers of APIs and laboratory reagents continued to enjoy a tax holiday (from 2023–2032) if they produced API molecules domestically.
- No advance income tax (AIT) applicable for API producers on importation of chemical compounds (technical grade/chemically pure).
- Firms established between 1 July 2019 and 30 June 2024 eligible for phased or partial tax exemption for five to 10 years.
- No AIT applicable for API producers on importation of chemical compounds (technical grade/chemically pure)\(^{(46)}\).

Since Bangladesh has developed enough competency for local production of branded or blockbuster generic medicines, the anticipated patent cliff ought to present a huge opportunity for Bangladeshi manufacturers to expand their production and market of generic drugs.

According to Income Tax Ordinance 1984, section 46BB, newly established (between 1 July 2019 and 30 June 2024), pharmaceutical manufacturers — depending on the site of their manufacturing plant and business operation — will have the possibility to reduce their income tax as shown below.

For pharmaceutical manufacturing plants and businesses located in the Dhaka and Chattogram divisions, but excluding the districts of Dhaka, Narayanganj, Gazipur, Chattogram, Rangamati, Bandarban and Khagrachari, the period of tax exemption is for five years, starting after the month on which commercial production commences, at the following rates (table 3).
Table 3: Income Tax Ordinance 1984, section 46BB, newly established (between 1 July 2019 and 30 June 2024) - Rate of exemption for a 5-years period

<table>
<thead>
<tr>
<th>Period of exemption</th>
<th>Rate of exemption</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the first year</td>
<td>90% of income</td>
</tr>
<tr>
<td>For the second year</td>
<td>80% of income</td>
</tr>
<tr>
<td>For the third year</td>
<td>60% of income</td>
</tr>
<tr>
<td>For the fourth year</td>
<td>40% of income</td>
</tr>
<tr>
<td>For the fifth year</td>
<td>20% of income</td>
</tr>
</tbody>
</table>

* For pharmaceutical manufacturing plants and businesses located in the Dhaka and Chattogram divisions, but excluding the districts of Dhaka, Narayanganj, Gazipur, Chattogram, Rangamati, Bandarban and Khagrachari.

The Government of Bangladesh offers another ten-year tax exemption scheme for pharmaceutical manufacturing plants and businesses located in Rajshahi, Sylhet, Khulna and Barisal divisions, but excluding areas with urban corporations. This tax holidays also applies to pharmaceutical production plants set up in Bandarban, Rangamati and Khagrachari districts (table 4).

Table 4: Income Tax Ordinance 1984, section 46BB, newly established (between 1 July 2019 and 30 June 2024) - Rate of exemption for a 10-years period

<table>
<thead>
<tr>
<th>Period of exemption</th>
<th>Rate of exemption</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the first and second year</td>
<td>90% of income</td>
</tr>
<tr>
<td>For the third year</td>
<td>80% of income</td>
</tr>
<tr>
<td>For the fourth year</td>
<td>70% of income</td>
</tr>
<tr>
<td>For the fifth year</td>
<td>60% of income</td>
</tr>
<tr>
<td>For the sixth year</td>
<td>50% of income</td>
</tr>
<tr>
<td>For the seventh year</td>
<td>40% of income</td>
</tr>
<tr>
<td>For the eighth year</td>
<td>30% of income</td>
</tr>
<tr>
<td>For the ninth year</td>
<td>20% of income</td>
</tr>
<tr>
<td>For the tenth year</td>
<td>10% of income</td>
</tr>
</tbody>
</table>

# For pharmaceutical manufacturing plants and businesses located in Rajshahi, Sylhet, Khulna and Barisal divisions, but excluding areas with urban corporations.

There are import duty exemption policy relating to the local production of pharmaceuticals including medicines, vaccines, biologicals, medical devices and in vitro diagnostics:
- capital machinery systems are subject to a reduced rate of customs duties; and
- raw materials to be used for producing export goods are exempt from import duties.

There are incentive policies for the exportation of pharmaceutical products that promote local production, regardless of business locations:
- exemption of income tax on 50% earnings from exports (unless paying tax at reduced rate);
- no duty on exports;
- bonded warehousing facilities;
- duty drawback facilities; and
- additional benefits in the form of a subsidy or 2% cash incentive on pharmaceuticals.
2.2.3 Financing conditions and mechanisms in Bangladesh for manufacturers to produce vaccines and biologicals

The Government of Bangladesh does not finance directly local pharmaceutical production. However, the government has a policy to provide support in the form of bank loans to manufacturers for pharmaceutical production. The government also provides the various incentives and tax exemptions mentioned above. Furthermore, the government has budget allocations to strengthen the Directorate General of Drug Administration’s regulatory system for medicines, vaccines, biologicals, medical devices and in vitro diagnostics.

The total operating budget (revenue budget) in the fiscal year 2020 to 2021 was US$ 3.702 million.

The total development budget in the fiscal year 2020 to 2021 was US$ 2.372 million which was distributed as follows: US$ 2.09 million for procurement of lab equipment and US$ 0.282 million for other items.

The additional allocation from July 2020 to June 2023 to boost and expand the NCL testing facilities for vaccines and biologicals was US$ 2.731 million which was distributed as follows: US$ 1.412 million for procurement of lab equipment and US$ 1.319 million for other items(46).

2.2.4 Regulatory system (regulations, standards and requirements) for vaccines and biologicals

The Drug Acts was enacted in 1940 and implemented by the Directorate of Health Services of then undivided India. After 1947 it was regulated by the Directorate of Health Services, East Pakistan, until the independence of Bangladesh in 1971. It was then regulated by Bangladesh’s Directorate of Health Services until the Directorate of Drug Administration was formed under the Ministry of Health and Family Welfare in 1974. On 10 January 2010 it was upgraded to the Directorate General of Drug Administration (DGDA).

In Bangladesh, the Directorate General of Drug Administration is the only statutory authority for regulation of drugs, medicines, medical devices, in vitro diagnostics, biologicals and vaccines. Bangladesh meets 98% of its demand for medical products by local production, although almost all are generic(47). However, Bangladesh is still lagging behind in terms of ensuring production, supply and overall access to quality-assured medical devices, medical oxygen and assistive health technologies for maternal and child health (MCH) care, family planning and in cross-cutting areas.

The Directorate General of Drug Administration ’s mission is:
- to safeguard the health of humans and animals by ensuring the safety, efficacy and quality of medicines, alternative medicines and medical devices;
- to guarantee the availability, accessibility and affordability of essential medicines; and
- to implement good manufacturing practice (GMP) compliance in the production and quality control of health products to vouchsafe consumer safety and facilitate their exportation.

The Directorate General of Drug Administration ’s vision is of quality-assured, safe and effective medical products for all (Figure 4).
The legislative basis for vaccine registration and control:
- The Drugs Act, 1940
- The Bengal Drugs Rules, 1945
- The Bengal Drugs Rules, 1946
- The Drugs (Control) Ordinance, 1982
- National Drug Policy, 2005
- National Drug Policy, 2016
- Government Notification No.: 45.00.0000.182.89.001.21.93, dated 24 April 2021 on consideration of COVID-19 vaccine for EUA depending on country of origin and satisfactory clinical study data
- Bangladesh Gazette Notification dated 17 May 2020 mandating the Directorate General of Drug Administration to issue an EUA/NOC in a public health emergency
- Bangladesh Gazette Notification dated 28 June 2021 mandating the Directorate General of Drug Administration to perform clinical trials, pharmacovigilance and lot release functions.

Departments of the vaccine regulatory system:
- Registration and marketing authorization (MA) for vaccines and biologicals is responsible for registering and issuing product MA certificates as well as for bulk vaccine, post-market variation approval for vaccines and biologicals: legal mandates, established procedures and guidelines are in place.
- Licensing of premises issues premise licences for registering vaccine plants: established procedures and guidelines are in place. Inspections are carried out by a competent team of inspectors when evaluating premises and facilities.
- Vigilance is responsible for monitoring and following up adverse events (AEs) and regulatory decisions relating to vaccines: guidelines, SOPs and expert committees are in place. Countrywide
post-vaccination adverse events following immunization (AEFI) data were well captured, especially for COVID-19 vaccine, through the online reporting system prior to analysis, causality assessment and regulatory decision-taking.

- **Market surveillance and control** is responsible for sampling and supervising vaccine sales and distribution compliance.
- **Regulatory inspection** (RI) is responsible for good practice compliance and regulatory inspections: MA department receives inspection-related support from RI department.
- MA department receives test reports as well as dossier-based evaluations of test method validation from the laboratory access and testing department.
- MA department receives information from the lot release department about batch consistency.
- MA department is supported by the clinical trial oversight department which evaluates the non-clinical and clinical data in vaccine dossiers.

### 2.2.5 Existing R&D capability and capacity of each manufacturer in the country, particularly for production of vaccines and biologicals

No indigenous vaccine is commercially produced yet in Bangladesh. Incepta Vaccine Limited manufactures a total of 10 vaccines: hepatitis A and B, rabies, tetanus, influenza, meningococcus, cholera, human papilloma vaccine, typhoid, mumps and measles; four from seed, six from bulk. The latest product is a prefilled syringe machine used for human papilloma vaccine, hepatitis A and B and tetanus vaccine.

Popular Pharmaceutical Limited produces four vaccines, all from ready-to-fill bulk: hepatitis B, rabies, tetanus and human papilloma vaccine.

Incepta Vaccine Limited, Popular Pharmaceuticals Limited, Globe Biotech Limited and Healthcare Pharmaceuticals Limited have developed R&D facilities for manufacturing vaccines from master seeds or ready bulk. The manufacturers have no facilities for conducting clinical trials, but have the ability to receive technology transfer.

The Government of Bangladesh is planning to manufacture vaccines in the state-owned pharmaceutical firm Essential Drugs Company Limited (EDCL): as Gavi support is phased out gradually, EDCL will take up the slack to meet the country’s demand for routine immunization and public health protection.

At present there are eight approved contract research organizations (CRO) in Bangladesh. Bangladesh Medical Research Council (MRC) provides clearance and the Directorate General of Drug Administration protocol approval for clinical trials. Every CRO requires a licence from the Directorate General of Drug Administration.

### 2.2.6 Patent system and possible intellectual property rights barriers towards local production, particularly for vaccines and biologicals

The Government of Bangladesh has endorsed and published the Patents Act 2022 in its gazette. The Patents Act Chapter 8, Section 33, states that any innovator, researcher, institution or manufacturer can register the patent for their product or technology locally. According to Section 36, decisions made at the WTO meeting on 30 August 2003 will be applied following amendment of the TRIPS Council Agreement.
(Article 65). After Bangladesh graduates from LDC to developing country status in November 2026, compulsory licensing provisions may apply (35). The clauses are the same for all drugs including generics, vaccines and biologicals, and mRNA vaccines fall under the same criteria (36).

The Bangladesh Patents Act 2022 has been endorsed by the Legislative and Parliamentary Affairs Division and will mainly be applied and controlled by the Ministry of Law and Legal Affairs, the Ministry of Commerce and the Department of Patents, Designs and Trademarks.

Various experts have suggested that development of local capacity ought to be triggered by enhanced investment in R&D. It is therefore crucial that a new policy be formulated to encourage pharmaceutical manufacturers and companies to invest a specific portion of their profits in R&D. A significant percentage of such investment should be allotted to universities, which in turn should introduce institutional IP policies in order to increase joint research programmes with industrial entities.

In order to acquire the ability to prepare new medical products, i.e. new molecules, vaccines or biologicals, placement-based goals and plans have to be adopted in the pharmaceutical industry. The government ought to adopt a new incentive policy to encourage the development of new drugs, including new molecules. Globally accredited drug-testing laboratories should be set up under the Directorate General of Drug Administration to ensure medicinal quality.

A patent protection system for medical products is not yet established in Bangladesh, although the country will have to apply a patent protection system after 2026 (37). There are no specific legal provisions, regulations, policies and/or guidelines to meet the challenges related to research, development, manufacturing, control, distribution and supply of medicines, vaccines, biologicals, medical devices and in vitro diagnostics. Although the Directorate General of Drug Administration provides registration of medical products with specific trade names for protection in the local system, this is not identical with patent protection.

Following discussion with and collection of information from experts in the relevant department of the Government of Bangladesh, this breakthrough analysis has been made to determine the impact on domestic industries, as well as to diagnose the forthcoming hindrances and challenges facing the country when it graduates from LDC to DC status.

2.2.7 Analysis of bottlenecks and challenges for local production of vaccines and biologicals

The pharmaceutical sector in Bangladesh is undergoing rapid growth and market expansion especially for vaccines and biologicals. To keep up with this growth, ancillary service providers, such as competent private laboratories, are needed to support the pharmaceutical industry to perform analytical and cost-effective tests. The use of third-party laboratories could result in operational cost savings and help with the overburden of regulatory authorities due to the lack of staff and the unavailability of testing facilities. Standardized private laboratories that meet international standards could be used to provide regulatory QC testing services on behalf of the Directorate General of Drug Administration to provide surge capacity and/or carry out specialized testing of vaccines and biologicals.
The main challenges are:

- a lack of competent human resources;
- unavailability of national CRO working at WHO-PQ standards;
- the Directorate General of Drug Administration has yet to reach WHO maturity level 3 for vaccine regulation and lot release;
- subcontract research and testing laboratories do not exist; and
- academic research is not well established enough to support manufacturers in the development and manufacturing of vaccines and biologicals.
References

For more information, please contact:

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