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COVID-19

FAR FROM REACH

As countries rush to attain self-sufficiency in drug manufacturing, market dynamics might be difficult to overcome

Children play at an empty square in downtown Ronda, Spain, accompanied by their guardians as the government de-escalates six weeks of strict lockdown, despite over 24,000 deaths and 213,000 infections

PHOTOGRAPH: REUTERS

ANOTHER CURVE

The world witnesses a rare urban-to-rural exodus amid lockdowns and loss of livelihoods. Will our villages be able to support the millions of people again who had migrated due to distress conditions at home?

BY RICHARD MAHAPATRA

FOUR MONTHS into the COVID-19 pandemic, the world is at a crossroads. On the one hand the virus continues to appear in newer places, infecting thousands every day and forcing countries to extend their lockdown. But on the other hand, those already under COVID-19 lockdown for over six weeks in India are desperate to break free and resume economic activities at the earliest as millions have already lost livelihoods. And, as they ready to be out of this unprecedented situation, the world witnesses another challenge: a never-before-experienced exodus of people from economically active urban areas into their already distressed rural homes. They also carry back the threat of COVID-19 to areas that have so far remained untouched by the pandemic. In May, the pandemic will show its other deadly side.

On April 26, Spain allowed children under 14 to venture out though with stringent guidelines. They can go out for an hour in a day; they must be accompanied by parents or guardians; they must remain within one kilometer of their residence; and they must adhere to social distancing mechanisms. They will stroll only as parks and playgrounds remain closed. Still, as television channels beamed, there

were smiling faces. As one parent said, after a lockdown of 40 days, small joys like feeling the fresh air on the face made it appear like a rebirth. And this is despite the 24,275 deaths and 213,000 infections as on April 30, which have transformed this European country known for tourism into a graveyard of despairs. The country is finally limping back to normalcy. From May 2, adults would also be allowed to exercise and stroll outside. The epidemiological curve has been flattened in Spain, and would soon be squashed going by experts.

Now, all top five countries in terms of infection and human mortality are on their way to loosen the lockdown. Starting from China—the origin of SARS-COV-2, as the virus is known—to the US to Germany, Italy and Spain, there are plans to allow normal human movement, though in a staggered way. The US—with the highest number of cases of COVID-19—has also announced exit plans for lockdowns in states (see infograph 'Death spree' on *p*29). In Germany, the government has formed a 26-member group of philosophers, scientists, historians, theologians and legal experts to start the process of lifting the lockdown. But it has been cautious to do so in one go. Rather, its strategy is to gauge the social and economic impacts of a prolonged lockdown and how communities would endure it. India has allowed certain business activities with low-staff attendance and the Union government has opened its offices. Inter-state migrant workers and students have been allowed to move to their respective states.

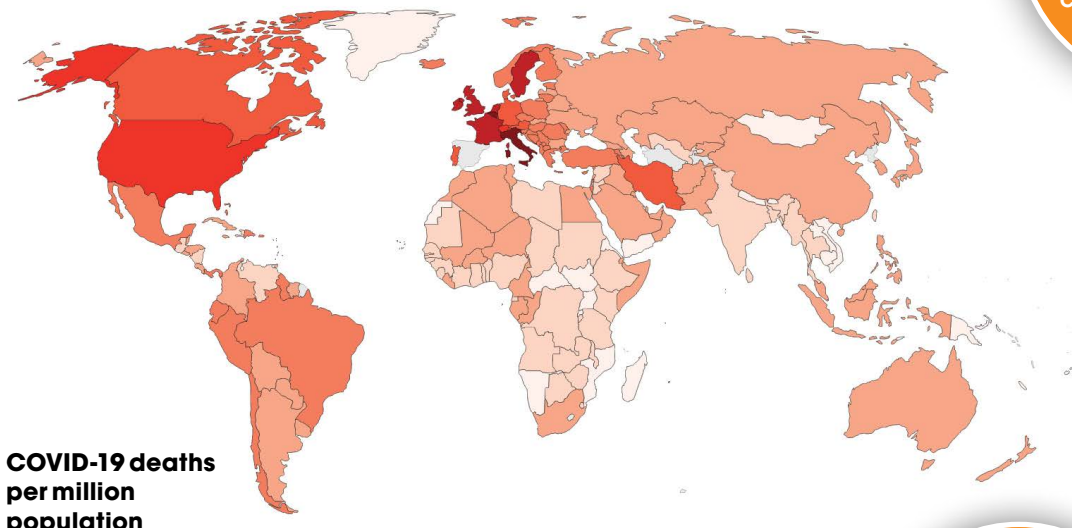
Certainly, our endurance with the pandemic has taken a different curve. However, as governments discussed these exit plans sensing that the infection is finally peaking—as after the peak, the infection falls away—there were developments across the world that indicated how challenging the situation would be post the lockdown.

There were protests against lockdowns, with a common demand: restore business to save lives. In India, stranded migrant workers in Gujarat and Maharashtra took to streets protesting non-availability of food and basic facilities and demanded return to their states. By this time, key states like Uttar Pradesh, Odisha, Rajasthan, Bihar and Jharkhand had put in place elaborate plans to not only bring the workers back but also to create quarantine facilities for them before they enter villages. Barring the ruling party, most other political parties supported lifting of the lockdown and allowing economic activities, though with restrictions necessary for curtailing the infection.

In the US, there were anti-lockdown protests across the states. Reportedly, these protests were encouraged by President Donald Trump, who has been staunchly against a nationwide lockdown. In the Polish-Germany border area of Saxony on April 29, commuter workers protested against the over six-week lockdown. It is estimated that some 10,000 Polish travel to neighbouring German towns every day for work but have been kept away from work due to the lockdown. "Let us work, let us home," read a protester's banner. South Africa reported food riots in West Cape areas

DEATH SPREE

Belgium has the highest COVID-19 death ratio per million people at 647, followed by Spain (519) and Italy (457). The world average is 29



COVID-19 deaths per million population

No data | 0 - 0.01 | 0.01 - 1 | 1 - 10 | 10 - 50 | 50 - 100 | 100 - 200 | 200 - 400 | > 600

Africa	Asia	America	Europe	Oceania
34,743 cases	**502,955** cases	**1,293,607** cases	**1,288,663** cases	**8,136** cases
1,591 deaths	**18,203** deaths	**74,591** deaths	**132,543** deaths	**116** deaths

696 cases have been reported from an international conveyance in Japan 7

Source: European Centre for Disease Control and Prevention

GRAPHIC: SANJIT / CSE

and Johannesburg. Police had to fire at anti-lockdown protesters. Food stores were raided. In Malawi, the country's apex court struck down a nationwide lockdown as people protested against it citing total collapse of livelihoods. This is the first African country where the judiciary intervened to lift a lockdown.

Meanwhile, the International Labor Organization (ILO) has updated its estimate on livelihood loss. It says half of the global workforce who are also informal workers would lose livelihoods in immediate terms. It means some 1.6 billion informal workers, more than the population of the world's second most populous country India, would be without jobs. In March, about 2 billion informal workers lost almost 60 per cent of their wages. With such meager income which might not be adequate for a few days of basic survival, they faced an imminent loss of work in April and a situation of zero-income. "For millions of workers, no income means no food, no security and no future. Millions of businesses around the world are barely breathing," says Guy Ryder, director-general of ILO, adding, "They have no savings or access to credit. These are the real faces of the world of work. If we don't help them now, they will simply perish."

In Asia and Africa, several countries were going through an economic slowdown or just recovering from other crises when COVID-19 hit them. Like in India, the economic growth rate was the slowest in 11 years while unemployment among informal workers was very high. Though Africa was recording a relatively better economic growth, several countries were under stress. Take the case of West African countries, Burkina Faso, Mali and Niger. The Food and Agriculture Organization (FAO) warns that at least 5.3 million people will face extreme hunger in these countries. Alarming levels of internal conflicts, insecurity and an early lean season affecting agro-pastoral activities are touted to be responsible for an unprecedented displacement and food insecurity in these countries. In the 2020 Global Report on Food Crises, released on April 21, the UN body warns about acute food insecurity in these countries due to increased violence, displacements and disrupted agriculture and trade. Nearly 1.2 million people have already been displaced by internal conflict and violence in these countries. FAO predicts that more are likely to be displaced over the next three months if current levels of insecurity persist. Their ordeal does not end here. To contain the pandemic, the three countries have adopted measures such as closure of borders and restriction on markets. These measures have impacted pastoral areas as well, says Coumba Sow, FAO resilience coordinator for West Africa. Movement of herders and livestock has been restricted due to the closure of international borders. In early April, the Food Crisis Prevention Network had expressed concerns regarding COVID-19-related risks such as collapse of food crop production, impact on pastoralists and a lack of food availability.

The situation is no better in India. In the days immediately after the

nationwide lockdown was imposed on March 25, we witnessed the desperate migrant workers returning homes. Now, at least 10 states have crafted elaborate strategies to get at least 11 million migrant workers back to their villages. The relief packages of the Union government and various states have put feeding people, ensuring a livelihood security for a few months and access to immediate health facility at the core. In India, inter-state migration for work is common, accounting for 43 per cent of the total work-related rural-to-urban migration. These migrants are also heading to villages, besides the inter-state ones. But how would they be absorbed for productive livelihoods?

It is the time of harvesting rabi crops and beginning of the new crop cycle. Both are labour- and capital-intensive. But the agriculture sector's capacity to create employment and generate income has saturated in the country. During the monsoon season, activities across the construction sector too remain subdued, failing to absorb more employment-seeking people. This means, villages will soon get flooded with people searching for livelihoods but without any hope of getting so. It would be a rare sight for India and, for that matter, several other developing countries where millions who had left villages due to one distress are returning home due to another. In both the situations, inequality in development and distribution of wealth, created from economic boom in all these decades, are responsible for pushing the economically deprived people further into distress.

In this pandemic, the world has learnt two lessons at a deadly cost. First, we did anticipate the pandemic but never bothered to follow it up with the level of preparedness required to prevent it. Second, a health emergency without a precedent doesn't have to be tackled with a clinical approach. The pandemic is now a global development challenge that is yet to be fathomed for a future strategy to tide over it. In both these lessons, there is a realisation: inequality is a much bigger catalyst, which has the power to convert a health emergency into a long-term development problem. DTE @richiemaha

THE BIG PHARMA MESS

The pandemic has exposed a serious fault line in the global pharmaceutical supply chain, created by an industry that flourished by putting profit before public health. Amid shortage of life-saving drugs, countries now scramble for self-sufficiency. But circumventing market dynamics may not be easy

VIBHA VARSHNEY AND **KUNDAN PANDEY**

In February-end, when the United States confirmed 60 cases of the coronavirus disease (COVID-19), President Donald Trump dismissed it. "This is like a flu," he said. Within weeks, the US had 0.2 million cases and the number of deaths crossed that of the 9/11 terrorist attacks in 2001. A grim-faced Trump now called the contagion "vicious" and to tackle the unprecedented crisis, the US scrambled to get life-saving medical supplies by hook or by crook. In India, Tamil Nadu had ordered 0.4 million rapid test kits from China to tackle a sudden spurt. The consignment was to reach the state on April 9, but Washington, in all likelihood, put pressure on Chinese manufacturers and the kits were swiftly diverted to the US.

Like the US, all nations are scurrying for medical supplies and they are ready to play dirty. With close to 3 million people hit by COVID-19 globally and over 0.2 million dead, pharmaceuticals have turned out to be the most vital sector. It's about national security, say countries, and each wants to reduce its dependence on foreign supplies. On March 25, for instance, when the coronavirus, SARS-CoV-2, was spreading rapidly, the European Union included health, medical research and biotechnology as part of its "restrictive list" of foreign investment. Italy was then the worst affected after China and begged EU member nations for face masks. Instead of offering help, Germany and the Czech Republic promptly banned export of masks and other protective equipment. Germany intercepted a truck, on way to Switzerland with 240,000 masks, before it left German soil. Turkey and Russia followed suit.

80%
OF THE BULK DRUGS IN THE US COME FROM CHINA AND INDIA

97%
OF ANTIBIOTICS IN THE US COME FROM CHINA

90%
OF VITAMIN C IN THE US COMES FROM CHINA

90%
OF THE BULK DRUGS IN THE EU COMES FROM CHINA AND INDIA

As deep cracks appeared in the global supply chain of masks, personal protection equipment (PPE), testing kits, drugs and ventilators, this has triggered infighting within countries. In the US, the federal government has seized masks, thermometers and other essentials ordered by different states. In France, the government has requisitioned all available masks for its own use. Israel has deployed its intelligence agency, Mossad, to take control of all ventilators in the country. Worldwide, there is a demand for at least 880,000 ventilators. Germany has 25,000 ventilators with 10,000 more on way, but the country is unwilling to share it. NITI Aayog on April 3 estimates that India would need 27 million N95 masks, 15 million PPE, 1.6 million diagnostic kits and

ILLUSTRATIONS: RITIKA BOHRA / CSE

50,000 ventilators within two months.

India has further been pushed into the eye of the storm with experimental drugs like hydroxychloroquine (HCQ) becoming part of the politics. As stocks of active pharmaceutical ingredients (APIs)—basic therapeutic chemicals that act as raw materials for producing tablets, capsules and syrups—dwindled globally, India put 13 APIs, also called bulk drugs, and their formulations on the restricted list for exports on March 3 and then banned their export on April 4. These accounted for 10 per cent of India's total pharma export.

The anti-malarial HCQ was part of the list. But India was forced to lift the ban on humanitarian grounds. The US, in fact, threatened India with retaliation. On April 6, India's Directorate General of Foreign Trade (DGFT) had to permit export of APIs and formulations made from them. Export of formulations made from paracetamol were also allowed, though DGFT continues to restrict export of the API for paracetamol. This medicine for fever is part of the arsenal to provide relief to COVID-19 patients.

The pharmaceutical industry has developed in a way that makes every country vulnerable during crisis, says Ashok Madan, executive director of Indian Drug Manufacturer Association. As every country scrambles for medical essentials, it has enormously strained the global supply. At the same time, the scramble has also exposed a faultline in the global supply chain, created over the years by an industry that has flourished by putting profit before public health. With bulk of the production of

pharmaceuticals and medical essentials occuring only in China and India, global reliance on these countries is overwhelming.

THE API CRISIS

BIGGEST DRUG PROVIDERS TO THE WORLD LOCKED DOWN

Developed countries make APIs only for patented drugs. It is left to India and China to produce APIs for generic drugs. The US imports 80 per cent of the APIs from the two countries. China is the biggest player. It provides 97 per cent of the antibiotics and over 90 per cent of vitamin C used in the US. In 2018, 95 per cent of ibuprofen, 91 per cent of hydrocortisone, 70 per cent of acetaminophen and 40-45 per cent of heparin in the US was procured from China. Similarly, some 90 per cent of the APIs for generic medicines in the EU were sourced from India and China, indicates a paper prepared in March for the EU pharmaceutical committee.

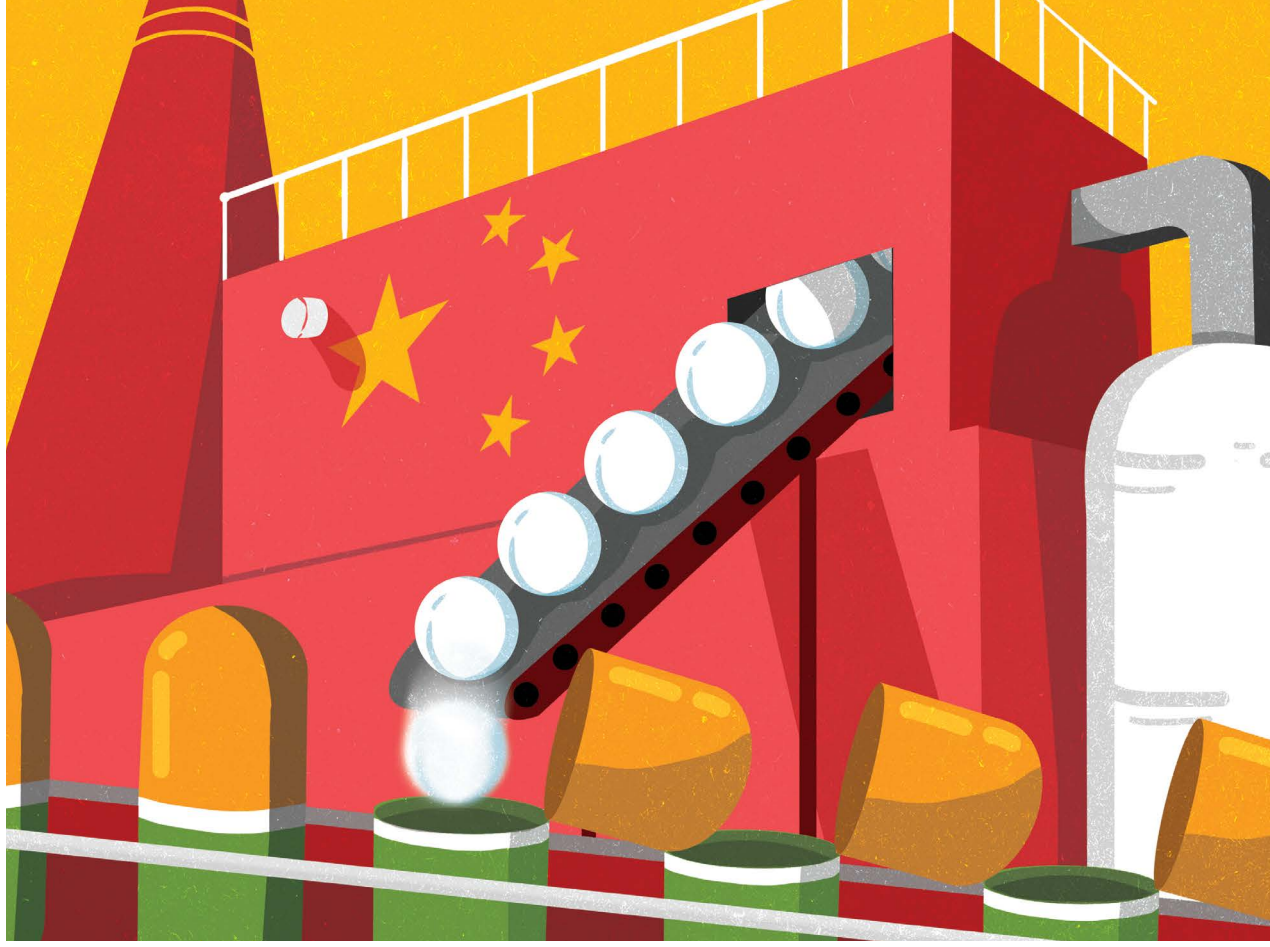
According to UK's Medicines and Healthcare Products Regulatory Agency, China manufactures around 40 per cent of all APIs used worldwide although the World Health Organization (WHO) puts this figure at 20 per cent. The China Chamber of Commerce for Import and Export of Medicines and Health Products says the export value of Chinese APIs in 2018 was US $30.48 billion and the export volume reached 929.72 million tonnes.

The reason for Chinese supremacy in API manufacturing is because when the sector first developed in China, it was state-owned. The government strategically supported the industry and gave them incentives such as cheap electricity, water and labour, negligible financial costs and no charge on land; it also established special industrial zones. "In the late 1980s, when global corporations started shifting their production base to developing countries, their interest was to get cheap labour and raw materials in an effort to maximise the benefit," says K M Gopakumar, legal advisor and senior researcher with Third World Network, an international research and advocacy organisation. China emerged the winner and managed to kill India's existing pharmaceutical sector. "For example, China dumped cheap Penicillin G in India, outperforming Indian manufacturers like Hindustan Antibiotic in the public sector and Torrent Pharmaceuticals Ltd, Alembic Pharma, Southern Petrochemical Industries Corporation Ltd and JK Pharmachem in the private sector," explains Madan of the Indian Drug Manufacturer Association.

THE REASON FOR CHINESE SUPREMACY IS THAT GOVERNMENT SUPPORTED THE INDUSTRY AND GAVE INCENTIVES SUCH AS CHEAP ELECTRICITY, WATER AND LABOUR; IT SET UP SPECIAL INDUSTRIAL ZONES TOO

With the pandemic, China had to lock down its production hub in Hubei province, which hit hard its supply to the world. The region has 44 companies which are either approved by the US Food and Drug Administration (FDA) or meet EU standards. These units have been shut since January 24.

Unlike China, India is more involved in producing finished products. The country is the world's largest provider of generic medicines, accounting for 20 per cent of global generic drug exports in volume terms. Small wonder, India is also called the "pharmacy to the world". In response to a Rajya Sabha question, the government said on March 13, 2020 that India exported medicines worth $14,389 million in 2018-19. Medicines were sent to more than 200 nations—from the highly regulated North American and European markets to countries with limited drug manufacturing capacity, including most of sub-Saharan Africa, wrote researchers at the University of Oxford in *F1000 Research*, an open access publishing platform, in April this year. Indian manufacturers represent 67 per cent of the 563 WHO pre-qualified pharmaceutical products for HIV/AIDS, diarrhoea, hepatitis, malaria, influenza, reproductive health, tuberculosis and neglected tropical diseases. Unfortunately, production of 130 of these drugs is dependent on APIs sourced from China. Of the total import of APIs in



India, 67.56 per cent is from China.

On March 13, when the BJP and Congress leaders Prabhakar Kore and Selja Kumari questioned in the Rajya Sabha about drug security, chemicals and fertilisers minister D V Sadananda Gowda said that according to the Central Drugs Standard Control Organisation, the present stock-in-hand of APIs would be sufficient only for two to three months to produce formulations. The government's ban on export of APIs and formulations was a result of this fear.

A DEPENDENT WORLD

COUNTRIES PUT ALL THEIR EGGS IN ONE BASKET

Chinese dominance in the pharmaceutical sector has been questioned across the world. In an April-6 note, the US Congressional Research Service observed that COVID-19 "is drawing attention to the ways in which the US economy depends on manufacturing and supply chains based in China". White House trade adviser Peter Navarro is working towards relocation of medical supply chains to the US. Japan and Australia have similar plans.

In September 2019, the European Fine Chemical Group, a non-profit association of European fine chemical manufacturers, published a briefing paper asking countries to reduce their dependence on China and India.

Maggie Saykali, director of Specialty Chemicals, a grouping of over 50 sectors of Europe's fine and consumer chemicals industry, says that massive offshoring of API production and Registered Starting Materials leaves the EU dependent on China and India for close to 80 per cent of its medicinal products. COVID-19 has underlined these dark spots of global supply chain, says Saykali.

Only 28 per cent of the manufacturing facilities making APIs for the US markets were based in that country. This was told to a US House of Representative subcommittee by Janet Woodcock, director, Center for Evaluation and Research, US FDA.

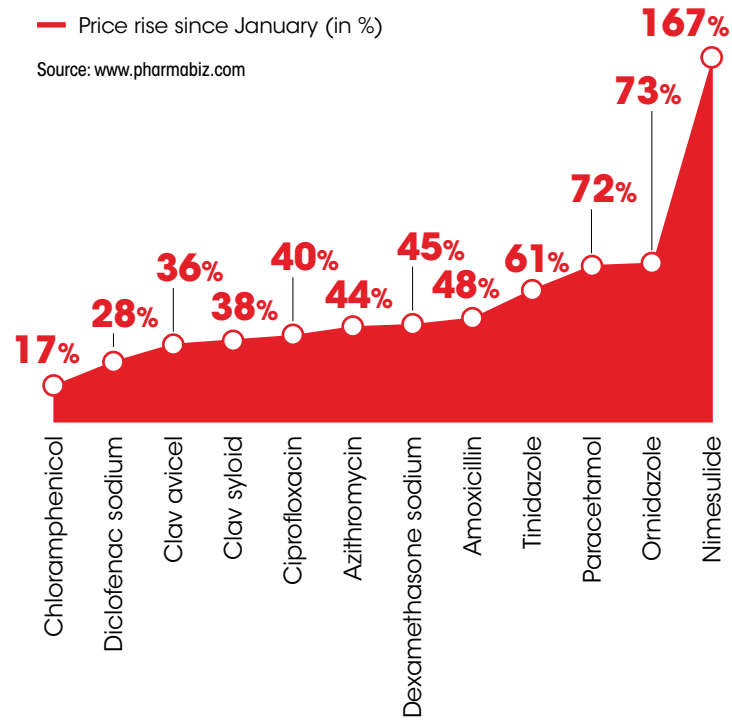
In her testimony, Woodcock quoted two papers to highlight why China and India are in advantageous position when it comes to producing APIs. Referring to a

2009 paper by the World Bank—"*Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines*"—she said if a typical Western API company has an average wage index of 100, the index is as low as 8 for a Chinese company and 10 for an Indian company. Referring to a 2011 FDA report—"*Pathway to Global Product Safety and Quality*"—Woodcock said China and India enjoy advantage of low labour costs which reduces the API manufacturing costs.

API manufacturing in India can reduce costs for US and European companies by 30 to 40 per cent. Manufacturing in China gets benefit of lower electricity, coal and water costs. Chinese firms are also embedded in a network of raw materials and intermediary suppliers and, therefore, have lower shipping and transaction costs. They face fewer environmental regulations regarding buying, handling and disposing toxic chemicals, leading to lower direct costs for these firms, Woodcock said.

On a high

Prices of active pharmaceutical ingredients, used in making drugs, have risen steeply since the spread of COVID-19



TOWARDS SELF-SUFFICIENCY

INDIA UNDERSTANDS DEPENDENCE ON CHINA IS A NATIONAL THREAT

India, too, has been worried about its increasing dependence on China. In 2014, Rajya Sabha member Motilal Vora raised the issue of inappropriateness of importing API from a single country in the House. The same year, National Security Advisor Ajit Doval called the rising dependence on Chinese drug makers a "national threat". In 2013, a high-level committee on promoting domestic manufacture of APIs had already been set up under V M Katoch, the then director general of Indian Council of Medical Research (ICMR) and secretary of the department of health research under the Union Ministry of Health and Family Welfare. In July 2018, a parliamentary standing committee report presented to the Rajya Sabha pointed out there was an urgent need to revive the country's capability to produce APIs. The committee noted that China had increased the prices 1,200 per cent in the last two years. This slashed the profit margin for India's industry.

To increase self-sufficiency, the Katoch committee's report, submitted to the Ministry of Chemicals and Fertilizers in February 2015, recommended the creation of three to six mega parks. These parks should provide free or shared water, electricity, effluent treatment plants and testing facilities to the pharmaceutical industry. The government would have to invest ₹750-1,000 crore for each of these. The committee recommended that the private manufacturers should be provided benefits like 15-year tax-free status, access to loans and foreign investment. It also pushed for reviving the public sector Indian Drugs and Pharmaceuticals

Limited with an infusion of ₹500 crore.

While this committee's report was awaiting implementation, the government formed another task force in 2018, chaired by Mansukh Mandaviya, the Union Minister of State for Chemicals and Fertilisers. This, too, reiterated the recommendations of Katoch committee. India has already started work to revive the industry. Department of pharmaceuticals has approved development of mega parks in Andhra Pradesh, Telangana and Himachal Pradesh and is providing assistance up to ₹100 crore for creation of Common Facility Centre (CFC) in these under the scheme Assistance to Bulk Drug Industry for CFC. India's record in creating such parks has, however, not been good (see 'India has poor track record').

AFFORDABILITY IS THE KEY

GOVERNMENT MUST STEP IN TO REDUCE PRICES OF CRITICAL DRUGS

Manufacturers say it is not easy to cut the umblical cord with China for supply of basic drugs. The government needs to regulate drug prices to ensure that people have access to cheaper medicines. This, in turn, makes the pharmaceutical sector look for ways to cut prices, thus increasing their dependence on the low-cost Chinese model.

Beside availability, the affordability of medicines is a major challenge for India. Media reports already demonstrate that API prices in India have shot up after the pandemic (see 'On a high' on *p*36). China provides 75 per cent of APIs used in the formulations of drugs in the National List of Essential Medicines (NLEM) and there could be an increase in prices of medicines in the list. In a recent interview to the national daily *Financial Express*, Mandaviya said increased self-sufficiency in manufacturing of critical bulk drugs would ensure the availability of essential drugs listed under NLEM at affordable prices.

The government has to mandatorily ensure that prices are low as these drugs are part of the Essential Commodities Act, 1955, which regulates the prices of essential supplies like grains, foodstuffs and medicines. The list of drugs under price control has steadily expanded from 74 in 1995 to nearly 860 in 2019. According to brokerage firm Centrum Broking, going by the wholesale price index of 2019 and 2020, the increase in prices of drugs under NLEM would not be steep. However, prices of non-NLEM drugs would continue to increase at 10 per cent. "With China resuming supplies of raw materials, potential disruption in manufacturing is now no longer a concern. There has been inflation in select raw material supplies but the

MEGA PHARMA PARKS

India has poor track record

India's experience with dedicated vaccine "parks" has been disheartening. In 2008, the Union government decided that an Integrated Vaccine Complex would be set up at Chengalpattu near Chennai by HLL Biotech Limited (HBL), a subsidiary of HLL Lifecare Limited, which is a government of India corporation. Production was to start in 2012 with an estimated cost of ₹594 crore. But in 2018-2019, additional funds of around ₹300 crore were asked for. This demand was rejected. Though the infrastructural facilities have been set up in the park, production has not yet started. Recruitments began in HBL in 2013, but the employees who were supposed to set the research and production facilities at the park, have not been paid since July 2019. In June 2019, the workers were given the option to go on unpaid leave for up to five years and pursue other career options.

In November 2017, the Ministry of Health and Family Welfare announced the intention to sell 100 per cent government equity in HBL. The workers claim the decision was taken on the recommendations of the NITI Aayog to dismantle public sector organisations and promote private players which were already supplying vaccines at high costs.

In January, Bharat Biotech International, a private vaccine manufacturer based in Hyderabad, wrote to health minister Harsh Vardhan and showed interest in partnering with the government to revive the unit and invest in it. Bharat Biotech was willing to work with HLL Lifecare Ltd to manufacture and market several of their vaccines. But nothing has happened since then.

same should only have a minor impact on gross margins during the quarter," brokerage firm Nirmal Bang says.

Private manufacturers have not been keen to provide medicines that are under price cap. They say it does not help as the poor are still not able to afford them. "The problem is that India spends too little on healthcare," writes Amir Ullah Khan, professor of economic policy at the Indian School of Business and the Nalsar University of Law, in the national daily *Mint*. Instead of price control, he suggests that options like trade margin rationalisation, centralised procurement, social health insurance schemes, cross subsidisation and state financing o f e ssential drugs should be used.

India has to keep the drug costs low. Its public spending on health is very low. It is unlikely that the country would be able to procure much if it buys at the private sector prices. Public sector pharmaceutical companies, therefore, become relevant as they can provide drugs at the cost price even after including the cost of pollution control.

PHARMA POLLUTION

NO TIME FOR QUICK-FIX MEASURES. INDIA NEEDS STRICTER LAWS

Environmental pollution is, obviously, the most devastating byproduct of the drug-making race, but global efforts to reduce it have been tardy. In 2014, the EU issued a draft strategy to ensure that companies which supplied antibiotics to them were responsible and non-polluting. Under this, the EU members could have environmental clauses in international agreements. This would have allowed EU inspectors to visit factories in Asia or Africa to ensure that they were not polluting. But the draft was diluted. The replacement passage in the new 2018 draft merely gave the countries an option for "the possibility of using procurement policy to encourage greener pharmaceutical design".

The dilution was linked to lobbying by drug companies. Voluntary declarations show that the pharmaceutical industry spent nearly €40 million (about $37 million) on lobbying EU institutions in 2015. Public records show the European Federation of Pharmaceutical Industries and Associations had over 50 meetings with the Juncker commission in its first four-and-a-half months of office.

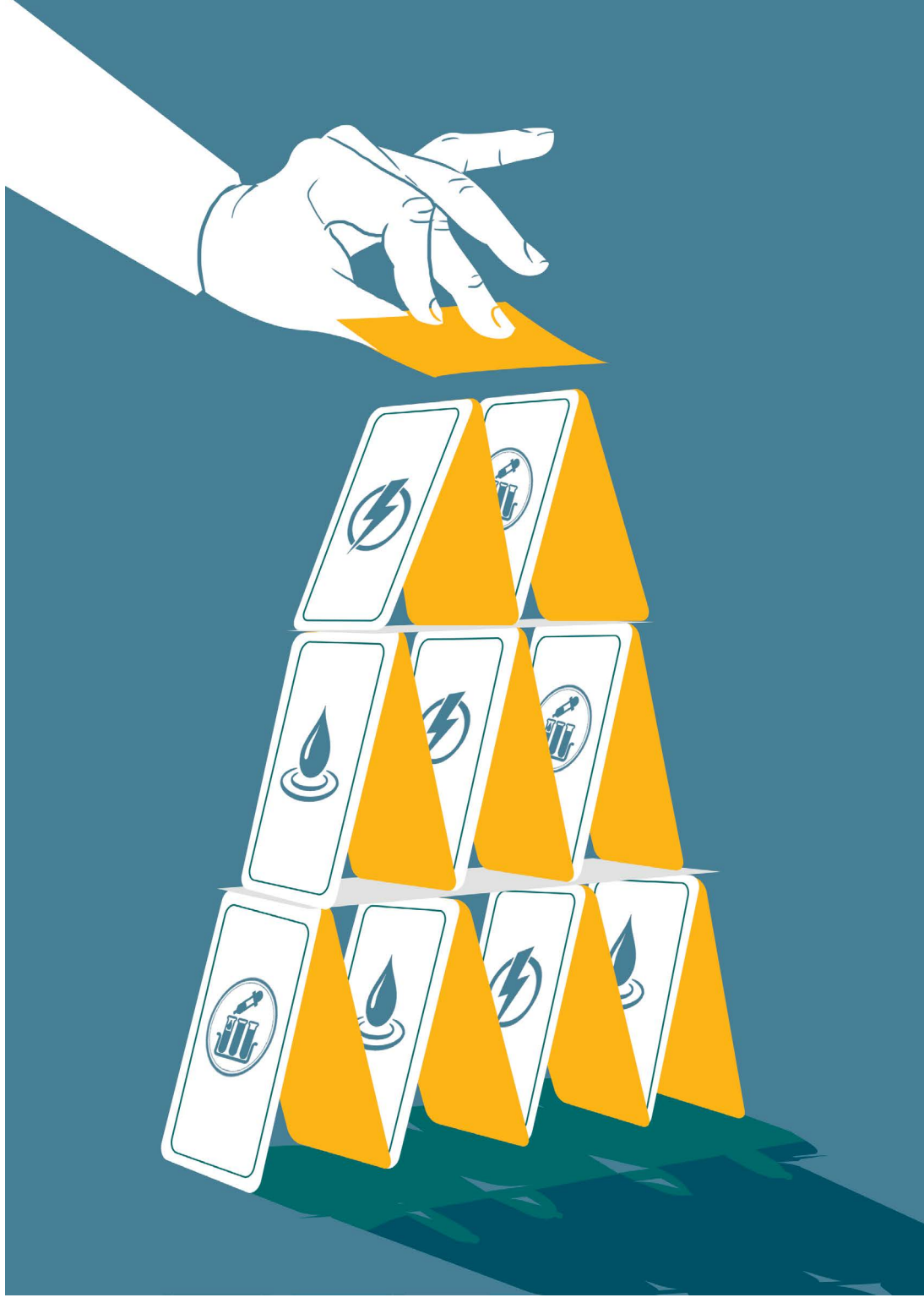
DESPITE THE ENVIRONMENT (PROTECTION) RULES, 1986, INDIA HAS BEEN UNABLE TO CONTROL POLLUTION IN ITS PHARMA HUBS, IN TELANGANA, HIMACHAL PRADESH AND TAMIL NADU

Fortunately, the European Parliament is demanding stricter measures again. Its environment committee has unanimously backed a call to go tough on pharmaceutical pollution, including reductions in drug use, greener manufacturing and better waste management.

Developing countries, too, are formulating policies to control pharmaceutical pollution. On January 23, India released a draft Environmental Standards for Bulk Drug and Formulation (Pharmaceutical) Industry to limit the concentration of toxins in effluents released by bulk drug manufacturers. It specifies maximum residues for 121 antibiotics that can be present in the treated effluent of bulk drug and formulation industry and in the outlet of the common effluent treatment plants. The draft notification also prescribes maximum concentration for various other parameters, including heavy metals and hexavalent chromium.

China, too, is trying to reduce environmental pollution. In 2002, it formulated the China Safety Production Law which controls all industries, including chemical and pharmaceutical. But the industry continued to pollute. With President Xi Jinping at the helm, it is taking action to ensure that the Chinese industry is in line with global environmental standards. Between 2016 and 2018, inspections led to the closure of 150 factories producing APIs, according to a white paper published by consultancy firm Beroe in July 2019.

In case of antibiotics, China issued strict guidelines in its National Action Plan 2016. It promotes green manufacturing of antibiotics and monitoring of effluents. In January 2018, China came out with an "environmental tax declara-



tion" under which less polluting industries are eligible for tax reductions. A 25-per cent tax relief is allowed if the discharge, mainly wastewater and air pollution, is 30 per cent lower than the national or provincial standards. If a company is able to maintain its pollution level at 50 per cent lower than the standard concentration, they can apply for a 50 per cent tax reduction. According to the Beroe white paper, China also plans to put in measures so that polluters would face a levy of between 1.2 yuan ($0.18) and 12 yuan ($1.8) for every 0.95 kg of nitrogen oxide or sulphur dioxide they release. According to estimates, taxes up to 50 billion yuan (about $7.68 billion) will be collected annually from manufacturers.

Such stringent pollution norms would increase manufacturing costs and take away China's competitive edge. Earlier too, diligently operating European firms went out of business because they could not compete with a non-compliant China, according to an article published in *Chemical & Engineering News* in 2018. It says a strict inspection regimen could trigger a migration of business back to the West as environmental compliance would increase the cost of operating in China.

India, however, has been unable to control pollution in its pharmaceutical hubs like Patancheru-Bollaram Industrial Estate in Telangana, Baddi Industrial Area in Himachal Pradesh, and SIPCOT Industrial Estate in Cuddalore, Tamil Nadu. This despite the Environment (Protection) Rules, 1986, in force. India's new pharmaceutical parks are planned in these very places.

At a recent meeting with NITI Aayog, the Department of Phar-maceuticals promised fast environmental clearances to the industry. Such quick-fix measures would be detrimental in the long run unless strict regulations are put in place. India has to be more cautious now.

TIME TO RETHINK

COUNTRIES HAVE TO MANAGE COSTS AND COMPETITIVE MARKET FORCES

China claims it has resumed production of APIs and says it is unlikely that there would be any shortage in India or globally. The pandemic, however, has given the world a chance to do a rethink on the pharmaceutical industry. Countries have realised that their over-dependence on one can cause big trouble. They are now trying to become self-sufficient (see 'Big opportunity for India' on *p*42). India is developing legislations and employing public spending to bring API development back. The US and EU are also contemplating legislation to bring both APIs and Finished Dosages (FDs) back home.

But industry experts say this is not the way to go. "This would be a knee-jerk reaction," says Kiran Mazumdar-Shaw, chairperson and managing director of Biocon Limited, a biotechnology company based in Bengaluru. "The surge in demand has caused an acute shortage of medical supplies, diagnostics and medicines which ought to point fingers to the failure of global healthcare systems to stockpile inventory as a preparedness response to any public health crisis. Once the surge in demand recedes, countries would need to manage costs and competitive market forces will favour economies of scale," she says.

Others concur. "We believe that production of both APIs and FDs must be global, with trusted trade partners, to ensure that any type of national or international disaster does not cause a collapse of the manufacturing and supply of pharmaceuticals," says David Gaugh, senior vice-president, Association for Accessible Medicine, a trade association representing the manufacturers and distributors of generic prescription drugs.

Industry favours pharmaceutical parks as these would be SEZ-like structures with fiscal incentives, common utilities and common effluent treatment plants that can create economies of scale and lower operational costs. But some fear this would help only the private industry. Y Madhavi, scientist at the National Institute of Science, Technology and Development Studies, New Delhi, says public sector is crucial in the regulation of the sector. Citing an example from 2008, she says public sector vaccine manufacturers were closed down with the assurance from private manufacturers that they would give affordable vaccines for the universal immunisation programme. This never happened. The industry makes huge profits with trade margins that can sometimes be 4,000 per cent of the cost price. In October 2019, the Department of Pharmaceuticals proposed a maximum trade margin of 43 per cent over cost price for 10,600 non-scheduled drugs.

INDUSTRY FAVOURS PHARMA PARKS AS THESE WOULD BE SEZ-LIKE STRUCTURES WITH FISCAL INCENTIVES, COMMON UTILITIES AND COMMON EFFLUENT TREATMENT PLANTS

Gopakumar says the solution lies in increasing the capacity, both in public and private sectors. "You need to have a new kind of public sector, maintain the assets that the private players can operate. The government has to spend the money. The private sector will make the money and pay the government back," he says.

Whatever mix be the strategy—private versus public sector or domestic production versus import—the industry cannot be permitted to pollute. This would result in a price hike. S Srinivasan, who runs a generic drug company LOCOST, says the price would not increase beyond 5 per cent if the chemicals are made in large quantities. "Much of it will be capital costs which need to be apportioned over time," he says.

This gives hope. "No doubt API production is highly polluting, but new technology must be brought and upgraded constantly to minimise the impact of pollution," says Sakthivel Selvaraj, director of health economics, financing and policy at Public Health Foundation of India, New Delhi, adding that the additional cost due to pollution control measures would be negligible. Even if these costs are factored in, India would still have an edge both in API and formulation business. DTE

(*With inputs from Banjot Kaur*)

BIG OPPORTUNITY FOR INDIA

India can replace China as the world's preferred source of pharmaceutical ingredients

BY REJI K JOSEPH

BULK OF the active pharmaceutical ingredients (APIs) required by the pharma industry across the world is produced in China and India. The COVID-19 pandemic has exposed the risks of global supply chains being focused on a single country, which currently is China. COVID-19 has sent alarm bells to national security establishments in many countries, including India, on the risks of relying on a single country for the supplies. So far, the economic efficiency argument prevailed, but now the security dimension is on the forefront, which would result in many countries adopting measures to reduce reliance on China. In such a scenario, India is likely to become the preferred country for sourcing APIs.

Many countries have declared intention to resort to Compulsory Licenses (CL), if required, for ensuring the adequate supply of drugs for treating COVID-19. (Compulsory licensing is when a government allows someone else to produce a patented product or process without the consent of the patent owner or plans to use the patent-protected invention itself, according to the World Trade Organization.) Israel issued a CL in March to import generic versions of Kaletra of AbbVie, which is used for treating HIV/AIDS and has been found to be useful in COVID-19 cases. The Indian Patent Act, 1970, has a provision that enables export under CL. Exports under CL, if countries resort to it, would be an immediate opportunity for Indian pharmaceutical industry. But India's gains from the opportunity in the API business would depend on how swiftly its policymakers respond to it.

While India is an exporter of certain APIs, it is quite dependent on China for many others, especially those produced through fermentation, and intermediates (chemical compound which is in the process of becoming an API from a raw material is called an intermediate). When supplies from Wuhan were affected, the price

of paracetamol went up 40 per cent in India. In order to eliminate the dependence on China for APIs and intermediates and to promote their domestic production, the Union Cabinet, on March 21, decided to launch a scheme at a cost of ₹10,000 crore. Under the initiative, ₹3,000 crore will be used to create common facilities in three API Parks, which are expected to be established by the private sector, while ₹6,940 crore will be used for the Production Linked Incentive (PLI) scheme over a period of eight years. Though this is a welcome initiative, it may not achieve the objective unless additional measures are incorporated to overcome the constraints India has compared to China.

It is expected that common utilities at API Parks and PLI are sufficient to offset the price disadvantage that Indian API manufacturers have as compared to their Chinese counterparts. But it might not turn out to be so. Price competence that Chinese firms have acquired has two key aspects—their larger scale of operations and superior technologies. The average size of SEZs in India is about 1 per cent of the average size of SEZs in China. They use technologies that rely on cheaper raw materials like cauliflower for fermentation whereas our firms use glucose and lactose which are much costlier. Moreover, it may take about eight years to set up API Parks and begin commercial production. By then, the Chinese are likely to have come up with even better technologies that further push the prices down. This possibility would amount to business insecurity for the potential Indian investors in the proposed API Parks.

INDIA'S GAINS FROM THE OPPORTUNITY IN THE API BUSINESS WOULD DEPEND ON HOW SWIFTLY ITS POLICYMAKERS RESPOND TO IT. WHILE INDIA IS AN EXPORTER OF CERTAIN APIS, IT IS QUITE DEPENDENT ON CHINA FOR MANY OTHERS

As we have a structural disadvantage in terms of the size of SEZs, we need to focus on cost-effective and greener technologies. This technology component has been missing in India's recent initiatives to boost domestic production of APIs and intermediates. Development of appropriate technologies has to be done in a mission mode and the large network of Council of Scientific and Industrial Research laboratories and public sector universities can be used. The business insecurity will be overcome if API Parks with common utilities are established by the government and then enterprises are invited to establish their production units there. This will considerably reduce the cost for producers and partly offset the disadvantage India has in terms of size of operations as compared to China. DTE

(The author is an associate professor in Institute for Studies in Industrial Development, New Delhi)

BETWEEN A CURE AND ACCESS

As researchers scramble to come up with therapies to treat COVID-19, patents could keep the drugs out of reach for many

LATHA JISHNU

ILLUSTRATION:. RITIKA BOHRA / CSE

IT IS a feverish hunt for ways to treat one of the deadliest infections the world has known since the 1918 Spanish flu. As millions more are infected by COVID-19, researchers are scrambling to come up with a range of items to cope with the pandemic—from easy-to-use diagnostic kits and medicines to the holy grail of them all: a vaccine against the severe acute respiratory syndrome (SARS) coronavirus-2, which causes the COVID-19 disease.

Vaccines, however, are a long way off even though over a hundred pharma companies, research institutions and global collaborations have been set up to find the magic bullet (see 'Hope or hype?' on *p*46) to halt the pandemic. The vaccine hunters may be attracting big money and headlines, but as much of the research attention is focussed on existing therapies to help patients—especially those who become critically ill—to fight the virus. These endeavours are as fascinating as they are varied, drawing in systems biologists, Big Pharma, universities, start-ups and a host of others in an effort to stop SARS-COV-2 from reaping a deadly harvest.

Since every virus is different, new drugs have to be developed to fight diseases. But this takes time—of several years—and requires humungous amounts of money. COVID-19 does not allow us that kind of luxury; it spreads extraordinarily fast and that is the danger that hangs over the world, although compared to other viruses such as Ebola and Zika it is not so deadly. So readily available drugs are under the scanner in laboratories across the world where researchers are narrowing their search to find medicines that work best against the virus. Repurposing is the new strategy.

It was the Chinese who showed the way. They used an experimental drug, remdesivir, developed by Gilead Sciences of the US to fight Ebola, in combination with chloroquine, the tried and tested warhorse in the battle against malaria (see 'The great coronavirus drug hunt', *Down To Earth*, 1-15 March, 2020). Remdesivir did not work against Ebola, but is one of the drugs showing promise in tackling COVID-19. There is also favipiravir, which was developed in 2008 by Fujifilm Toyama Chemical Co of Japan to treat the West Nile virus, foot and mouth disease and yellow fever, and is reported to have shown "excellent results" in the treatment for COVID-19 in China in January and February this year. Several countries, notably Russia, are betting on favipiravir, marketed as Avigen, to fight the COVID-19 pandemic.

THE BIGGEST BLOCK IS THE PATENT PROTECTION ON DRUGS THAT ARE MAKING NEWS. THIS MEANS GENERIC DRUG FIRMS CAN'T MAKE INEXPENSIVE GENERIC VERSIONS OF THE MEDICINES

Elsewhere, too, innovative therapy involving a cocktail of drugs meant for different ailments has found to have been effective in treating patients. In Thailand, a combination of oseltamivir—used to treat influenza—and HIV drugs, lopinavir and ritonavir, have been used to cure a few patients with severe symptoms, according to press reports from Bangkok, but later reports from China said the tests had proved negative.

Is it now a simple matter of producing enough remdesivir, favipiravir and certain HIV drugs to come up with a cure? For one, there is the patent hurdle. For another, precious little research has gone into repurposing drugs in the country.

The biggest block, of course, is the patent protection on drugs that are making news. This means generic drug firms cannot make inexpensive generic versions of the medicines. In India, the main patent on favipiravir expired in August last year, but there is a catch: Fujifilm Toyama holds four other patents on the molecule, one of which lasts till 2028. In the case of remdesivir, the patent claim was filed in October 2015, which means it will stay in force till 2035. Curiously, India approved the patent claim only in February this year soon after reports emerged from China

HOPE OR HYPE?

Numerous companies are in the fray to make a vaccine. But can they deliver?

IN EARLY April, TV channels in India went to town on a story that a Hyderabad-based drug company would soon be coming out with a vaccine against the severe acute respiratory syndrome (SARS) coronavirus-2 or SARS-COV-2. With panic spreading about the pandemic, the news quickly made headlines since Bharat Biotech's announcement put a desi company as a front-runner in the vaccine race.

For Bharat Biotech, it meant good publicity. The CorFlu vaccine, for which it will only start clinical trials in the fall of 2020, is being developed in the US by the University of Wisconsin in collaboration with vaccine company FluGen. This means the vaccine is at least 18 months away. At the last count, five other Indian companies, among these Zydus Cadilla and Mynvax, had also thrown their hats into the ring with one or more candidates.

The most interesting collaboration is between the Serum Institute of India, which produces the largest number of vaccine doses in the world and Germany's Max Planck Institute for Infection Biology. The project has a more modest aim: to provide an immunity boost until a vaccine specifically effective against COVID-19 is developed. Based on repurposing, the German institute is trying to find out if its vaccine candidate VPM1002, an improved version of the 100-year-old BCG tuberculosis vaccine, can be effective. The large-scale study is to be carried out at several hospitals in Germany and will include two groups most at risk: older people and healthcare workers. The other partner is Vakzine Project Management (VPM), which is now majority owned by the Serum Institute, and has been granted the licence for the new TB vaccine.

On the global landscape, there are over 100 companies jostling for funding and limelight. Some companies have received generous funding from the Coalition for Epidemic Preparedness Innovations (CEPI), a global organisation based in Oslo. Backed by the Bill & Melinda Gates Foundation, CEPI is raising US $2 billion to funnel more money into companies that have emerged as the frontrunners.

But let's assume that some vaccines are developed soon. Then who will benefit from the breakthrough? CEPI says that there are no rules in place for a fair allocation system, but is working on a plan to ensure this. A better solution would be for WHO to act on an ambitious proposal made by Costan Rican President Carlos Alvarado Quesada to pool rights to all technologies that are useful for the detection, prevention, control and treatment of the COVID-19 pandemic (see 'Patent pool to fight the pandemic', *p*48). The EU has backed the move.

about its success in treating COVID-19 in a combination therapy. A patient aid group has contested the patent, pointing out that remdesivir lacks novelty, creativity and an inventive step, which are perquisites for grant of patents.

There are, however, other drugs which could be repurposed if the Indian generics industry is willing to do some research. The Quantitative Biosciences Institute (QBI) at the University of California, San Francisco, is offering such drugs on a platter. It first mapped how COVID-19 attacks human cells. It then worked round the clock, through a network of 22 labs, to identify existing drugs that can disrupt the pathways of the new virus. It has so far identified 27 FDA-approved drugs that could accelerate the development of a treatment and bring it to the market much faster than a new drug would take. Since many of the drugs are no longer patent generics, firms could use this research to select those drugs that are best suited to their expertise.

For the moment, it is the hype and desperation that are driving reports of successful treatments rather than the proven efficacy of the repurposed drugs. The problem is that no controlled, randomised tests have been conducted so far. For instance, Gilead rushed to publish a study "Compassionate use of remdesivir for patients with severe COVID-19" on April 10 in *The New England Journal of Medicine* which was assailed by pharma experts. Duncan Richards, clinical pharmacologist and professor of clinical therapeutics at the Oxford University who described "compassionate use" as unlicensed therapy, said: "Research based on this kind of use should be treated with extreme caution because there is no control group or randomisation, which are the hallmarks of good practice in clinical trials."

For Gilead, that was a major setback, coming in the wake of a major disappointment after China cancelled two clinical trials on remdesivir. On April 15, the Chinese authorities notified the US multinational that it was unable to conduct the test on patients with severe symptoms because the epidemic had been controlled and no eligible patients could be enrolled. A similar trial on patients with mild or moderate forms of COVID-19 was halted earlier. Gilead is now pursuing bigger trials.

In India, no work appears to have started on therapies and there are indications that the health authorities are banking on remdesivir to see the country through. The chief of the Indian Council of Medical Research has said that it would be using the drug if local companies could make it.

Can they do so? Yes, if they secure a voluntary licence (VL) from Gilead. This appears to be a distinct possibility since some companies have announced plans to work on remdesivir in recent days. Besides, Gilead is known for using the VL route in India, which allows the company to dictate the terms of manufacture, from price and quantity to marketing restrictions.

IN INDIA, NO WORK APPEARS TO HAVE STARTED ON THERAPIES. THERE ARE INDICATIONS THAT HEALTH AUTHORITIES ARE BANKING ON DRUG REMDESIVIR, DEVELOPED BY GILEAD SCIENCES OF USA, TO SEE THE COUNTRY THROUGH

Compulsory licences (CLs) should be the preferred option since India's patent law allows their use in the case of a public health crisis. However, the Narendra Modi government is unlikely to plump for CLs since it could mean a confrontation with drug multinationals and the Trump Administration. This has become clear since Modi first came to power. The latest instance of such pusillanimity was the alacrity with which Delhi revised its policy barring exports of hydroxychloroquine after Donald Trump warned of retaliation if India did not supply the drug.

This is in sharp contrast to what is happening elsewhere. A swathe of countries—from Germany to Chile and Israel—have recently passed laws to allow them to issue CLs and use other such measures to cope with the crises caused by the pandemic.

The possibility of India coming out with its own treatment seems extremely slim at the moment. Yusuf Khwaja Hamied, the iconic chairperson of leading drugmaker, Cipla, has spoken of repurposing its HIV drug Lopimune—which is a combination of lopinavir and ritonavir—for the treatment of coronavirus. He also said that work would commence on other promising anti-viral compounds—favipiravir, remdesivir and bolaxavir. But Hamied who gave hope to millions afflicted with HIV/AIDS may find himself hamstrung now.

His company, like others in the country, is facing an acute shortage of active pharmaceutical ingredients (APIs)—raw materials used to make drugs—which is supplied by China. Over the past decade, the Chinese had become the principle supplier of APIs to India by undercutting domestic firms. The recklessness of such a short-sighted policy that allowed local API manufacture to die out has come back to haunt the country.