REVA Pharma
Caring for Healthier Lives

NEWS LETTER
For Private Circulation only

Regulators Come Knocking on The Doors of Drug Companies

The last few months have seen several drugmakers outline remedial measures that they are undertaking, following action by the US regulatory authority. The US Food and Drug Administration, and other local and foreign regulators, come knocking on the doors of drug companies to inspect manufacturing plants that make products soon to be sold in their respective countries. And it goes without saying, compliance is key, especially so for India, a major producer of medicines for multiple countries. But even a fleeting glance at recent statements to the stock exchanges reveal USFDA directives that range from serious import alerts, warning letters or OAIs (official action indicated) to "Form 483" observations. And the companies receiving these directives include Glenmark, Lupin, Sun Pharma, Cipla, Panacea Biotec and Jubilant Pharmova, to name a few. In fact, in August, Wockhardt said it was shutting down its Illinois plant in the US, and looked to continue making products for the region, by outsourcing its manufacturing. The site had received "483 observations" and warning letters from the USFDA and had entered into a Consent Decree with the Department of Justice which resolves and settles all matters with the USFDA, it had said.

Changing dynamics

A revival of USFDA and other regulatory inspections was expected this year, as Covid-19 linked travel curbs were eased. But warning letters and OAIs are directives that Indian drugmakers can ill afford, say pharma-industry veterans, given their global footprint and the changing world dynamics. There was a lull in inspections during the peak of the pandemic and there is a revival in inspections now, observes Sujay Shetty, PwC's Global Health Industries Advisory Leader. "But companies will have to up their game, as there is an increased focus on quality," he says, for multiple reasons. Less expensive generic drugs will become important, as Governments are faced with limited funds to spend. During the pandemic, several Governments have given onshoring support to local companies to make products locally, he says, to not be entirely dependent on foreign companies. And, the Gambia-incident, potentially linked to paediatric syrups made by a company from India, could also contribute to increased scrutiny.

Not just one-time

Industry-insiders, speaking off-record, point out that several large drugmakers in the country have been investing in quality compliance measures and many have been clearing regulatory inspections, as well. But compliance is not a one-time investment and requires continuous attention, they point out. Clarity is awaited on the deaths in Gambia being possibly linked to consumption of a product made from India, an industry-hand says. And while there's no taking away from the gravity of that issue, the lesson for Indian drug companies is to ensure that such incidents – involving possibly adulterated raw material and dodgy record-keeping - do not happen on their watch. It becomes a concern when all of industry is tarred with the same brush, without distinguishing between companies with established practices and the rest, they point out. Another fallout from this incident, is the concern on local regulatory inspections and how companies are able to slip through the cracks in the framework, says an industry-veteran, calling for strengthening of the Indian drug regulatory framework to build greater confidence.

Skills issue

In September, a Motilal Oswal Financial Services report indicated to a regulatory overhang for drugmakers looking to sell into the US generics market, as inspections revived. India witnessed 38 USFDA inspections over the 12-months (up to September), the report said. "Of these, four sites have received OAI (Official Action Indicated) citations. Around 18 inspections are awaiting citation (or an outcome) from the USFDA. Indian sites have received 60 OAI citations over Sep'19-Sep'22. Of these, 50 are yet to be re-inspected," the report said, pointing to unresolved OAIs.

India has about 665 production sites approved by the USFDA, the largest in the world.
But does it have to do only with a revival of inspections or is something amiss? A veteran regulatory-hand explains, it's largely a "skill issue" that results in large companies continuing to trip-up, despite the management's stated commitment to quality compliance. The more the products in the portfolio, the more complex it becomes, he says, adding that it requires repeated training of staff. In fact, companies are looking to take in trained hands with pharmaceuticals-linked qualifications and they are having regulatory requirements translated into the vernacular languages as well, to ensure that instructions are understood in their entirety, he added. Manufacturing continues to strive for less defects, across geographies, sectors and companies, says an industry-hand and on that count the pharma industry has its task cut out. Remediation efforts take time and that would delay product approvals from the said plant etc, impacting its operations and revenues. More importantly, though, this industry has to do with making medicines and saving lives. And that makes it all the more critical to have their operations upto scratch, he adds. (Source: Business Line)

Truth Seekers. Causality Behind Deaths In Gambia Being Investigated: WHO

The World Health Organization said the causality behind the death of 66 children in Gambia was being investigated, even as serious concerns persist on the presence of contaminants in paediatric cough syrups. About a month ago, WHO issued a medical alert on four cough syrups made by an Indian company (Maiden Pharma), following the death of 66 children in Gambia. Giving an update on the incident, WHO's Dr Mariângela Simão said the causality of the deaths and potential ingestion of the contaminated products was being investigated. However, she added, there was serious concern about on the presence of contaminants in the cough syrups. Similar cases were being reported out of Indonesia, as well. The UN health agency was trying to trace where the excipients came from, Dr Simao, WHO's Assistant Director-General for Access to Medicines, Vaccines and Pharmaceuticals, said at a media briefing.

The development comes even as media reports from Gambia indicate that a link was still to be established between the deaths and the cough syrups. Investigation against the company has been initiated in India as well. However, after early action in October, when the alleged contaminated products were red-flagged by the WHO, there has not been any follow-up information from the UN agency or the Indian regulator on the incident. Covaxin information Responding to another query on Covaxin, the Covid-19 vaccine from Bharat Biotech, Dr Simao said, they were awaiting information on the corrective and preventive action being taken by the manufacturer.Presently, the procurement of the vaccine for UN agencies stands suspended after a series of irregularities had been found in the good manufacturing practices, she said. The vaccine was in the news recently, over alleged discrepancies during the clinical trial. The company has not officially responded to the report. (Source: Business Line)

Pill To Prevent Pre-eclampsia Gets UK Fast Track For Development

A new pill that could prevent pre-eclampsia has become the first pregnancy drug to be fast-tracked for development by the UK's drug regulator. Scientists at MirZyme Therapeutics, a biopharmaceutical company, believe they have developed a drug that when given to women from 20 weeks of pregnancy could stop them developing the condition. Pre-eclampsia endangers the lives of thousands of expectant mothers and their babies in the UK each year, and has no therapeutic options. Globally, it affects between 2% and 8% of pregnancies and kills up to half a million babies and 100,000 women a year. MirZyme Therapeutics has been awarded an innovative licensing and access pathway (ILAP), or so-called innovation passport, by the UK's Medicines and Healthcare products Regulatory Agency (MHRA). The passport was established in January 2021 to expedite access to essential new drugs at the height of the Covid pandemic. It is granted to medicines that address the needs of patients with life-threatening and unmet medical needs, with a view to getting the drug to the market as quickly as possible.

MirZyme's new drug, MZe786, is a single pill to be taken once a day by women deemed at risk of the condition, from the 20th week of pregnancy. Pre-eclampsia is usually detected during the second half of pregnancy or soon after birth and can lead to serious complications if it is not found during midwife appointments. Early signs include high blood pressure and protein in the urine. It is thought to stem from an overproduction of a molecule from the placenta, which results in damage to the blood vessels of the pregnant woman. MirZyme claims to be the first company to develop products that can interfere with this molecule's production, offering the possibility for women to be able to protect their babies and in some cases themselves from the condition. When tested on mice, the drug was found effective in improving maternal and foetal outcomes, reducing blood pressure, preventing major organ damage in the expectant mother, improving foetal weight and decreasing foetal mortality. There were no detected negative side-effects on the mice or their offspring.

Archie Bland and Nimo Omer take you through the top stories and what they mean, free every weekday morning The treatment will be offered to women who are identified in the early stages of pregnancy to be at a high risk of developing pre-eclampsia. MirZyme has also developed a diagnostic tool that it says can accurately detect pre-eclampsia in a pregnant woman prior to being symptomatic. Prof Asif Ahmed, Mirzyme's executive chair, said he was confident that the company would be able to recruit women for trials of the drug. He said: "If you get pre-eclampsia, it's so devastating that women are prepared to take medication. We want to give pregnant women choices and we have a string of other drugs in the pipeline."

An MHRA spokesperson said: "The ambition of this new licensing and access pathway is to reduce the time to market for innovative medicines. The ILAP combines the MHRA's globally recognised strengths of independence and high standards of quality, safety, and efficacy, with improved efficiency and flexibility, readying the MHRA for a new era in medicines approvals in the UK." … we have a small favour to ask. Tens of millions have placed their trust in the Guardian's fearless journalism since we started publishing 200 years ago, turning to us in moments of crisis, uncertainty, solidarity and hope. More than 1.5 million supporters, from 180 countries, now power us financially – keeping us open to all, and fiercely independent. Unlike many others, the Guardian has no shareholders and no billionaire owner. Just the determination and passion to deliver high-impact global reporting, always free from commercial or political influence. Reporting like this is vital for democracy, for fairness and to demand better from the powerful. And we provide all this for free, for everyone to read. We do this because we believe in information equality. Greater numbers of people can keep track of the events shaping our world, understand their impact on people and communities, and become inspired to take meaningful action. Millions can benefit from open access to quality, truthful news, regardless of their ability to pay for it. (Source: The Guardian)

Study Suggests That HDL or 'Good' Cholesterol is Less Beneficial Than Previously Thought, Especially For Black Adults

High-density lipoprotein, or HDL, cholesterol – often referred to as the "good" cholesterol – may not be as useful in predicting the risk of heart disease and protecting against it as previously thought, according to new researched funded by the National Institutes of Health. A study from the 1970s found that high levels of HDL cholesterol concentration were associated with low coronary heart disease risk, a link that has since been widely accepted and used in heart disease risk assessments. However, only White Americans were included in that study.

Now, research published Monday in the Journal of the American College of Cardiology found that low levels of HDL cholesterol were associated with higher risk of heart attack among White adults, but the same was not true among Black adults. Also, higher levels of HDL cholesterol were not found to reduce the risk of cardiovascular disease for either group. "It's been well accepted that low HDL cholesterol levels are detrimental, regardless of race. Our research tested those assumptions," said Nathalie Pamir, a senior author of the study and an associate professor of medicine at the Knight Cardiovascular Institute at Oregon Health & Science University, Portland, in a news release. "It could mean that in the future, we don't get a pat on the back by our doctors for having higher HDL cholesterol levels."

The researchers used data from thousands of people who were enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. Participants were at least 45 years old when they enrolled in the program between 2003 and 2007, and their health was analyzed over an average of 10 years.

The researchers found that high levels of low-density lipoprotein (LDL) cholesterol and triglycerides "modestly" predicted heart disease risk among both Black and White adults. But they suggest that more work is needed to understand what's driving the racial differences in the link between HDL and heart disease risk.

And in the meantime, current clinical assessments for heart disease risk "may misclassify risk in Black adults, potentially hindering optimal cardiovascular disease prevention and management programs for this group," they wrote. CNN Medical Correspondent Dr. Tara Narula, associate director of the Lenox Hill Women's Heart Program, said the study "highlights the very important need for more race- and ethnic-specific research and that there is not a one-size-fits-all approach. Additionally, this research emphasizes the continued need to educate that high levels of HDL are not a free pass and focus must be placed on controlling elevated LDL and other known markers of increased cardiovascular risk. " (Source: CNN)

Indian Drug Firms Including Zydus, Aurobindo Pharma Recall Various Products in US Market

Indian drug firms like Marksans Pharma, Aurobindo Pharma, Zydus and Jubilant are recalling products in the US market, as per the latest enforcement report by the US Food and Drug Administration (USFDA). While Marksans Pharma is recalling diabetes drug, Zydus Pharmaceuticals (USA) is recalling drug which is used to reduce stomach acid. Similarly, Aurobindo Pharma (USA) is recalling pain relieving drug, while Jubilant Cadista is recalling a medication used to treat schizophrenia. As per the USFDA, Marksans Pharma is recalling close to six lakh bottles of diabetes drug Metformin Hydrochloride extended-release tablets in strengths of 500 mg and 750 mg in the US market. The medication lot has been manufactured at the company's Goa-based manufacturing facility.

As per the USFDA, the company is recalling the product due to deviation from the current good manufacturing practices (CGMP). "FDA analysis detected N-Nitrosodimethylamine (NDMA) impurity above the acceptable intake level," it noted. NDMA has been defined as a probable human carcinogen. Metformin Hydrochloride extended-release tablet is a prescription oral medication indicated as an adjunct to diet and exercise to improve blood glucose control in adults with type-2 diabetes mellitus. Various companies across the globe have announced similar recalls for the product after the USFDA pointed out presence of NDMA above permissible limits.

FDA's testing has shown elevated levels of NDMA in some extended release (ER) metformin formulation, but not in the immediate release (IR) formulation or in the active pharmaceutical ingredient. NDMA is classified as a probable human carcinogen based on results from laboratory tests. It is a known environmental contaminant and found in water and food, including meats, dairy products and vegetables. Further, the USFDA said Zydus Pharmaceuticals (USA) is recalling 14,748 cartons of Lansoprazole delayed-release orally disintegrating tablets due to failed dissolution specification.

The product has been manufactured by Ahmedabad-based Cadila Healthcare. The USFDA has classified the initiatives taken by Marksans and Zydus as class II recalls. As per the USFDA, a class II recall is initiated in a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Further, the US health regulator said Aurobindo Pharma USA is recalling 7,440 bottles of Ibuprofen oral suspension drug for labelling error. Besides, Jubilant Cadista Pharmaceuticals, Inc is recalling 23,616 blister packs of Olanzapine orally disintegrating tablets for being "subpotent", the USFDA noted. The recalled lot has been produced by Roorkee-based (Uttarakhand) Jubilant Generics. The US health regulator classified both the recalls as class III.As per the USFDA, a class III recall is initiated in a "situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences". (Source: IBN Live)

Vaccines Business Potential In A Post-COVID World

The COVID-19 pandemic has been a key catalyst to reinvigorate the global vaccines market as pharmaceutical companies, armed with deep expertise and tailored strategies, rediscovered vaccines as an important business. As there are massive unmet needs for certain infectious diseases around the world, especially in low and middle-income countries, which present a huge market with future growth potential. Pharma companies are bullish about what's next. Available data suggests that the global vaccines market is expected to grow to USD$125.49 billion in 2028 from $61.04 billion in 2021 at a compound annual growth rate (CAGR) of 10.8 percent largely driven by increased awareness about vaccination and immunization benefits in emerging markets.

According to Fortune Business Insights, the global vaccines market value was recorded at $55.4 billion in 2020. The opportunities are self-evident. Take, for example, Japan's Takeda Pharmaceutical's dengue fever vaccine Qdenga. The company recently announced that the vaccine has been approved and will be launched in the near future in Indonesia. According to reports, the pharma company expects to generate up to $1.6 billion in annual sales from the vaccine in about 30 countries. Another example is the British drugmaker GlaxoSmithKline. In June this year, the company announced that its respiratory syncytial virus (RSV) vaccine for older adults showed "statistically significant and clinically meaningful efficacy" during its phase three results. RSV is a common contagious virus affecting the lungs and breathing passages.

Every year, RSV causes over 360,000 hospitalizations and 24,000 deaths globally in adults. Currently, there are no vaccines or specific treatments for RSV, one of the world's major infectious diseases. Besides GlaxoSmithKline, a fleet of global pharmaceutical companies such as Pfizer, Moderna, Johnson & Johnson, and Bavarian Nordic—the only pharma company with an approved vaccine (Imvanex) for monkeypox—are all working on RSV vaccines for older adults. Increased awareness among patients for vaccine adoption post-pandemic has made pharmaceutical companies invest time, money, and resources in the vaccine business. Global pharmaceutical companies have realized the potential of a promising vaccine in a post-COVID world. This has led to redesigning research and development (R&D) facilities, ramping up manufacturing units, and acquiring niche pharma and biotech start-ups to strengthen the R&D pipeline and foster innovation.

Early this year, GlaxoSmithKline announced about $1.2 billion investment in its R&D over a period of ten years to boost its research work focusing on new vaccines and medicines to prevent and treat malaria, tuberculosis, HIV, neglected tropical diseases, and antimicrobial resistance, which accounts for more than 60 percent of the disease burden in many lower-income countries. Currently, the British pharma company's Global Health innovation hubs have a pipeline of more than 30 potential vaccines and medicines targeting 13 high-burden infectious diseases. Another key focus area for pharma companies is accelerating manufacturing units.

According to a Bloomberg report, Pfizer will likely pump in $470 million to expand its vaccine research facilities near New York City. The investment is expected to provide Pfizer "an edge" over the competition in the mRNA space, the technology behind its coronavirus vaccine. Pfizer aims to repeat its COVID-19 success by applying mRNA technology to other diseases. This August, GlaxoSmithKline acquired the United States-based start-up Affinivax to strengthen its research pipeline. Affinivax is developing a pneumococcal vaccine that offers protection against illnesses such as pneumonia, meningitis, and others. Pfizer's Prevnar and Merck's Vaxneuvance are already dominant in this space.

For developing countries, participating in this global research will also benefit the research community, allowing the public access to potential lifesaving vaccines, and developing a knowledge-based economy. The recent pandemic has increased the importance of vaccination to safeguard against infectious diseases. According to Airfinity, a London-based data firm, over 100 mucosal vaccines for COVID-19 are now in the development stage globally, and around 20 have reached clinical trials in humans. Recent data from World Health Organization reveals that the COVID-19 vaccination rates in low-income countries stand at 19 percent, compared to almost 75 percent in high-income countries. The roll-out of new lifesaving COVID-19 treatments, including oral antivirals in low and lower-middle-income countries, remains limited or non-existent. Recent data from World Health Organization reveals that the COVID-19 vaccination rates in low-income countries stand at 19 percent, compared to almost 75 percent in high-income countries.

The roll-out of new lifesaving COVID-19 treatments, including oral antivirals in low and lower-middle-income countries, remains limited or non-existent. If the government and private sector, including healthcare providers, local authorities, and logistics, work together, low-income countries will get vaccines for everyone. For example, an international organization named Gavi connects the public and private sectors to provide impartial and sustainable use of vaccines. And many other organizations and foundations can bridge the supply gap between wealthy and poor countries. Besides COVID-19, Southeast Asia observes many mosquito-borne infectious diseases such as zika, dengue, malaria, and chikungunya that have become rising public health concerns infecting millions of people. They provide a large market for vaccine manufacturers. According to the WHO, about 70 percent of the disease burden of dengue rests in Asia. Malaria causes an estimated 219 million cases globally, resulting in more than 400,000 deaths yearly. Seeing more room for growth, Japan's Takeda is also exploring a potential solution targeting the zika virus.

While the pharmaceutical majors have an entire value chain, such as R&D, manufacturing, distribution, and sales, every country is different. Smaller biotech companies only have part of the value chain. They, therefore, need to partner with larger players. Pricing is also a key factor for higher adoption among the masses. Vaccines promise a brighter future for everyone, and their successes start from the beginning by ensuring that the local population, including researchers and the public, are supportive of the research. Further strategy post-development, including leads to sales and adoption, will also depend on the type, pricing, and accessibility for the public. (Source: The Jakarta Post)