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A Case of Slipping Quality

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Touted as the Pharmacy of the World, Indian pharma is on a spree to launch new drugs and supply them globally. However, amidst launching new drugs, companies are failing to adhere to norms when it comes to maintaining the quality of the products where The United States Food and Drug Administration (US FDA) is keeping a hawk's eye on the drugs being manufactured. Stringent regulatory measures and keeping an eye on bribery/corruption are likely to have a positive impact on the quality measure being followed without fail.

The Indian pharma industry is somehow embroiled in controversies related to quality issues. Be it larger companies or smaller ones, the quality issue remains a major concern for companies more or less. Termed as Pharmacy of the World, quality-related issues related to deaths and other adverse events are taking a toll on the goodwill which is getting tarnished by these issues. Though pharma companies are taking steps to address the quality issues with certain measures, a harsh law in place will mean a lot for both the companies and patients alike.

Recalls & Adverse Events

The government of India has taken the issue seriously and started random testing of the drug samples manufactured by companies from across the pharma sector such as multinationals, local leading giants and small and medium scale pharma companies. Since December 2022 the Central Drugs Standard Control Organisation (CDSCO), India's national regulatory body for cosmetics, pharmaceuticals and medical devices, has increased the spot inspection of the pharma facilities to do sample testing.

Till May 2023, CDSCO on an average conducted 1300-1400 sample tests per month and issued notices to those including big pharma players to recall the poor quality or substandard medicines from the market. This noticeable action from CDSCO has resulted in drastic improvement in quality of drugs as companies started giving priority to quality issues. The number of 'not of standard quality' drugs has dropped from 70 in December 2022 to 27 in May 2023 with a case each of spurious drugs detected in April and May 2023 respectively. The action from CDSCO has to continue till the number of 'not of standard quality' drugs touch zero.

On the other hand the pharma companies both local and multinationals felt the pinch and started recalling the drugs from local and international markets. Baddi-based Magtech Enterprises Katha in Himachal Pradesh, was found producing fake diabetes medicines and multivitamins bearing the names of renowned pharmaceutical companies of Mankind and Intas Pharma. The medicines worth Rs 55 lakh bound for Delhi were confiscated in July 2023.

In June 2023, Hyderabad-based Bharat Biotech had to recall typhoid vaccine due to its poor quality. India's Central Drugs Standard Control Organisation declared a batch of Typbar typhoid vaccine "not of standard quality" after it failed standard testing. According to health officials, the levels of a particular molecule – O-acetyl – did not comply with national specifications.

The company in May 2023 also recalled pre-filled syringes of a drug, used to treat infertility in women, in the US market due to a manufacturing issue. It recalled 24,194 prefilled syringes of Fyremadel (ganirelix acetate) injection.

Also, Pfizer India in May 2023 has initiated a voluntary recall of certain life-saving antibiotics in the wake of quality concerns. In a letter to stockists, distributors and hospitals across India, Pfizer has asked for a temporary suspension of the sale and distribution of Magzex, Zosyn, Magnamycin injections and Magnex forte supplies. The recall follows technical issues at its contract manufacturing site.

In April 2023, Mumbai-based drug maker Abbott India, recalled a batch of Thyronorm tablets used to treat hypothyroidism due to a labelling error. There are reports that the batch was sold only in Madhya Pradesh and Telangana. The company has denied any quality issues.

Ahmedabad-based Zydus Lifesciences in March 2023, has recalled over 55,000 bottles of generic medication in the US market due to failed impurities specifications. The company recalled 21,936 (30 counts) and 33,096 (100 counts) bottles of Colchicine tablets, which are used to treat gout.

Dr. Reddy's Lab recalled over 4,000 bottles of generic drugs in the US. The Hyderabad-based drug major is recalling 4,320 bottles of Tacrolimus Capsules which are used to prevent the body from rejecting a transplanted organ in March 2023.

Chennai-based Global Pharma in February 2023 voluntarily recalled its eye drop from the US after it was linked to a drug-resistant infection. The eye drop has been linked to 55 incidents of infections, loss of vision, and even death due to the infection entering the bloodstream.

Lupin had to recall 5,720 tubes of a skin medicine over quality issues in February 2023, according to the US Food and Drug Administration (FDA). Lupin's US arm, Lupin Pharmaceuticals has recalled the tubes of Clobetasol propionate cream from the US market. The medicine was recalled after the US FDA found it to be of poor quality. The cream is used in the treatment of various skin conditions, such as dermatitis, eczema and psoriasis. The tubes in question were manufactured at Lupin's Pithampur plant in Madhya Pradesh. It may be noted that in January 2023, the company also had to recall over 16,000 bottles of generic tuberculosis drugs in the US citing manufacturing issues.

Mumbai-based Sun Pharma in February 2023 recalled over 34,000 bottles of generic drugs in the US after they failed the quality test. The company recalled lots of Diltiazem Hydrochloride extended-release capsules which are used to treat angina, high blood pressure, and some types of irregular heartbeats. The company produced the lot at its Halol-based manufacturing facility in Gujarat. The affected lot was later distributed in the market by its US-based unit.

In February 2023, Mumbai-headquartered Galentic Pharma was in news when there were complaints raised from at least five international buyers where the company was forced to recall all its tetracycline hydrochloride ointment batches from 2020 till February 2023.

Mumbai-based Macleods Pharmaceuticals in January 2023 recalled 10,052 bottles of Levofloxacin pills from the US market, according to the US health authorities.

Mumbai-based Aurobindo Pharma units have recalled various products in the US market for manufacturing lapses. In November 2022, the company recalled 9,504 bottles of Quinapril and Hydrochlorothiazide tablets due to manufacturing

lapses. This apart, Aurobindo Pharma said that the US Food and Drug Administration (FDA) conducted an inspection at Jawaharlal Nehru Pharma City, Parawada Mandal, Anakapalli District, Andhra Pradesh, from May 15 to 19, 2023 and the unit has received Establishment Inspection Report classifying the facility as 'Voluntary action indicated' (VAI).

It may be noted that in October 2022, the World Health Organisation (WHO) had issued an alert stating that four cough syrups exported to Gambia by New Delhi-headquartered Maiden Pharmaceuticals were of substandard quality. The cough syrups were linked to the deaths of 66 children due to acute kidney injuries in Gambia. However, the company denied any wrongdoing. The company had sought to reopen the plant after an Indian government lab mentioned that the cough syrups were safe. There were rumours that a local pharmaceutical regulator, in return for a bribe, helped switch samples of cough syrups that WHO had linked to the deaths of children in Gambia.

However, things are not the same now. The regulators have become strict in ensuring the quality of the drugs are safe for human consumption. A Sonipat court sentenced two pharmaceutical company executives of Maiden Pharmaceuticals to two-and-half years in jail for exporting substandard drugs to Vietnam a decade ago, in February 2023, months after the WHO linked their cough syrups to the deaths of children in Gambia.

Maharashtra Food and Drug Administration recalled a batch of the iron supplement infection Orofer FCM in November 2022. The FDA issued an order asking Pune-based Emcure to recall its product Orofer following the death of a 55-year-old man in Mumbai. However, in May 2023, the company launched Orofer FCM 750, a new extension of its parenteral iron brand containing Ferric carboxymaltose (FCM).

According to an Associated Press report, in November 2022, when three inspectors from the US Food and Drug Administration visited the Ahmedabad-based Intas Pharmaceuticals, they found hundreds of trash bags full of shredded documents tossed into a garbage truck. Over the next 10 days, the inspectors assessed what looked like a systematic effort to conceal quality problems at the plant, which provided more than half of the US supply of generic cisplatin and carboplatin, two cheap drugs used to treat as many as 500,000 new cancer cases every year.

New Jersey-based Glenmark Pharmaceuticals Inc, a subsidiary of a Mumbai-based drug firm, in August 2022 recalled over 72,000 units of blood pressure lowering drug due to 'blister package issues'. The lot was produced at Glenmark’s Pithampur (Madhya Pradesh)-based manufacturing facility.

In August 2022, Bengaluru-based Strides Pharma Science recalled 1,032 bottles of Prednisone tablets in the US, a medication used to treat many conditions, including asthma, allergic reactions, arthritis and inflammatory bowel diseases, among others. The company initiated the class-II voluntary nationwide recall on July 19 this year.

Cipla has recalled 7,992 bottles of Difluprednate Ophthalmic Emulsion in August 2022, used to treat swelling and pain after eye surgery, in the US market. The FDA stated that New Jersey-based Cipla USA, Inc, a unit of a Mumbai-based drug maker, has recalled the lot due to a 'lack of assurance of sterility'. Adding to it, Cipla announced that its wholly-owned subsidiary, Cipla USA Inc, has voluntarily recalled six batches of Albuterol Sulfate Inhalation Aerosol, 90 mcg (200 Metered Inhalation) in July 2023 that was manufactured in November 2021. This recall is being conducted with the knowledge of the US Food and Drug Administration. The company initiated a recall in the US due to a market complaint for one single inhaler (Batch Number - IB20056), where leakage was observed through the inhaler valve. And the list goes on.

Sharing his thoughts on these issues, **Girdhar Balwani, Professional Mentor & Independent Director, Cadila Pharmaceuticals**, says “I don't think that this is frequent. All pharma companies are expected to follow the specifications as laid down by regulatory authorities and internal requirements. Companies must follow good manufacturing practices. All products are released only after being checked for quality against the set standards. Apart from self-regulation, there are regular inspections by the drug inspectors appointed by the government to ensure that the manufacturing facilities, processes and quality assurance mechanisms and quality controls are in place. There are some cases wherein there is a deviation from the foregoing. In such cases, contaminated medicines may get into the market. These deviations are usually not intentional. In such a situation, a proper investigation needs to be done to find out the cause. Consequently, measures need to be taken to correct the situation and preventive action to ensure that this is not repeated.”

Digital innovation

Digital tracking of products is possible to ensure that the products are distributed under the required conditions of temperature and humidity. Any deviation can result in potential deterioration of quality and is subject to recall. One can also build a mechanism to ensure that counterfeits are tracked and appropriate action is taken against them. All this of course comes at a cost and the pricing mechanism should be considered. All wholesale and retail outlets are subject to not only self-regulation but regular inspection and certification by the regulatory authorities appointed by the government.

The Indian pharmaceutical industry is a global supplier of high-quality, affordable medicines throughout the world. This is well-recognised and respected globally. There are a few who do not follow the standards required in this industry. Such companies must be taken to task.

A database with the list of accredited vendors should be developed and manufacturers can use them for procuring the raw material. Implementation of automation has been shown to reduce the potential breach of data integrity as data trails are meticulously captured and any wrongdoing can be detected.

Manoj Saxena, President-elect, Organisation of Pharmaceutical Producers of India (OPPI) and Managing Director, Bayer Pharma, says “Prioritising patient safety and product quality is the prime objective of pharma manufacturers, which requires investing in robust quality management systems and conducting thorough risk assessments. Promoting a culture of compliance with global best practices such as Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) is important to ensure that manufacturing and distribution processes meet the required quality and safety regulations. The use of emerging technologies such as AI can enhance transparency, traceability, and accountability throughout the supply chain. In addition, continuous training and education, and proactive monitoring of manufacturing processes can help prevent issues and maintain high-quality standards. The sector must collaboratively work towards strengthening the ecosystem to ensure we continue to deliver high standards of quality.”

Regulatory issues

A weak regulatory mechanism in place is taking a toll on the drug manufacturing sector. Random bribery and getting things done through the backdoor have had a cascading effect on the reputation of India’s pharma sector.

Top management of Indian pharma companies also needs to understand the negative impact of poor-quality drugs. There are several cases where pressure to release batches comes from top management and thereby material with questionable qualities is cleared. In many cases, regulatory audits are not done regularly due to a lack of auditors and a lack of expertise among the auditors. Recruitment and training of auditors must be done on an urgent basis. Auditors should be empowered to take strict action against manufacturers who are compromising the quality of drug products and data integrity.

Talking on the sidelines at the 9th International Pharmaceutical Exhibition (iPHEX), **Dr Rajeev Singh Raghuvanshi, Drugs Controller General of India (DCGI)** stated, “Pharma, besides being a regulated industry, is also a knowledge-driven industry. If we put the purpose before the individual and follow a knowledge-based approach rather than focusing only on profitability, most of the quality issues and aberrations will get resolved. Today, the cost is offset by the quality towards increasing profitability. Unless quality is taken as the basic ingredient of the product, the issues around regulatory compliances cannot be taken care of."

Making his thoughts on the quality issue, **Ranjan Chakrabarti, Former Vice President and Global Biologics, United States Pharmacopeia, India** says, “I think price pressure is one of the major issues here. Most of the time, many of the old/traditional generics are sold at a very low profit and even at a loss. Thereby big companies have little interest in making them and they are switching to high-priced generics or preparing different quality materials for different markets. Several smaller companies are then taking up the manufacturing of these drugs. Unfortunately, many of them do not have enough financial strength, expertise and/or infrastructure to ensure the quality of the products. Another major problem is data integrity. In most facilities, the culture of strict data integrity is compromised, and they follow practices which raise several concerns about the integrity of the data developed. This is one of the major points in most of the 483s.”

Is there a way out?

Indian Pharmaceutical Alliance (IPA) during its recently held 8th edition of the Global Pharmaceutical Quality Summit in Mumbai, had the theme ‘Patient Centricity: New Paradigm of Manufacturing and Quality’. Speakers from key regulators such

as Drugs Controller General of India (DCGI), US Food and Drug Administration (US FDA), Medicines and Healthcare products Regulatory Agency (MHRA), European Directorate for the Quality of Medicines & HealthCare (EDQM), and others as part of the conference, shared their perspectives on observations on inspection, GMP, global regulatory view, resilience in end-to-end operations, and increased focus on quality compliance and excellence. Having said so, what can the pharma fraternity learn from the discussion remains a big question. On whether companies will follow the recommendations discussed during the event, only time will say.

Commenting on the issue, **Sudarshan Jain, Secretary General, IPA** says, “Quality is the fundamental tenet of the pharmaceutical industry. Quality should be imbibed as a culture across the supply chain and the verticals – right from senior leaders to floor/field employees. As processes and technology are evolving, the regulatory standards need to be aligned accordingly and implementation of Revised Schedule M. India should move towards membership for Pharmaceutical Inspection Co-operation Scheme PIC(s)/ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Capability building adept in both life sciences and technology skills will be critical. The industry-academia collaboration will be critical in this regard. Each manufacturer needs to ensure that there should be no compromise on the quality of the medicinal products manufactured by them. Raw materials play an important role in drug manufacturing; accordingly, quality should be ensured both at the raw material and final product stages. Indian Pharmacopoeia/Regulators can work with global Pharmacopoeias/Regulators in developing guidelines and specifications to ensure the quality of the raw material and the end products."

At present, there are three layers of testing – manufacturer’s Certificate of Analysis (COA), Central Drug Laboratories (CDL) testing and country-specific testing. Regulators should ensure that the testing guidelines are followed at each place and product specifications are met. Presently the percentage of products with compromised quality is very minimal as compared to the large volume of drugs Indian companies are exporting.

But there are disturbing trends and if action is not taken immediately, it can cause severe damage to the drug industry. The quality consciousness of both regulators and manufacturers needs to be enhanced. Scientists at the floor level should be regularly trained not only on scientific techniques but also on drug quality and data integrity. Regulators need to develop proper guidelines for testing with specifications, increase their audits and be strict when some deviations are noticed.

A decision needs to be taken on the pricing of the drug products. Due to pressure from governments, manufacturers are forced to sell their products at an unrealistic price. Affordability is important, but quality is supreme. The government needs to discuss this issue with manufacturers and address this.

Adding to it, the Government of India is trying hard to tackle the issue of pharma quality and taking serious note of it. The **Union Health and Family Welfare Minister, Dr Mansukh Mandaviya**, during the recently held meeting with pharma MSMEs appealed to pharma manufacturers to maintain the quality of drugs they produce. The minister while emphasising the role of MSMEs in making India ‘The Pharmacy of the World’ called for self-regulation in the MSME pharma sector. The minister assured that Schedule M would be made compulsory for the MSME pharma sector. Schedule M under the Drugs and Cosmetics Act, deals with the practices associated with the manufacturing of pharmaceuticals that must be followed in India.

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