INDIA:

The World's Pharmacy Expands Its Reach in Global Health

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India: The World's Pharmacy Expands Its Reach in Global Health

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Global Health Strategies

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18/1, 2nd Floor Shaheed Bhawan,
Aruna Asaf Ali Marg, New Delhi, 110 067

www.globalhealthstrategies.com

Twitter: @GHS

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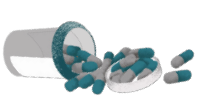
Executive Summary

India's pharmaceutical industry is already playing a pivotal role in the scale-up of pharmaceuticals and diagnostics to combat the global COVID-19 pandemic. It is poised to play an even more dominant role as biological products – preventive vaccines and cutting-edge biotechnology such as monoclonal antibodies– come to the fore.

Even before the pandemic, Indian manufacturers produced vast quantities of generic antiviral drugs that turned HIV from a death sentence to a chronic manageable condition in developing countries. India's global dominance in generic drugs and vaccine manufacturing has earned it the label "Pharmacy of the World". COVID-19 only strengthens the case for this moniker. So far, India has supplied medicines to 133 countries to fight the pandemic. Six Indian manufacturers have been granted royalty-free licenses by Gilead to manufacture the first antiviral drug approved by the U.S. Food and Drug Administration (FDA) for use against COVID-19. As many as 20 Indian companies currently manufacture the steroid dexamethasone, which is known to control inflammation in COVID-19 patients.

India is the largest producer of vaccines in the world, manufacturing over 60% of all vaccines sold globally.[1] One manufacturer, Serum Institute of India (SII), plans to deliver up to 1.4 billion doses of a COVID-19 vaccine between now and the end of 2021. Thirty different Indian companies are developing COVID-19 vaccines, of which seven Indian vaccine manufacturers - including Bharat Biotech and Zydus Cadila - currently have a vaccine candidate either in pre-clinical or trial phases.[2,3] Of these, Covaxin, developed by Bharat Biotech, and Covishield (Oxford-AstraZeneca vaccine in India), manufactured by SII, received emergency use authorization from the Indian Government on January 3rd, 2021.[4]

In diagnostics, India has launched a first-of-its kind COVID-19 testing mechanism using CRISPR technology. This was created by the Council of Scientific and Industrial Research's constituent lab, the Institute of Genomics and Integrative Biology (IGIB) in New Delhi, to address the urgent need for affordable, easy-to-use technology for accurate mass testing. India is also working on the development of its own monoclonal antibodies to fight against SARS-CoV2.



India's pioneering pharma industry was not an overnight success. Innovative policy decisions and industrial regulation since independence have helped develop the indigenous research, development, and production capacity that it is lauded for today. This white paper provides a comprehensive overview of the role of Indian pharma in addressing COVID-19 around the world. In addition, it reviews the evolution of India's pharmaceutical sector since independence and includes case studies that follow the industry's climb up the value chain.

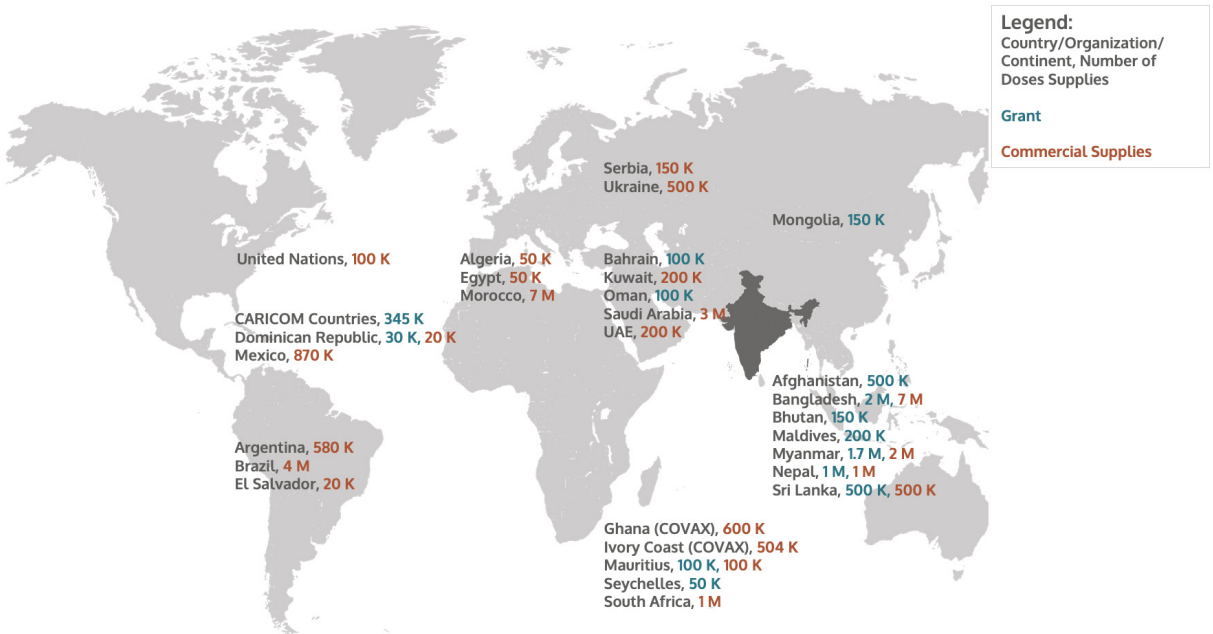
Finally, the white paper looks ahead to envision a fully integrated, self-sufficient Indian pharmaceutical industry that makes everything from active pharmaceutical ingredients (currently largely sourced from China) to the global pharmaceutical industry's "holy grail" – the original drug molecules that drive profitability and growth for the US, Europe and Japan's pharmaceutical industries.

India's response to COVID-19

India is playing a critical role in the fight against COVID-19 by boosting the production of pharmaceuticals that are in high demand for treating the virus and ramping up production capacity to manufacture the COVID-19 vaccine.[5,6]

"Without India, we will not be able to provide enough COVID-19 vaccines to the world's population"

- Dr. Peter Piot, Director, London School of Hygiene and Tropical Medicine



India is exporting the Oxford-Astra Zeneca vaccine manufactured by Serum Institute of India.

Source for Map of India: Ministry of External Affairs, Government of India

India, dubbed as the 'Pharmacy of the World', has remained true to its name through the COVID-19 crisis.[7] India has supplied medicines to 133 countries to fight the pandemic whilst battling the deadly virus itself.[8] The Indian pharma industry is supporting global efforts against COVID-19 by supplying highly sought after medicines such as Remdesivir, Dexamethasone and other treatments.[9,10] By December 2020, India had exported over 20 million PPE kits and 40 million N-95 masks to a number of countries.[11]

India has also started export of the COVID-19 vaccine to countries across the globe. Till 1 March, 6.9 million doses of the vaccine have been gifted to a number of countries. As per the Ministry of External Affairs, a total of over 36 million doses of the vaccine have been supplied to countries across the globe as grant-in-aid and commercial supplies.[12] India will export the vaccine to 110 countries requesting for the made in India vaccines.[13] Keeping in mind the need for vaccines manufactured in India, production capacity may also be scaled up to 500 million doses per month for export.[14]

Pharmaceuticals and Biosimilars

India swiftly responded to the urgent need for pharmaceuticals to treat patients with mild to severe COVID-19 symptoms and ramped up production of generic drugs, anti-virals, corticosteroids and biosimilars as their efficacy against the virus was being tested.

Remdesivir

In May, after the FDA authorized emergency use of Remdesivir, Gilead, the original maker of the drug, entered a licensing agreement with generic drug makers from India, Egypt and Pakistan for manufacturing and distribution to 127 countries.[15,16] A total of six Indian manufacturers have entered a royalty-free licensing agreement with Gilead to manufacture Remdesivir.[17] This increase in production is not only filling a supply gap but also has also brought down the price of the drug, making it seven to eight times cheaper than the original drug price in the US market.[18] However, in November 2020, the World Health Organization (WHO) recommended against the use of Remdesivir as latest evidence suggests the drug does not have a significant effect on patient outcomes including mortality and time to clinical improvement.[19]

Favipiravir

Favipiravir is an anti-viral drug used to treat influenza. Originally Japanese, the drug received authorization from the Drug Controller General of India (DCGI) for emergency use in COVID-19 patients. The drug has shown some promise in reducing treatment time of patients with mild to moderate symptoms. Indian pharma company Glenmark was the first to market this drug. However other major Indian pharma companies soon followed suit with Lupin, Dr. Reddy's Laboratories, and Cipla launching the drug as well.[20] The Council of Scientific and Industrial Research (CSIR) – Indian Institute of Chemical Technology in Hyderabad developed a synthetic route[21] for Remdesivir and Favipiravir which has been licensed out to Cipla for production.[22]

Dexamethasone

Dexamethasone is a corticosteroid which has been proven effective in patients with severe COVID-19 symptoms. According to a clinical trial by the University of Oxford, the drug reduced deaths by 33% in patients on a ventilator and by 25% in patients with severe respiratory complications and on oxygen support. In 2019-20, India exported 535,000 tons of Dexamethasone to 107 countries, with the US being the biggest importer of the drug. While at least 20 established companies sell the drug, 96% of market share is held by just two companies- Zydus Cadila (80%) and Wockhardt (16%).[23,24]

Monoclonal Antibodies

In October 2020, SII entered an agreement with the International AIDS Vaccine Initiative (IAVI) and Merck to develop COVID-19 neutralizing monoclonal antibodies co- developed by IAVI and Scripps Research. Phase 1 trials are expected to begin in early 2021, with SII and Merck playing a key role in ensuring the treatment is widely available and accessible, should it prove to be safe and efficacious.[25]

Furthermore, vaccine manufacturer Bharat Biotech has received sanction from CSIR to lead a project to develop human monoclonal antibodies as therapy for COVID-19 infections. This program brings together academia — National Centre for Cell Science, Indian Institute of Technology, Indore — and industry – PredOmix Technologies and Bharat Biotech –for a public health emergency.[26]

The International Centre for Genetic Engineering and Biology (ICGEB) and Translational Health Science and Technology Institute (THSTI) (both autonomous institutions under the Department of Biotechnology), in collaboration with the Indian Council of Medical Research (ICMR), are also attempting to identify human monoclonal antibodies with therapeutic potential by screening patients who have successfully resolved the infection.[27]

Considering the unmet medical needs to treat COVID-19, the DCGI approved the restricted emergency use of Itolizumab, developed by Biocon India, for treatment of moderate to severe acute respiratory distress syndrome in COVID-19 patients.[28] The National Task Force on COVID-19, however, has not included its use in the National Clinical Management Protocol for the indication of cytokine release syndrome.[29] While Itolizumab is an already approved drug for psoriasis, Phase 4 trials of the drug are underway to test its efficacy for use in COVID-19 patients with moderate to severe symptoms.[30]

Vaccines

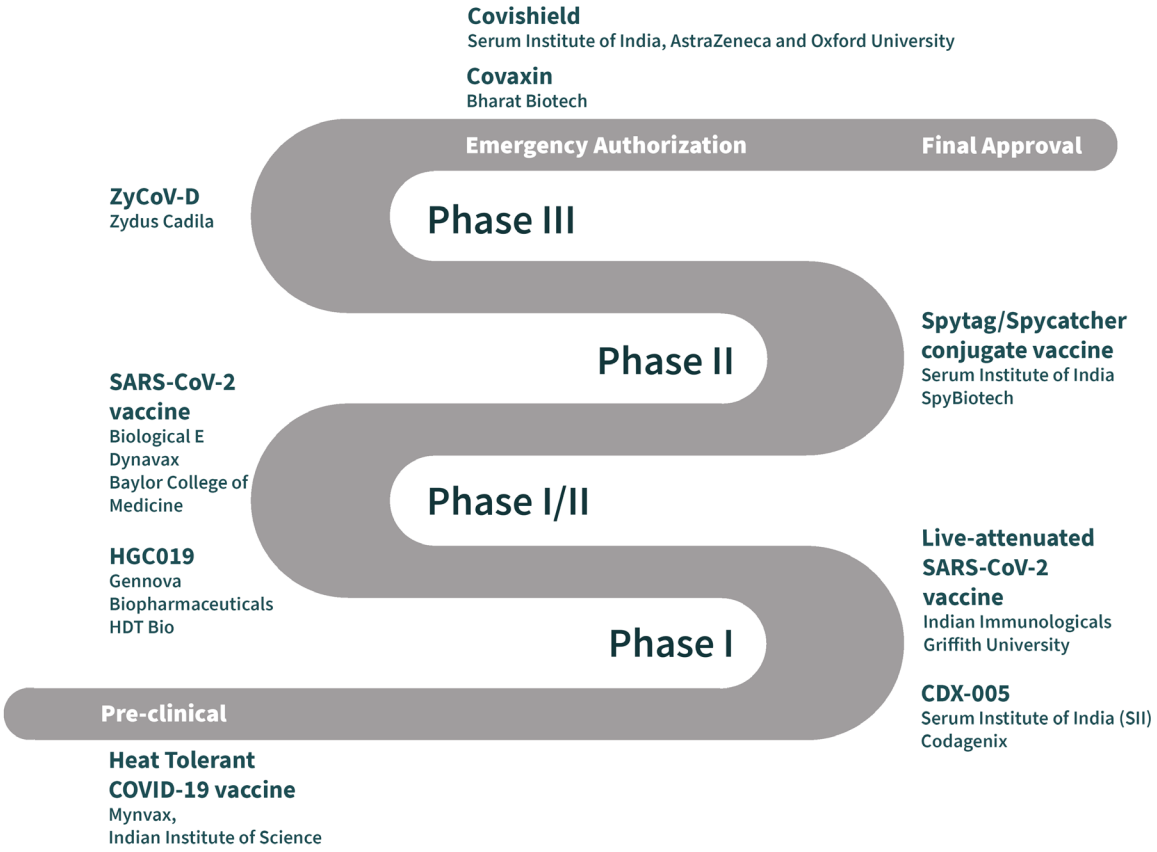
India is the largest producer of vaccines in the world, manufacturing over 60% of all vaccines sold globally.[31] Thirty different Indian companies began developing a COVID-19 vaccine. Seven Indian vaccine manufacturers including SII, Bharat Biotech, Zydus Cadila and Biological E have a vaccine under development either in pre-clinical or trial phases.[32, 33]

The UK and Argentina were among the first countries to give the Oxford-AstraZeneca vaccine emergency authorization in December 2020 following which, in January 2021, India authorized emergency use of the vaccine (dubbed Covishield in India). SII entered agreements to manufacture the Oxford AstraZeneca and Novavax COVID-19 vaccines in 2020.

India's first indigenous COVID-19 vaccine, Covaxin - developed by Bharat Biotech - has also received emergency use authorization.[34] On 16 January 2021, India started administering Covishield and Covaxin in what will be the world's largest inoculation drive against the novel coronavirus.[35]

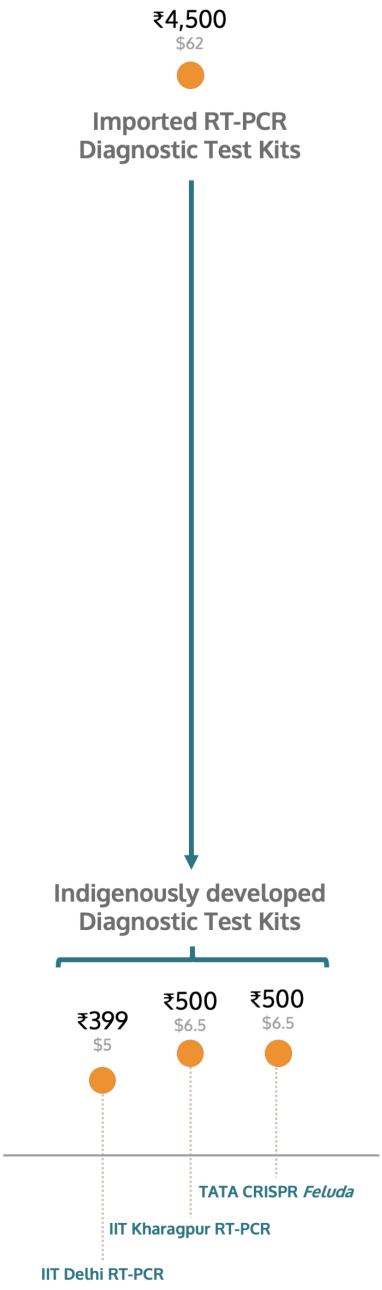
SII is planning to manufacture about 1 billion doses over the course of a year, with 400 million due before the end of 2020. These doses will be sold at cost until the end of the pandemic. In a recent deal to supply 100 million doses to Low and Middle-Income Countries (LMICs), SII capped the price at $3 per shot till the pandemic ends.

In addition to Covishield and Covaxin, four more vaccine candidates - by Zydus Cadila, Biological E, Gennova and Dr. Reddy's (Sputnik V) - are in advanced-stage trials and may also soon receive emergency use authorization.[36]



Diagnostics

During the initial few weeks of the pandemic, there was a severe shortage of diagnostics in India. The RT-PCR test was initially being imported which led to the cost of the test being very high at ₹4,500 (~$62), even after the Government capped its price. However, Indian companies rapidly scaled up manufacturing of testing kits and by August 2020, India had the manufacturing capacity of 1 billion RT-PCR kits. Indigenously developed new innovative technologies for testing also helped reduce the cost of these tests to as low as ₹399 ($5), making them widely accessible.



One of these testing kits, developed by the Indian Institute of Technology Delhi, is the world's most affordable RT-PCR based testing kit at ₹399. The kit received the highest score from ICMR and the DCGI also approved it as having "very high sensitivity and specificity".[37]

A first-of-its-kind testing kit based on an indigenously developed, cutting-edge CRISPR technology for detection of the genomic sequence of SARS-CoV-2 virus was created at the CSIR's constituent lab, the Institute of Genomics and Integrative Biology (CSIR-IGIB) in New Delhi and will be manufactured by the Tata Group.

The Tata CRISPR test, 'Feluda', is the world's first diagnostic test to deploy a specially adapted CAS9 protein to successfully detect the virus causing COVID-19. Similar to a pregnancy strip, the Tata CRISPR test changes color if the virus is detected and does not need expensive machines for detection. Priced at ₹500 (~$6.5), almost one third the price of the RT-PCR test that is currently in use. It can differentiate between SARS-CoV-2 and other coronaviruses even if genetic variations between them are minute. The test meets high quality benchmarks with 96% sensitivity and 98% specificity for detecting the novel coronavirus.[38] Furthermore, the test takes 45 minutes and provides better accuracy and specificity over the rapid antigen test, which takes 30 minutes. It is also much faster than the RT-PCR test, which takes 1.5 hours.[39]

In an effort to provide research capacity for new and better methods of diagnosis as well as investigating immune responses, THSTI established a COVID-19 Bioresource Repository making royalty-free biospecimens available for research institutions. This makes conducting diagnostic and vaccine research in India significantly easier by ensuring that all materials for research are available within the country, along with mechanisms to transfer biomaterial easily.[40]

Another testing kit, developed by the Indian Institute of Technology Kharagpur, uses a new testing method that includes a highly reliable and accurate molecular diagnostic procedure and can be conducted by an ultra-low-cost portable device. The test can deliver results within an hour via a mobile application and is priced at ₹500 (~$6.5).[41]

Evolution of India's pharmaceutical industry

India's pioneering pharma industry was not an overnight success. Innovative policy decisions and industrial regulation since independence have helped develop the indigenous research, development, and production capacity that it is lauded for today.

As an LMIC, India's ability to provide vital support in a global public health crisis is remarkable. Today, the country supplies nearly all of the developing world's high-quality, inexpensive generic medicines. Indian pharmaceutical companies meet over 50% of the global demand for various vaccines and 20% (by value) of the global generics market.[42] In addition, India supplies over 80% of the antiretroviral drugs (ARVs) needed globally for AIDS (Acquired Immunodeficiency Syndrome).[43] This comes as no surprise, as India is the third largest producer of pharmaceuticals in the world by volume. With the largest number of FDA-approved plants outside the US, India is estimated to supply over 40% (by volume) of drugs available in the US.[44]

The strength of today's Indian pharmaceutical industry is a result of a series of developments - including changes in patent law, industrial policy and investments in building indigenous capacity in times of need - since the country's independence in 1947. In fact, up until 1969, Indian pharmaceuticals only had a 5% share of the market in India, while foreign-owned pharma companies held a 95% share. In contrast, in 2020, Indian companies held close to an 85% share of the Indian pharmaceutical market. In the 73 years since independence, India has grown substantially in pharmaceutical prowess and has produced life-saving technologies and methods that have benefitted the world at large. By encouraging generics over branded products and regulating prices through the Drug Prices Control Order (DPCO), India has paved the way for the growth of public-sector companies and renowned private companies such as Sun Pharma, Dr. Reddy's and Cipla.[45]

Changes in legal structures such as the India Patent Act of 1970 created a conducive environment for the booming generic drugs industry of India - last valued at $33 billion in 2017 - making India the largest provider of generic medicines globally.[46,47] With the liberalization of the economy in the 1990s, India joined the World Trade Organization (WTO) and had to sign on to the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement.[48] While these patent laws presented new challenges for the industry, importantly, India worked closely with other LMICs for the inclusion of compulsory licensing in the agreement.

Alongside global policy changes, India managed to continue building on its advantages and produce lifesaving and affordable drugs, diagnostics, and vaccines earning it the moniker of "Pharmacy of the World."[49]

Milestones

Changes related to policy or industry

India's contribution to the world

Cipla launches the HAARTmedication at $1 a day per patient

2001

Shantha Biotechnic's Hep B recombinant vaccine gets WHO prequalification

SII partners with the Meningitis Vaccine Project (MVP) to develop a conjugate vaccine

Serum Institute of India (SII) was established and began producing vaccines in India

1966

1970

The India Patents Act of 1970 passed enabling the development of a booming generics industry

India joins the WTO and signs the TRIPS agreement - alters patent law

1995

1992

SII receives WHO prequalification for a Measles vaccine and starts exporting vaccines

1954

Hindustan Antibiotics Ltd. established to provide affordable drugs for India

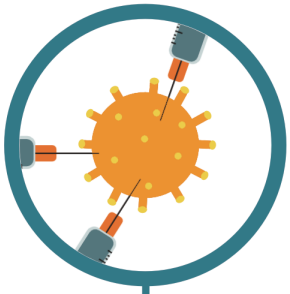
1961

Indian Drugs and Pharmaceuticals Ltd. established to produce essential life-saving medicines for the country

1949

Patent Laws Review Committee established

Indian ResearchFund Association redesigned and converted into the Indian Council of Medical Research



Biocon launches its insulin glargine injection under the brand Semglee in the US

SII commits to producing 1 billion COVID-19 vaccine doses, 400 million by the end of 2020

2020

2017

India's generic drugs industry valued at $33 billion

2010

MenAfriVac by SII – the first internationally qualified vaccine developed outside a major multinational pharma company, gets WHO prequalification

WHO prequalified two PCV vaccines developed by SII

WHO prequalified an MR vaccine developed by Biological E

2019

Bharat Biotech launched Rotavac 5D - the world's first and only liquid formulation

2015

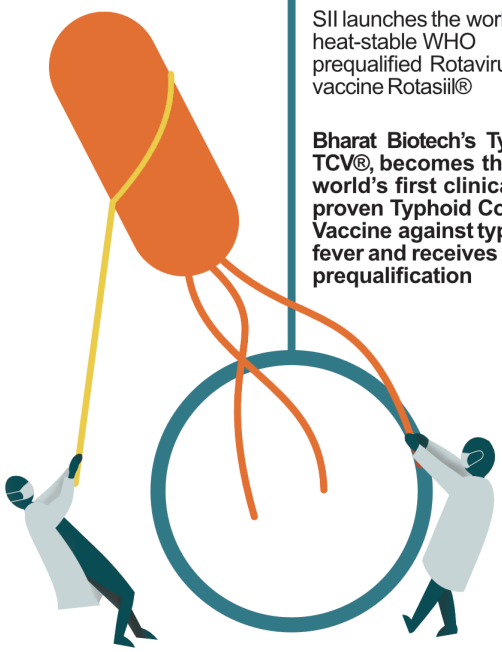
Bharat Biotech launched ROTAVAC-the cheapest Rotavirus vaccine in the world at $1 per dose

2018

The ROTAVAC® vaccine developed by Bharat Biotech granted WHO prequalification

SII launches the world's first heat-stable WHO prequalified Rotavirus vaccine Rotasiil®

Bharat Biotech's Typbar TCV®, becomes the world's first clinically proven Typhoid Conjugate Vaccine against typhoid fever and receives WHO prequalification



Biocon launches ALZUMAb™ (Itolizumab), the world's first anti-CD6 monoclonal antibody for treating chronic plaque psoriasis

2012

Case Study

The world's first Hepatitis B vaccine for less than $1 per dose

In 1992, WHO recommended that every child be vaccinated for Hepatitis B. Merck and GlaxoSmithKline (formerly SmithKlineBeecham) had developed recombinant vaccines for Hepatitis B in 1986 and, together, they held a monopoly with over 90 patents covering manufacturing processes such as isolation and purification. In the late 1980s, prices in developing countries were as high as $23 per dose. With most Indian families living on $1 a day, with multiple children and three doses required per child, vaccination was simply unaffordable.

Shantha Biotechnics, a pioneering Indian biotechnology company founded in 1993, saw an unmet need domestically, and decided to develop novel processes for manufacturing a Hepatitis B vaccine and reduce prices to less than $1 per dose.[50] Shantha was one of the first Indian biotech companies to create a recombinant product, and obtained WHO prequalification for it in 2002. Further expansion enabled low-cost mass vaccination globally through organizations such as UNICEF.

In 2009, Shantha sold over 120 million doses of its Hepatitis B vaccine (Shanvac-B) to dozens of developing countries around the world, and had revenues exceeding $90 million. A double-blind comparative study showed that Shanvac-B was equivalent or superior to the competitor's product on all counts - immunogenicity was found to be higher; side effects fewer; and seroconversion was high enough that only two doses of the vaccine were required in contrast to the three doses required by the competition. This helped change perceptions of manufacturing capacity of developing countries to produce high-quality life-saving vaccines.[51]

Although it took additional time to develop good manufacturing practices that adhered to International Conference on Harmonization (ICH) - WHO norms, the decision to focus on process innovation right from the beginning led Shantha to become the first Indian company to be prequalified by the WHO. Since its launch, other Indian companies such as Bharat Biotech, Cipla and SII have also started producing a HepB vaccines such as Bharat Biotech, Cipla and SII.[52]

Case Study

Cipla providing Anti-retroviral Drugs for less than $1 a day

Cipla Ltd. was established in 1935 and grew to become one of the leading pharmaceutical companies in India. In 2001, the company had a ground-breaking year that put the Indian pharmaceutical industry on the map for launching Nevirapine - an antiretroviral (ARV) drug used to prevent the transmission of AIDS for less than $1 a day.

In 1991, Rama Rao, the research head of an Indian government laboratory, Indian Institute for Chemical Technology, developed a chemical synthesis of AZT - a compound that postponed the onset of AIDS. At the time, only one company – Burroughs Wellcome in the US was making it and selling it for $8,000 per patient a year. Cipla manufactured it and launched the drug in 1993 at $2 a day. Even at a fraction of the price, it was beyond what most Indians could afford, leaving Cipla's sales at zero. Yusuf Hamied, chairman of Cipla, requested the government to purchase and distribute the drug. However, the Indian government refused as it had money only for HIV detection and prevention, not treatment.[53]

A few years later, HAART (highly active anti-retroviral therapy) medications started being used to treat HIV. There is currently no cure for HIV, but the availability of HAART meant that HIV became manageable through lifelong treatment. HAART's triple-drug cocktail was demonstrated to be effective in 1996. But at the time, each drug was manufactured by a different multinational drug company and the combined price for it was around $12,000 a year. To produce a more affordable version, Cipla developed the AIDS cocktail for roughly $800 a year at first, as compared to Western prices of $10,000-$15,000 a year. However, in 1997, intellectual property rights under international trade agreements were being contested, bringing Big Pharma and developing countries to a stalemate.

At the European Commission's Conference on HIV/AIDS, Malaria, Tuberculosis, and Poverty Reduction in 2000, Hamied declared that he had three offers. He would sell the AIDS cocktail for $800 a year; provide the technology for free to any African governments willing to produce its own drug; and provide Nevirapine for free. AIDS activists from around the world strongly supported Cipla's proposals.

At the time, the global pharmaceutical marketplace was crowded by patents and trade agreements, and countries did not take up the offer. Aside from dealing with international trade and intellectual property rights laws, Cipla also suffered from negative perceptions about drug development in India. In February 2001, after an internationally published announcement of Cipla's commitment to reduce the price and provide the drug at less than $1 a day (roughly $350 a year per patient), multinational drug companies dropped their lawsuits, waiving their patents so that generic fixed-dose combinations of the AIDS cocktail could be sold cheaply.

More than 25 million people around the world are now being treated with ARVs and a wide range of Indian pharma companies now produce the drugs including Sun Pharma, Hetero and Aurobindo Pharma. In total, India supplies nearly 80% of the world's ARV drugs and plays a significant role in the global fight against AIDS by helping scale up access to treatment across developing countries.[54,55]

Case Study

MenAfriVac: India develops a life-saving affordable vaccine for Africa

Vaccine development can cost between $500-$750 million per vaccine, making profitability of the final product a determining factor in deciding which vaccines will be developed. This limits opportunities to fight diseases that are unique to low-income countries that cannot afford expensive vaccines. Meningitis was a persistent issue in sub-Saharan Africa, prone to frequent deadly epidemics. There was a need for a meningococcal-A conjugate vaccine for the region, which would only prove to be sustainably if distributed at a low price of about $0.50 per dose.[56]

In 2001, the Meningitis Vaccine Project (MVP) was created with the support of the Bill & Melinda Gates Foundation (BMGF), as a partnership between WHO and PATH. The project had a single goal: developing, testing, licensing, and introducing an affordable Meningitis-A conjugate vaccine for Africa. No Big Pharma company in the developed world was ready to take on the task of developing a vaccine to sell at the proposed price. So, the MVP decided to look for a vaccine manufacturing partner in the developing world. Serum Institute of India (SII) partnered with the MVP in 2002 and successfully manufactured and licensed MenAfriVac in 2010, the first internationally qualified vaccine that was developed outside the major multinational pharma companies.[57]

An export license was granted to SII for the vaccine in December 2009, and WHO prequalification was obtained in June 2010. The vaccine was first introduced at public scale in Burkina Faso that December. Between 2010 and 2018, planned mass vaccination campaigns targeted over 277 million people in 26 countries of the meningitis belt. MenAfriVac has been hugely successful as group A meningitis has virtually disappeared wherever the vaccine has been introduced. The success of MenAfriVac has brought recognition and acclaim to SII.

In 2012, SII started producing a controlled temperature chain (CTC) MenAfriVac which allowed the vaccine to remain stable outside the cold chain at temperatures not exceeding 40 degree Celsius for not more than four days.

The CTC vaccine helped in increasing vaccination coverage in a few areas where access was a problem and electricity was unreliable. This innovation reduced the cost of the vaccine campaign by 50% and enabled higher coverage.[58] MenAfriVac became a public health breakthrough and one of the biggest immunization success stories in Africa.[59]

Case Study

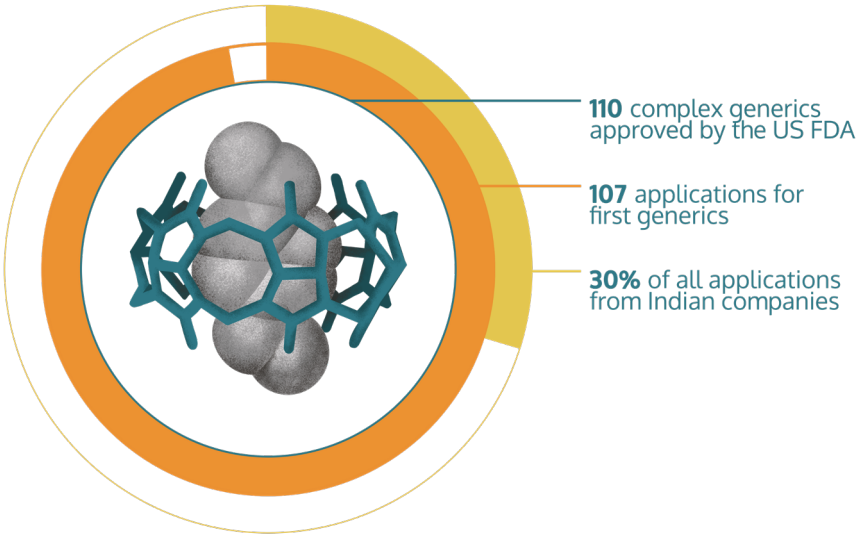
India diversifies into complex generics

Generic drugs that have complex active ingredients, complex formulations, complex route of delivery or complex drug device combinations are considered 'complex generics.'[60] While there is no official definition of 'complex' generics, they are often referred to in the same breath as specialized drugs, or non-biological complex drugs (NBCDs) or even likened to biosimilars such as monoclonal antibodies, depending on what makes them complex.[61] Since the drugs are developed for chronic and life-threatening diseases like Hepatitis C and cancer, there are fewer competitors. The market for complex generics is huge, provided companies are willing to make substantial commitment of resources and have a high tolerance for financial risk.[62,63]

While India has championed the manufacturing of affordable generic drugs and is a known global leader in that domain, many Indian companies are now focusing on developing differentiated complex generics. This shift in focus is primarily due to the fact that complex generics are harder to develop, face less competition, and command higher margins than generics.[64] In 2017, a report by the Yes Global Institute titled "India Pharma: Transitioning to Specialty Generics" noted that pricing pressures in the US generic market began reducing sales and profitability for Indian companies. In response, these companies have been investing in and preparing to transition into complex generic assets such as biosimilars, complex injectables and inhalers.[65] This is evidenced in by the fact that in 2019, the FDA approved 110 complex generics drugs and 107 applications for first generics with no generic competition, of which 30% of the applications were from Indian companies.[66]

The move to produce more complex generics has required increased investment in research and development. Deloitte's analysis of top five Indian pharma companies (by revenue), showed that there was an upward trend in both sales and research and development (R&D) investment between 2011 and 2017. However, after a dip in sales growth in 2018, investment in R&D also fell. Indian pharma companies, instead, have been betting on mergers and acquisitions, collaborations, partnerships, joint ventures and in-licensing to create high-value and high-margin asset pipelines which, for Indian companies, has focused on complex generics. The ability of Indian formulators to compete/close the gap created by large established global peers in the complex generic space will remain critical.

In 2019, Sun Pharma, a multibillion-dollar Indian pharma company, had a pipeline of 123 abbreviated new drug applications and six new drug applications under review, which included complex generics combination, first-to file opportunities, and pure generics. Similarly, Dr. Reddy's is a pharmaceutical company whose generic formulations business offers more than 200 high-quality generic drugs worldwide with over 20 assets falling under the category of complex generics.[67]



Case Study

Indian Company Biocon launches the cheapest insulin in the American market

Globally, close to 65 million people with type 2 diabetes need insulin, but only half of them are able to access it, largely due to high prices. Furthermore, all people with type 1 diabetes need insulin to survive, making access to the drug a priority with non-communicable diseases such as diabetes on the rise around the world and especially in LMICs, there is a dire need for cheaper insulin.[68]

Early in the 20th century, Frederick Banting discovered insulin as a treatment for diabetes and sold the patent for a dollar to ensure wide availability. At that time, the insulin available for treatment came primarily from animals. Today, insulin is brewed by microbes that have been genetically engineered with the gene for human insulin. Pharmaceutical companies now modify the chemical formula and delivery mechanism to produce faster-acting or longer-lasting insulins and create novel delivery devices and new patents for every improvement.

Three pharma giants control the bulk of the global insulin market – Novo Nordisk, Sanofi and Eli Lilly. Usually one of the three supply to a country based on a monopoly, setting prices as they wish.

Additionally, Insulin cannot be produced as a generic - it is a therapeutic biological product rather than a chemically synthesized molecule. Creating biosimilars is a lot more complicated and expensive than just duplicating a chemical molecule. There is little incentive to produce biosimilars as they cost nearly as much as making a new drug and must go through all the approval stages and trials that a new drug is required to go through. In addition to that, companies can engage in patent ever-greening, a process by which producers extend the lifetime of their patents that are close to their expiration date, and political lobbying has helped the big three to control the global insulin market.[69]

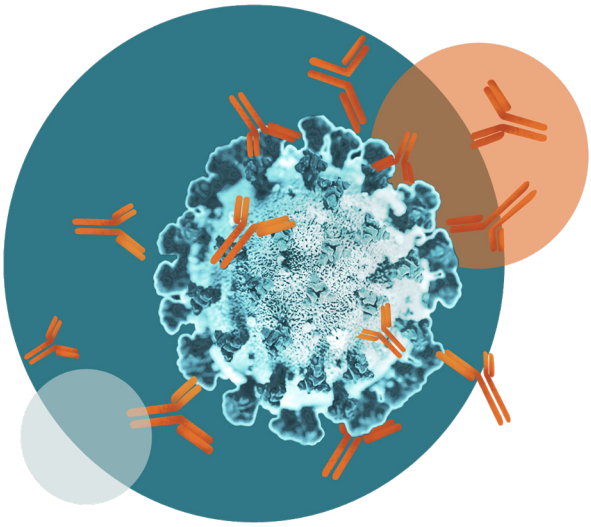
Many countries and international healthcare agencies rely on India for their medicine supply as India produces affordable generic versions of drugs. But despite this global predominance, India has failed to challenge the big three insulin producers in the global trade of insulin.[70] However, Indian companies like Biocon are beginning to make inroads into making insulin more accessible and affordable. Biocon and Wockhardt have been manufacturing insulin in India and even exporting insulin products globally.[71] Although they have developed the capacity to produce insulin, Indian companies still suffer from a lack of credibility and trust from doctors and patients within the Indian market. Despite this, Biocon set out to produce an affordable insulin injection pen with insulin glargine, a recombinant human insulin (rh-insulin). However, the drug had an identical amino acid sequence to international pharma giant Sanofi's Lantus. Sanofi retaliated with four cases on patent infringement triggering a 30-month stay on the product's approval.[72]

Kiran Mazumdar-Shaw, chairperson and managing director of Biocon, announced her personal commitment towards enabling universal access to high quality insulin by offering rh-Insulin at less than $0.10 per day in LMICs at a side meeting during the 2019 United Nations General Assembly (UNGA).[73] In 2020, after approval from the US FDA, Biocon and its partner Mylan N.V. launched their insulin glargine injection under the brand Semglee in the US in vial and pre-filled pen presentations.

Insulin will be sold at a wholesale cost of $147.98 per package of five 3ml pens and $98.65 per 10ml vial, making it the cheapest brand of insulin glargine in the US market.[74]

Case Study

India has begun manufacturing its own monoclonal antibodies – a first for LMICs



Monoclonal antibodies (mAb) are lab-made proteins that act like natural antibodies in fighting disease. Derived from human immune cells, these proteins act specifically against targets ranging from cancerous cells to viruses and bacteria, or alter precise immune pathways to augment a person's ability to fight disease.[75] Monoclonal antibodies have dramatically improved cancer survival rates and are being evaluated for their potential to prevent and treat infectious diseases including COVID-19, Ebola, and HIV, but they are among the most expensive pharmaceutical products in the world and inaccessible to most of the world's population.[76] A report released by the Wellcome Trust and the International AIDS Vaccine Initiative (IAVI) titled Expanding Access to Monoclonal Antibody-Based Products: A Global Call to Action, notes that availability and affordability are two of the biggest barriers to accessing monoclonal antibodies in LMICs.[77]

A growing number of Indian companies, including some without any biologics in their portfolios, are now in hot pursuit of top-selling therapeutics as generic substitutes of bio drugs gain increasing acceptance worldwide. mAbs constitute a sizeable portion of the biosimilars market, which is estimated to grow to $25 billion by 2020, according to Intercontinental Medical Statistics (IMS) Health figures. Foreseeing a boom, a few Indian generic producers started honing their skills in these highly specialized biotherapeutics years ago. Biocon Ltd. joined the global league of mAb developers when it launched Biomab EGFR – India's first indigenously produced novel monoclonal antibody to treat head and neck cancer – in 2006. Now, biogeneric mAbs form the core of the company's evolutionary innovation strategy.

In 2013, to meet the unmet need of treating psoriasis, Biocon launched its 'first-in-class' novel biologic ALZUMAb™ (Itolizumab), the world's first anti-CD6 monoclonal antibody for treating chronic plaque psoriasis.[78] The Bangalore-based company has an active pipeline comprising both proprietary and generic mAbs. ALZUMAb was approved by the DCGI for emergency treatment of acute respiratory distress syndrome (ARDS) in patients with COVID-19.[79]

Case Study

The world's cheapest and first thermostable vaccines for Rotavirus

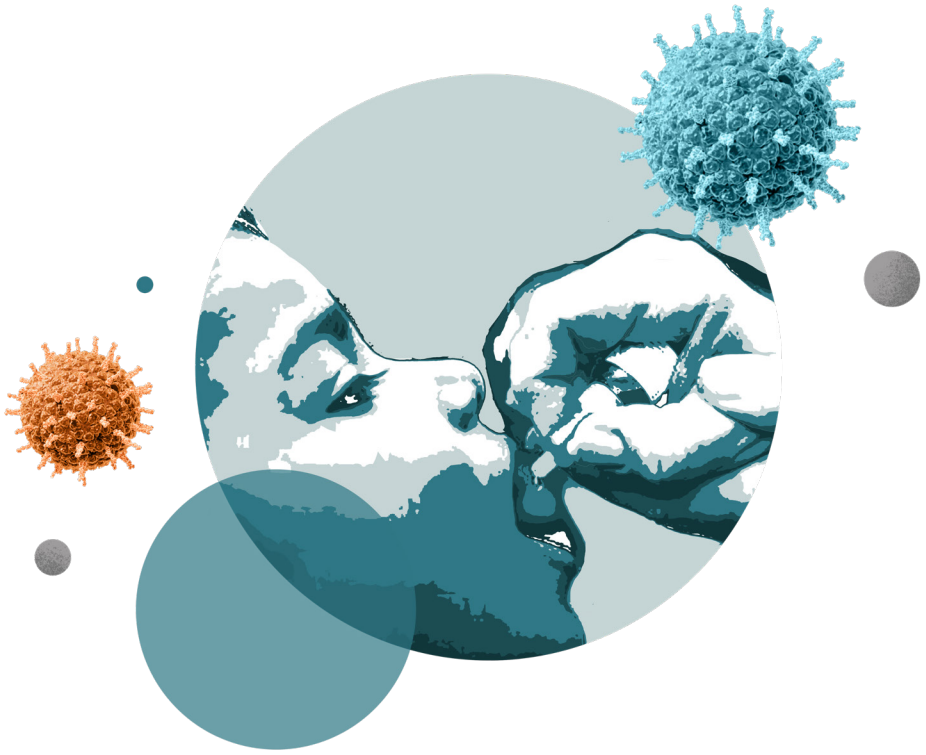
It was estimated that in 2010, rotavirus caused more than 440,000 deaths and 2 million hospitalizations in children under 5. The vast majority of these were in developing countries. In 2015, Bharat Biotech launched ROTAVAC- the cheapest Rotavirus vaccine in the world at $1 per dose.[80]

Rotavac was the third vaccine for Rotavirus globally, and in 2018, became the first completely indigenous vaccine to be pre-qualified by WHO, which meant that the vaccine was available for procurement by UN agencies and Gavi for use in other countries. The vaccine was developed from a weakened strain of rotavirus that was isolated at the All India Institute of Medical Sciences (AIIMS) in New Delhi in 1985- 86.[81,82]

In 2019, Bharat Biotech launched a new version of the vaccine - Rotavac 5D, which is the world's first and only liquid formulation and delivers similar clinical safety and immunogenicity profiles at 1/5th the dosage (0.5ml compared to the previous 2-2.5 ml). The vaccine can also be stored at higher temperatures of 2-8 degrees Celsius for 24 months and up to 37 degrees Celsius for seven days.[83] This leads to a reduction in logistic costs and easier cold chain management as well as low biomedical waste disposal.[84]

But Bharat Biotech was not the first to develop a thermostable vaccine for Rotavirus. In 2018, the WHO pre-qualified ROTASIIL - the world's first thermostable vaccine for Rotavirus developed jointly by the Serum Institute of India and the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health.

The vaccine can be stored at up to 25 degrees Celsius for 30 months.[85,86] It can be administered orally which reduces the cost of delivery and cold chains.



Case Study

The world's first clinically proven Typhoid Conjugate Vaccine

International Health Metrics and Evaluation (IHME) estimates that in 2016, there were approximately 12 million cases of typhoid fever globally, resulting in around 130,000 deaths. Typhoid fever is caused by the bacterium *Salmonella Typhi* (S. Typhi), which infects humans due to contaminated food and beverages from sewage and other infected humans. Currently a third of the global population is at risk of typhoid fever, which results in reduced school attendance, loss of work and wages, lowered pregnancy outcomes and impaired physical and cognitive development of children. In most developing countries, the cost of a course of treatment for typhoid fever ranges from $50 to $5,000 for outpatient and inpatient treatments.

In 2018, Bharat Biotech's Typbar TCV® became the world's first clinically proven Typhoid Conjugate Vaccine against typhoid fever and received prequalification from WHO.

Approval by WHO enabled the procurement and supplies of this life-saving vaccine to UNICEF, Pan-American Health Organization (PAHO) and GAVI-supported countries. Typbar TCV® was evaluated in Human Challenge Studies at Oxford University and typhoid conjugate vaccines were recommended by WHO's Strategic Advisory Group of Experts on Immunization (WHO-SAGE).[87]

Typbar TCV® was administered to children from 6 months of age to adults that conferred long-term protection against typhoid fever. Typbar TCV® was a result of a dedicated product development at Bharat Biotech since 2001, where all aspects of the product profile were studied and evaluated in human clinical trials. Dr. Krishna Ella, Chairman and Managing Director of Bharat Biotech, said "[when] we started this project, Typhoid fever was a neglected tropical disease. This success is a true reflection of Team Bharat Biotech's ability to develop novel vaccines and sustain long term product development for fighting infectious diseases. It demonstrates the power of global partnerships to achieve novel breakthroughs."[88]

Conclusion: Looking forward

Despite the Indian pharmaceutical industry's great progress, industry leaders and policymakers are eyeing two gaps that will need to be filled in order for the sector to achieve true self-sufficiency in the months and years ahead. Ironically, these gaps occupy the opposite ends of the value chain – active pharmaceutical ingredients (APIs) at the bottom and branded, original molecules at the top.

While APIs are generally regarded as commodity products and therefore, of secondary interest commercially, COVID-19 was a powerful wake-up call for the industry around the world, and especially for India. That is because India is dependent upon China for 80% of the raw materials that go into its drugs. The reliance of India's generic drug business on China was painfully illustrated when API supplies were disrupted, and prices spiked after COVID-19 first broke out in Wuhan.[89]

In March, the government moved to address the gap, announcing a ₹9,940 crore (~$1.3 billion) package to encourage the domestic production of APIs. This included ₹6,940 crore (~$940 million) for production-linked incentives and ₹3,000 crore (~$400 million) to establish three bulk-drug parks.

The Department of Science and Technology released a report on APIs in July 2020 calling for a scaling of API production in India to reduce import dependence and bolster self-reliance.[90]

The government is also moving to help the industry plug the gap at the top of the value chain by encouraging new R&D investments and collaboration between government, industry and academia to develop an original new drug molecule. Given the long road Indian pharma industry has already traveled since independence, the ingenuity of its scientists and the willingness of its policy makers to continue to create an enabling environment, this "holy grail" — an entirely novel, "made-in-India" medicine — is eminently achievable, showcasing India's abilities as not just a manufacturer, but also a leading research-hub.

The case with vaccines and drugs for COVID-19 will be no different. Over the past few decades, India has proven its mettle and always stepped up to the plate when the world needed affordable preventive and curative treatments and Big Pharma took a back seat. From affordable vaccines for Hepatitis B and meningitis, to making complex drugs like ARVs accessible to all, India's contribution to global health has been invaluable.

India's total pre-COVID-19 vaccine manufacturing capacity stood at 3 billion doses annually. One Indian manufacturer has already committed to manufacturing 1.4 billion doses of the COVID-19 vaccine throughout 2021 and others may follow suit. Ten vaccines, including those developed by Oxford-AstraZeneca, Pfizer, Moderna and Bharat Biotech, have been approved for emergency and early use in a number of countries including the US, UK and India.[91] In addition to administering the vaccines domestically, India has also started exporting the vaccine as both grant-in-aid and commercial supplies to a number of countries across the globe.[92]

With a number of vaccines in final trial stages and some already approved, all eyes will be on India's capacity to manufacture and deliver the cheapest COVID-19 vaccine globally and once again prove its befitting title as the "Pharmacy of the World."

The COVID-19 pandemic has been a watershed moment for India's public health system but also for the healthcare industry. The country is now poised to be more than a pharmacy to the world, offering solutions across the spectrum of preventives, diagnostics, and therapeutics, and the next great frontier of data-driven digital health technology.

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