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SCARCITY OF ACTIVE PHARMACEUTICAL INGREDIENT (API) DURING COVID-19 PANDEMIC: AN INDIAN CASE STUDY

Anil Kumar Patel
Research Scholar, Sunrise University, Alwar, Rajasthan

Dr. Manmeet Singh Saluja
Research Supervisor, Sunrise University, Alwar, Rajasthan

ABSTRACT

The pharmaceutical business is quickly becoming an important industrial sector due to the great promise it holds for the development of both novel therapeutics for the treatment of fatal illnesses and low-cost, high-quality generic equivalents. This industry is therefore not only accountable for providing the much-needed boost to the health of the society, particularly of the developing nations, but it is also a competitive but lucrative industry from a commercial standpoint. The pharmaceutical industry's current top priority is improving the standard of care, safety, and effectiveness of the drugs it produces and distributes worldwide. In the highly competitive pharmaceutical industry, a company's survival and success are directly tied to the quality of its products, the cost of its inputs, and the strength of the competitors in the market. On March 11, 2020, the World Health Organization (WHO) declared a worldwide pandemic due to the new coronavirus illness 2019 (COVID-19). The current epidemic has had an unacceptable effect on the health infrastructure and the pharmaceutical industry, which has ultimately led to tremendous problems in the daily lives of the patient population. The World Health Organization declared on March 11, 2020, that the new coronavirus illness 2019 (COVID-19) constituted a worldwide pandemic. The health industry and the pharmaceutical industry were both significantly impacted by the epidemic. These implications, both immediate and long-term, will need to be identified and properly planned for in order to lessen their societal and economic cost.

KEYWORDS: - API supplier selection; Pharmaceutical industry; API supplier change; COVID-19, Health and Government policy

INTRODUCTION

The months of April and October of 2020 were covered in this review of the relevant literature. The search engine returned results for a wide variety of alternative combinations of phrases, such as "active pharmaceutical ingredients," "coronavirus," "pharmaceutical industry," "COVID-19," "pharmaceutical raw material," "growth development index," and "future proposal of API industry." This investigation relied on current editions of academic journals, periodicals, and online media. Science Direct, Pub Med, the Web of Science, Scopus (free access to Medline), Google Scholar, and Google were among the electronic databases consulted. The most recent review research on API Scarcity during the coronavirus epidemic only utilised English-language sources. The stated sources in the articles were also verified for their authenticity.

APIs, or active pharmaceutical ingredients, are the chemical components of a drug. Take, for example, the active pharmaceutical ingredient (API) in a typical over-the-counter (OTC) drug used to treat minor symptoms like aches and fevers. Paracetamol, a drug used to treat pain and lower fever, is included in this product. The number of active pharmacological components in a fixed-dose combination has to be substantially higher than in a single-dose medication. Both inactive pharmaceutical ingredients (API) and active pharmaceutical ingredients (API) may be found in drug preparations. Both brand-name and generic drugs need clearance via the appropriate regulatory channels before they may reach the market. The generic equivalents of brand-name pharmaceuticals are safe and effective in the same ways. The USP has created a guide called the "USP pharmaceutical ingredient supplier qualification programme" to make it simpler to choose API providers. In light of the prohibitive expense of many brand-name pharmaceuticals, the procedure for approving generic versions of these drugs was established. There is a lot of competition in the generic drug market because all of the approved generic drug products are very similar to the innovative drug product. However, the price at which the generic drug product can be purchased is a major factor in allowing the generic drug product manufacturer to acquire a sizable portion of the market. The price of the active pharmaceutical ingredient (API) has the biggest bearing on the retail price of a generic medicine. The effectiveness of a generic medication also depends on the API's chemical and physical properties. Therefore, it is crucial for makers of generic medications to exercise caution when selecting both the API material and the API supplier they will use. Choosing an API provider is crucial in the development of generic pharmaceutical products since few generic pharmaceutical businesses develop their own APIs. Maintaining a reliable, long-term strategic relationship with API suppliers may help drug product makers get early access to high-quality active pharmaceutical ingredients and negotiate reduced pricing in the fiercely competitive generic market.

Generic medication producers face a number of challenges when trying to source a reliable API supplier. Quality and good manufacturing practises (cGMP) rules set by regulatory bodies throughout the globe have gotten increasingly stringent in recent years. Manufacturers of APIs frequently revise the CMC as part of their dedication to minimising production costs without compromising quality. Most API producers are well-versed in Good Manufacturing Practises (GMP) and adhere to the guidelines outlined in ICH (international conference on harmonisation) Q7. Quality control, change management, and laboratory quality control have long been staples in API manufacturing plants. GMP inspections have shown, however, that numerous API producers are still fighting an uphill battle to achieve and maintain long-term GMP compliance. Due to issues with laboratory controls, quality systems, equipment, records, and reports, the vast majority of producers of generic pharmaceutical goods have failed Good Manufacturing Practise (GMP) inspections.

The World Health Organisation (WHO) officially classified the COVID-19 infection as a worldwide pandemic on March 11th. It is estimated that 2.5 million persons would have contracted COVID-19 globally by April 23, 2020. The pharmaceutical industry was one area of the economy hit hard by the spread of COVID-19. In spite of the lack of a cure for this uncommon infection, the pharmaceutical industry is helping governments meet the unmet needs

associated with COVID-19 by exploring new treatment options and maintaining a steady supply of existing drugs. As the ultimate objective of any pharmaceutical system, providing citizens with access to low-cost necessary drugs has become increasingly difficult in the face of the current pandemic.

LITERATURE REVIEW

Food and Drug Administration (2012) The FDA's guidance guideline for the development and manufacturing of drug substances, known as Q11, has been released to the public. The ICH (International Conference on Harmonisation) commissioned the report as part of its effort to standardise the regulatory processes involved in the production of pharmaceuticals intended for human consumption. Guidelines for completing the different sections of the Common Technical Document (CTD) and methods for designing and analysing a drug substance's manufacturing process are provided. The purpose of the recommendations is to harmonise the three areas' methods of disseminating and evaluating data related to the discovery, development, and production of pharmaceuticals (both chemical entities and biotechnological/biological entities). The concepts presented in the guideline are only relevant to the manufacturing of drug ingredients, not finished drug products.

Aiba née Kaneko M et.al. (2015) Genotoxicity is a common endpoint used to determine whether or not a substance is carcinogenic. The International Conference on Harmonisation (ICH) M7 Guideline on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk provides guidelines on (quantitative) structure-activity relationship ((Q)SAR) methodologies that predict the outcome of bacterial mutagenicity assay for actual and potential impurities. Using a dataset of 342 chemicals culled from the literature, we examined how well the (Q)SAR approach works when DEREK NEXUS, an expert rule-based system, is combined with ADME Works, a statistics-based system, to predict not only mutagenic potential in the Ames test but also genotoxic potential in the mutagenicity and clastogenicity tests. DEREK NEXUS and ADME Works both had high sensitivity and concordance values when predicting mutagenic or genotoxic potential, but the combination of the two methods (battery system) had the highest sensitivity and concordance values. However, it also had the lowest specificity value. The amount of false negatives was reduced by using the battery technique. Of these 342, 41 are found in cosmetics and are listed in the International Nomenclature for Cosmetic Ingredients (INCI), for which we developed predictions about their mutagenic and genotoxic potential. The battery system's low specificity was more than made up for by its great sensitivity and consensus. These findings provide credence to the idea that the DEREK NEXUS and ADME Works battery system may reliably predict the genotoxic potential of chemicals, including those used in cosmetics.

Valerio LG Jr et.al. (2015) Prevention and reduction of human exposure to any genotoxic pollutants discovered in the therapeutic components or final products should be a primary focus of preclinical safety investigations of innovative medicinal products. According to the FDA's draught guidance on genotoxic and carcinogenic impurities in drug substances and products from 2008, computational quantitative structure-activity relationships (QSAR) are allowed for the

purpose of identifying structural alerts for known and expected impurities present at levels below qualified thresholds. This study provides toxicologists with fresh information that may be used to develop in silico toxicology models for predicting the mutagenicity (Ame's test result) of drug impurities and other chemicals. We comprehensively assess its prediction capacity by cross-validation and external validation tests, as well as case studies, and present a full analysis of the model's chemical make-up and toxicity fingerprint in terms of compound space, molecular and structural toxicophores. The model was externally evaluated using 2368 additional compounds known to produce mutations that were not included in the original model. This demonstrated the model's sensitivity (81%) and negative predictivity (81%) are compatible with the regulatory purpose that was intended. When a database of drug impurities was built using FDA filings and public media, it was found that there was substantial overlap between the structural features of medicine impurities and training set chemicals. For the goal of assessing whether drug impurities are mutagenic to Salmonella, the model's prediction performance was deemed to be good.

Wollein U et.al. (2012) Here, we provide a sensitive, fast, and practical GC/MS method for the concurrent detection of methyl mesilate (MMS), ethyl mesilate (EMS), isopropyl mesilate (IMS), methyl besilate (MBS), and ethyl besilate (EBS) in pharmaceutical products. The samples were processed through liquid extraction. The analytes were loaded into the chromatographic equipment together with an internal standard made of methyl tosylate (MTS), and the results were recorded using isocratic standard time and distance (ISTD). All of the alkyl and aryl esters may be detected with excellent sensitivity at the usual target analyte level (EMA), meeting the acceptance requirements given in the European Medicines Agency's Guideline on the Limits of Genotoxic Impurities, published in 2007. There was a minimum average recovery of 71% for methanesulfonic acid esters (mesilates), and a minimum average recovery of 94% for benzenesulfonic acid esters (besilates). A linear range with an R2 of 0.9998 was discovered between 0.01 and 1.33 g/ml. The method was first confirmed using a sample matrix consisting of APIs as mesilate salts (Bromocriptinemesilate, Doxazosinmesilate) and then verified with finished products including these salts at therapeutically relevant concentrations (MMS, EMS, IMS, MBS, and EBS).

Koenig SG et.al (2019) To improve APIs' sustainability and competitive pricing, the pharmaceutical industry has partnered with contract providers for several areas of the supply chain. It's possible to save money by going this method, but there are also some logistical hurdles to overcome. On the other hand, it opens up possibilities for green chemistry and engineering to more fully include sustainable science. The Green Chemistry Institute at the American Chemical Society (GCIPR) provides a multi-sectoral viewpoint on how to strengthen the pharmaceutical industry's long-term sustainability in the face of increasing challenges and expenses.

IMPACT OF COVID-19 PANDEMIC

It has become apparent that there is a major shortage of active pharmaceutical ingredients (APIs), which are needed in huge amounts in the creation of medications and other medical supplies, as the world fights to contain the spread of the coronavirus pandemic. India's pharmaceutical industry relies heavily on the country. The majority of India's APIs are produced

using materials brought in from other nations. The COVID-19 pandemic issue has resulted in periodic lockdowns in both countries, substantially impeding international supply and export-import. Bilateral relations between the two countries are becoming more tense. As a consequence, these problems are all contributing to India's APIs shortage.

India is especially vulnerable since it is a major supplier of raw materials for numerous pharmaceuticals, including those used to treat HIV/AIDS, cancer, epilepsy, malaria, and even common antibiotics and vitamins. Experts are concerned that the coronavirus might trigger a scarcity of cardiovascular and antibacterial medicines. To the tune of over 60%, active pharmaceutical components including cephalosporins, azithromycin, and penicillin are imported to supply the needs of the local pharmaceutical industry. Given that 90% confidence is possible. Contamination concerns and other supply-side bottlenecks are seen as primary drivers of certain medicine shortages.

As a result of the COVID-19 pandemic, drug costs soared. The cost of penicillin's main component, for instance, jumped by 40 percent in only one month. As of the time this article was written, the price of the active pharmaceutical ingredient (API) penicillin had risen to Rs. 639.00 ($8.69) per unit from Rs. 454.00 ($6.16) in January 2020, according to data from the Pharmaceutical Export Promotion Council (PHARMEXCIL), which is part of the Ministry of Commerce and Industry. Antibiotic active pharmaceutical ingredients (APIs) such Azithromycin, Doxycycline, Amikacin, Ornidazole, Dexamethasone Sodium, etc., are mostly imported into India, and current data from API makers suggests a 13-18% rise in price. In January, the price of API paracetamol, often used to treat pain and fever, increased by 26%.

More than 50 active pharmaceutical ingredients (APIs) of essential medications, vitamins, and hormones or steroids may become unavailable in the event of a prolonged lockdown in India, according to the Indian regulatory authority. The cost of 'Montelukast sodium' (an anti-asthmatic medication) has risen dramatically over the last several months, from a range of Rs. 33,000 to Rs. 38,000 ($447.99-$515.87) per kilogramme. Similarly, the price of vitamins and antibiotics has increased by more than 40 percent, with many vitamins now selling for two or three times their original price. It is possible that the companies may exhaust their supply of active ingredients if demand is very strong. This is because the majority of these components are created in the province, the initial centre of the COVID-19 outbreak. From all around the world, India has imported APIs valued about Rs. 17,400 crores. There are between 30 and 40 distinct types of APIs, basic compounds, and intermediates.

The Indian government has raised the price cap for essential medications like heparin by 50% till the end of 2020. For quite some time, patients at risk for developing lung, heart, or other blood clots have been treated with heparin, an anticoagulant or antiplatelet drug. Stroke, heart attack, and pulmonary embolism prevention is its major focus. Patients in critical care who require kidney or dialysis transplants often get this medicine.

During the pandemic, the Ministry of Health and Family Welfare (MoHFW) that the medication be used in intensive care units (ICUs) treating patients with Covid-19. Despite this, allegations of

drug shortages in the middle of the outbreak have surfaced. The National Pharmaceutical Pricing Authority (NPPA) has been granted emergency powers to implement paragraph 19 of the Drugs Prices Control Order (DPCO), 2013. Since December 2019, the price of medicines that fall within NPPA's price limits has increased by an average of 50%. Twenty-one drugs, including several primary therapies, have seen price increases. These pharmaceuticals are essential to many public health initiatives.

Table 1: World-wide impact of COVID-19 on the pharmaceutical sector

Impact			Middle East	EU Countries	United States	Reference
Short term impact	Induced Demands and Medication shortage	Covid-19 related	↑in10% of OTC category (cold and cough) drugs	↑ in10% of OTC category (vitamins, minerals, etc.)	Investigational treatments have seen a 2-fold ↑	21
			↑403% in Personal hygiene	↑in 62 % of personal hygiene	Medicines used in hospitals for the treatment of Covid-19 have ↑ between 100% and 700% since January 2020	
			↑in67% of ICU medications			
		General like Panic buying	↑in23% of Lipid-lowering drugs	↑in7% of highest volume growth in ATCN class of Rx-category in Spain	Excess of prescriptions for hypertension-7, Mental health-6, Respiratory-5, Diabetes-4 (in million)	
			↑in40%of Anti-diabetes drugs	-	-	
			↑in29.1% of antihypertensive drugs	-	-	
		Shortage of supply	Medicines for chronic diseases were at high risk of shortage or supply chain.	-	The supply shortage of both active APIs and finished products	
		-	-	-	The supply shortage of Covid-19 related complications treatment	
	Research and development Shifts		156 clinical trials are running for Covid-19	140 clinical trials are running for covid-19	-	
	Shifts towards telemedicine	WhatsApp call is the most preferred digital channel for both communications	↑ in 320% (v. PY) in remote interactions in Spain. The ↑in Italy (v. PY) was 471%	70-80% ↓in the number of patient visits to doctors	-	
	-	Digital channel has wide adoption with over 75%	↓ in 51%in specialist consultations and ↓in 25 % in GPs visits	Tele-medicine growth accounts for 23% of interactions	-	
Wide impact	Approval delays (Non-Covid-19 products)	Clinical trial 8% delay existing enrolment	Pharma companies report a delay in new trial starts	-	-	
	-	16% delay new trials only 32% delay new trials and existing patient enrolment	Product launches delayed, disrupted, or impacted	-	-	
	Shifts towards self-sufficiency in the pharma industry	-	Direct investment and free movement of capital	-	-	

v. PY: versus Previous Year, APIs: Active Pharmaceutical Ingredients, OTC: Over the Counter, ATCN: Anatomical Therapeutic Chemical Classification Nervous system, GPs: General Practitioners, RandD: Research and Development, ICU: Intensive Care Unit, EU: European countries, ↑: Increase, ↓: Decrease.

The tuberculosis (TB) vaccine Bacillus Calmette-Guerin (BCG), vitamin C, antibiotics like metronidazole and benzylpenicillin, anti-malarial drugs like chloroquine, and leprosy treatment drugs like dapsone are all examples of critically important pharmaceuticals. India is the primary

supplier of the active pharmaceutical ingredient (API) used to produce heparin injections. This means that if there is a disruption in the supply chain, medicines made in India may not reach the rest of the globe. This crisis threatens the availability of medicines in any nation that buys them from India. Paracetamol, erythromycin salts, vitamins B1, B6, and B12, acyclovir, and progesterone are just some of the medicines that companies have reported having trouble obtaining a no-objection certificate (NOC) to import. There was a severe COVID-19 pandemic lockdown in effect at the time in the nations that source the bulk of these APIs. The effects of the COVID-19 pandemic on the pharmaceutical industry are shown in Table 1.

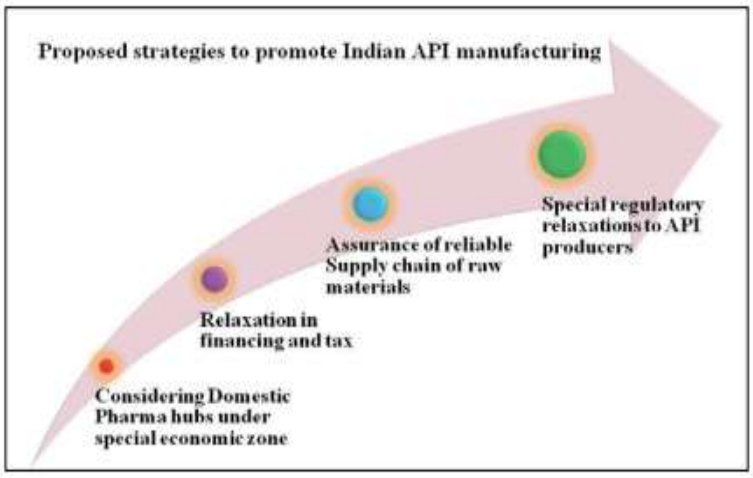

Fig. 1: Proposed future strategies to make self-resilient India in API manufacturing

The Indian pharmaceutical industry has to quickly develop and implement a solid strategy to deal with the dramatic increase in API prices seen during this epidemic. First, policymakers should establish intermediate goals. The current domestic players need to be nurtured and rewarded so that they can compete on a global scale. More startups and manufacturers will enter the domestic pharmaceutical market if regulations and other barriers to entry are reduced. The long-term goal should be to become financially independent within the next three years. In such a case, the government should order the relevant agencies to speed up policy implementation according to a predetermined schedule [fig. 1]. The appropriate State Governments must also take the necessary steps.

Telangana, Haryana, Gujarat, and Himachal Pradesh are just a few of the states whose governments have started allocating land for pharmaceutical production on a massive scale. Now is a good time for businesses to begin building infrastructure. It is also necessary to take additional steps to help businesses succeed, such as providing tax breaks and gaining early clearance from various pollution boards and other authorities. Policies should be uniform throughout the country's many states. The primary objective is to implement everything very rapidly to have a significant positive impact within the next several years. It's also important to stress that the government's attempts to elevate India to the status of API industry superpower shouldn't end with COVID-19.

The establishment of an all-conducive supply chain in our country demands decisive and forceful action. This will help to boost domestic output and find ways to become less reliant on imported goods and ideas. In order to increase raw material production and promote the return of more API manufacturing inside India, the Indian government has given targeted financial incentives. The Union Cabinet of India has lately taken the brave step of building three API parks with shared utilities, identifying and reducing dependency on, and adopting the Production Linked Incentive (PLI) programme, all in an effort to further emphasise India's objective of self-sufficiency. The government should make efficient use of the existing API units. Lack of distribution points and medicine accessibility continue to be obstacles despite pharmaceutical companies' best attempts to expand into the domestic market. Medicine costs will decrease as a result of rising incomes and more access to health insurance. Government-funded programmes and healthcare services need more funding to expand into rural areas. Economic growth has to be bolstered in order to raise disposable incomes and pay for healthcare system upgrades. Due to the high demand for COVID-19 vaccine and medical equipment in the Indian market, numerous countries have begun investing in India's pharmaceutical industry, providing the country with a unique chance to achieve complete pharmaceutical independence.

CONCLUSION

Given the present and projected growth of the API industry, innovative business models are desperately needed to bring pharmaceutical prices in line with local production costs. Our country requires international and bilateral cooperation, the provision of emergency services, the removal of barriers to exports and imports, and the settlement of issues relating to taxes and customs charges in order to recover from the present economic and social crisis. Since people's health is at the centre of this pandemic, it will need international cooperation to develop a solution that works for everyone. Generic pharmaceutical product manufacturers put a high value on selecting an API supplier early in the development phase to guarantee that their final medicinal product is of high quality and compliant with international regulatory laws. Generic drug manufacturers who also develop APIs are not obligated to take part in the transition to a new API provider. However, those who want to have generic versions of products approved should use scientific approaches, such as doing comprehensive risk evaluations of API features, critical qualitative attributes, and materials. To help you decide between main and secondary APIs, this website contains the technical information, regulatory discussion, and samples you need. It's possible that a generic pharmaceutical product's API provider might switch at any point during development or thereafter. It is now more important than ever that all national leaders unite behind a unified health care agenda and forge partnerships with a wide range of healthcare organisations.

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