LEGAL AND REGULATORY CHALLENGES IN INDIAN PHARMACEUTICAL INDUSTRIES -ENSURING UNRESTRICTED PRODUCTION IN THE CONTEXT OF COVID-19

-ALPANA PHUKAN

CONTEXT

As Bill Gates had correctly predicted in 2015, the greatest threat to humanity was not nuclear missiles, but microbes. COVID-19 presents an unprecedented challenge to humanity. While this piece of analysis, India overtook Brazil as the country with the second highest recorded cases of Covid-19 after the US. The pandemic continued its unprecedented surge in India, with fresh cases close to 90,000 on Saturday (05th September 2020).

In meeting the global health challenge, the role of the pharmaceutical industry is of prime importance. With the current state of affairs, it’s a harsh reminder of what’s at stake and its responsibility. Despite all the bad news, the Indian Pharmaceutical Industry needs to see the current Covid-19 crisis as an opportunity. In my experience of working with the Industry, this is the most opportune time for the pharmaceutical industry and the Indian government to implement the Katoch Committee recommendations and implement many of the suggested incentives to position India as the global pharmaceutical hub.

Globally, the Indian pharmaceutical industry is the largest provider of generic medicines and ranks 3rd worldwide for production by volume and 13th by value; thereby, accounting for around 10% of the world's production by volume and 1.5% by value. According to the Department of Pharmaceuticals (DoP), India is the source of 60,000 generic brands and home to 3,000 pharma companies with a strong network of over 10,500 manufacturing facilities. The DoP aims to make the country a hub for end-to-end drug discovery under its ‘Pharma Vision 2020’.

As indicated in a 2015 McKinsey report, the Indian pharmaceutical market will grow from a market size of USD 12.6 billion in 2009 to USD 55 billion by 2020, with the potential to reach USD 70 billion in an aggressive growth scenario. It was last valued at USD 40.2 billion by the National Investment Promotion and Facilitation Agency (Invest India) in 2019.

REGULATORY AND COMPLIANCE CHALLENGES

This is a promising ‘horizon’ for the pharma industry, and to arrive at the ‘tipping point’ of true potential of the sector, the Indian Pharmaceutical Industry needs couple with the stringent regulatory and compliance requirements (both of national and international), which will ensure a ‘swift and smooth’ sailing of the sector.

A few such regulatory and compliance requirements are in the areas of clinical trials, inspections and the continuity of supply in medicinal products and medical devices, as well as the proposed postponement of implementation of the medical device regulation (MDR) and in vitro diagnostics regulation (IVDR). Indeed, the contagious concerns in the Indian...
pharmaceutical industries such as USFDA, CGMP norms, drug pricing, APIs related challenges are already identified as key challenges in accelerating the growth of the sector.

In a pessimistic scenario characterized by regulatory controls and economic slowdown, the market will be depressed and is not expected to reach its potential. The following challenges stand out:

**Rising number of US FDA inspections.** The number of inspections is at an all-time high. This comes as no surprise considering India has the most USFDA approved sites. In recent time, the U.S. Food and Drug Administration (FDA) and the Indian government work together on pharma supply chain issues. From January 28–30, 2020, for example, a joint action called Operation Broadsword prevented approximately 500 shipments of illegal and unapproved prescription drugs and medical devices from reaching U.S. consumers. Now, two Indian pharma companies are voluntarily recalling lots of Metformin Hydrochloride Extended-Release Tablets because FDA analysis revealed they could contain nitrosodimethylamine (NDMA), a known carcinogen, above the acceptable limit. The recall affects both 500mg and 1000mg tablets. Metformin is commonly used to treat type 2 diabetes. A complete list of all metformin products being recalled is available on the FDA website.

**Government Control on Drug pricing:** This is directly impacting the confidence levels of companies to invest respectable amounts in R&D

**Fake Products:** It does create a wrong perception globally especially when India is aspiring to be a superpower in this space

**India’s significant dependence on Chinese Active Pharmaceutical Ingredients (API):** The impact of the SARS-CoV-2 coronavirus outbreak, COVID-19, has exposed the dependency of the Indian pharma sector on China for its API procurement. Supply chain disruptions and product exportation restrictions from India resulted from manpower shortages in China’s manufacturing plants. This was caused by the quarantine policies adopted and adopted by different provincial governments in China in response to the virus. Supplies were further impacted by the disruption of logistic and transportation systems, restricting access and movement of products to and from ports. According to Bloomberg, 70% of India’s imports of APIs come from China, totalling $2.4 billion of India’s $3.56 billion import spending for those products each year.

**Impact of the pandemic on clinical research:** The COVID-19 pandemic has been a decisive point in clinical trials regulatory affairs. It has highlighted the complexity of managing multinational clinical trials that must meet changing national guidelines while maintaining patient safety and the scientific value of the research during a global crisis. The lesson learned is that a close collaboration between sponsors, CROs, local affiliates, investigational sites, and health authorities is of utmost importance in choosing the correct strategy in difficult circumstances and when no precedent applies. The role of the global CROs is significant in these circumstances, because they have the most comprehensive overview of the regulations and are in regular contact with a range of regulatory agencies. Thus, CROs are in the best position to act and advise quickly and decisively.

It is too early to assess the pandemic’s impact on clinical research fully. It is estimated that more than 2,850 clinical trials were being conducted during April 2020 in the world (including India) that became affected by COVID-19 restrictions, which included complete lockdown or more limited measures. About 900,000 patients were participating in clinical trials that faced an uncertain future as the crisis unfolded.
Patent and licencing issues*

In January 2020, Chinese researchers at the Wuhan Institute of Virology filed for a patent covering the use of remdesivir, an experimental antiviral drug, to treat COVID-19. Indeed, this drug was also researched and produced by Gilead Sciences, a California-based pharmaceutical company, which had filed patent applications at several patent offices, including in China, covering a “method for treating Arenaviridae and coronaviridae virus infection”.

It is worth noting that the Wuhan Institute of Virology’s patent application was filed before scientists started experiments investigating the effectiveness of remdesivir against COVID-19. In effect, the Wuhan Institute of Virology’s first IN VITRO studies suggesting that both remdesivir and an antimalarial drug called chloroquine could effectively inhibit COVID-19 was published in early February 2020.

In response to the public outcry, the Wuhan Institute of Virology defended its patent application by claiming it was made in the national interest. It added that it would be willing to forgo enforcing its patent rights if foreign pharmaceutical companies – in this case, Gilead – collaborate with Chinese authorities to stop the pandemic.

But this argument is weak. If the Wuhan Institute of Virology was really only concerned about public health and access to vital drugs in an emergency, there is already a mechanism that gives countries intellectual property (IP) flexibility in just such an event: compulsory licenses.

Compulsory licences are explicitly allowed under Articles 48–50 of Chinese patent law, although the country has yet to issue one, and they are in line with the World Trade Organization’s (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, which outlines global standards for protecting IP rights. The 2001 Doha Declaration on the TRIPS Agreement and Public Health, adopted by the WTO Ministerial Conference, confirmed that compulsory licences can be used subject to certain conditions. And where they have been granted, they have led to significant reductions in drug prices. In 2012, for example, the Indian generic drug-maker Natco was granted a compulsory licence for sorafenib, an anticancer drug, after that country’s patent office ruled that Bayer AG, sorafenib’s patent holder, had not done enough to make the drug available to Indian citizens. Natco was required to pay 6% royalties to the German company – a figure based on United Nations (UN) guidelines – and proposed selling its version for 97% below Bayer’s price.

Given the scale of the ongoing health crisis, a Chinese company filing for a compulsory licence would not necessarily be perceived as an attempt to unjustifiably circumvent Gilead’s patent rights. After all, in the wake of the coronavirus crisis, in March 2020, Israel issued a compulsory licence in relation to Kaletra, an HIV medicine that is currently being tested for effectiveness in the treatment of COVID-19. The patent is owned by the US pharmaceutical company AbbVie, and the licence will allow Israel to import the generic version of Kaletra produced by the Indian company Hetero. In addition, the Chilean parliament and Ecuador’s National Assembly have adopted resolutions that would pave the way for the issuance of compulsory licences to tackle the coronavirus outbreak, and the German government has started plans to limit patent rights in view of this pandemic. In North American, Canada is also following this lead. Hence, it is expected that India could take advantage of this compulsory licensing and make the life saving drugs for COVID-19 available to all.
The impact of the COVID-19 pandemic and the lockdown it triggered is both tangible and intangible. But there is still no clarity on the deeper impact that it will have on India’s healthcare manufacturing and the global supply chain. The rising prices of key ingredients are initial indicators. The prices for vitamins and penicillin are double or triple the price. Similarly, the cost of paracetamol has gone up. If the pandemic continues then stockpiles of pharmaceuticals, APIs, and other chemicals may decrease, resulting in shortages.

The current dependency of Indian pharmaceutical companies on Chinese APIs is a serious concern for national health security, prompting the Indian government to set up a taskforce to review the internal API sector. Several key representatives from the pharmaceutical industry and NITI Aayog (an Indian government policy think tank) suggested that fostering the approvals of pharmaceutical infrastructure developments, clearance from the environment ministry and providing tax exemptions and subsidies for the development and promotion of the pharmaceutical industry hubs could all benefit the market. Made-in-India drugs supplied to developed economies are known for their safety and quality. In recent years, India has seen increasing competition from China, which it has been able to leverage due to its inherent cost advantage, manufacturing intermediates and APIs at a cost much lower than those in India.

In response to the COVID-19 crisis, India’s Union Cabinet has approved an investment package worth $1.3 billion to boost the country’s pharma and API production and cut dependence on China. This is a major step in the creation of a self-sufficient healthcare ecosystem in the country.

**Allowing deviation from protocol in clinical trials, the Indian government is looking to relax clinical trial rules in the country temporarily to let pharmaceutical companies develop a vaccine for the novel coronavirus.** In a notification, India’s Central Drugs Standard Control Organization (CDSCO) aid there are various challenges that might arise during the conduct of clinical trials in the wake of COVID-19.

The CDSCO notification adds that, since it would be difficult to adhere to all the protocol and regulations while conducting clinical trials of COVID-19 drugs in the country, researchers would be forced to make some modifications.

The regulatory authority said while the rights, safety and well-being of trial subjects were of paramount importance, protocol amendment, deviation or modification might be necessary in some cases. The CDSCO order was conveyed to several pharmaceutical majors to speed up the process. Companies and laboratories conducting the trials, however, will have to convey any protocol tweaks to the government, the notification added. Indeed, these relaxations shall be applied only to the COVID-19 trials. Health Ministry sources said no fresh approvals at this juncture would be given for clinical trials, except for those related to COVID-19.
The scientific community is working at full speed to fight the pandemic. Currently, both the Serum Institute of India and Cadila Healthcare are racing to develop a COVID-19 vaccine. Though attempts by both the firms are in the pre-clinical stage, human trials would eventually be conducted. The World Health Organization (WHO) has already shared a list of 44 candidates in global clinical trials. Only two of these are in Phase I, with the rest still in the pre-clinical stage. Scientists and policymakers from over 70 organizations globally have also called for an acceleration of research on COVID-19. Since the regulations in place for human clinical trials in India are very stringent, only 1.2% of such trials currently take place in the country.

CONCLUSION

In a time of economic regression and global health fears due to Covid-19, the reputations of pharmaceutical companies are on the line and their impact on the fight against the virus will not be easily forgotten. Regulatory agencies and pharmaceutical companies are rethinking their regulatory approval and drug development strategies. India’s leading drug companies have had their manufacturing facilities cleared in the last few weeks by the US Food and Drug Administration (USFDA), a decision that comes at a time when supply-chain disruptions due to the Covid-19 pandemic are causing drug shortages across the world.

India will undoubtedly continue to cultivate its position in the global pharmaceutical industry. It’s actively modernizing its supply chain. For example, in April it replaced its Drugs Authentication and Verification Application (DAVA) with the Integrated Validation of Exports of Drugs from India and its Authentication (iVEDA) portal.

As countries look to give their economies a much-needed stimulus in the aftermath of the COVID-19 outbreak, there is a huge opportunity for the Indian pharmaceutical industry to further stimulate its economic potential.

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ii https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/Pharma%20and%20Medical%20Products/PMP%20NEW/PDFs/778886_India_Pharma_2020_Propelling_Access_and_Acceptance_Realising_True_Potential.ashx

iii https://www.europeanpharmaceuticalreview.com/


v https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7156563/
