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REVIEW ARTICLE

A brief insight to Pakistan's Pharmaceutical industry- A critical review study

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ABSTRACT

Aim: This is a review article, which focused upon Pakistan's pharmaceutical industry. This industry has fallen into the trap of our country's buckwheat. Basically, it's the main concern of pharmaceutical industries of Pakistan, one of the present standing position or top most sold products.
Method: This is a comparison between industry from start to form or global level. It has been a detailed review of Pakistan's import and export products over the years. This article gives an overview on APIs, how they are synthesized and major exporters of APIs. Drugs formulations are also discussed in it. Formulation of drugs are solid, liquid and semi solid. Moreover, it also focused at the limitations and strengths of the factors that are important in determining the strength.
Results: The pharmaceutical business has a strong capacity for innovation, and governments should conduct studies and encourage discussion on how to improve this capacity without endangering public health.
Practical implication: The strength of each pharmaceutical industry based upon quality goods, providing values, services excellence.There are concerns about the current rules in Pakistan for evaluating the quality of pharmaceuticals raw materials (APIs).The pharmaceutical industry strengths could include low operating overhead, firm fiscal management, low staff turnover, high return on investment (ROI), state-of-the-art laboratory equipment and an experienced research staff.
Conclusion: The medical system in a country is crucially dependent on the pharmaceutical sector. This study's goal was to shed light on Pakistan's entire pharmaceutical sector, including startups, imports, exports, and detail of APIs. The pharmaceutical industry in Pakistan is still in its early stages, but it has managed to establish a small presence in Asia-Pacific market.
Keywords: Brands, Ointment, ROI, spurious drugs and PIDB

Graphical abstract:

INTRODUCTION

After world war two there is a need of high consideration to pharmaceutical industry. It needed more and more research to invent new drugs[1]. Pharmaceutical industry is basically involves in the manufacturing and development of medicines and drugs by different organization controlled by private sector. The contemporary pharmaceutical industries are based on different processes such as separation as well as purifying the chemical compounds, formation of different compounds and drug design done through computer is basically started from 19th century, after thousands of experiments humans believed that plants, animals and minerals are great sources of medicines[2]. The integration of research in different fields such as chemistry and physiology enhanced the learning and recognizing of drug based procedures[3]. Medicine reach to the patient after passing through the following steps as represented in figure 1.

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Figure 1: Supply and discovery of drug

Nowadays, different challenges are faced by the pharmaceutical industries such as pointing out the new drug, achieving the acceptance from the agencies run by the government and different purifying techniques in the drug advancement. Enhancement and achievement in the pharmaceutical industries is the best way to stop and discard the different diseases all over the world. Basically the improvements in pharmaceutical industries took place in early 16 and 17th centuries[4]. The first collection of list of different drugs and chemicals with medicinal properties with proper instructions for preparing pharmaceutical chemicals were materialized in 1546, in Nurnberg, Ger. Other collections took place in Basel in 1561, in Augsburg in 1564, in London in 1618. The collection of London embellished legally for the England and thus embellished as a national collection of list of drugs[5]. The pharmaceutical industries has established themselves many times. Globally, the industry may be differing but the procedures of working may be similar at some points, every industry has its own rules and regulations. It is reported by the pharma letter that the worth of pharmaceutical industry in 2019 was to be 1.3 trillion dollar all over the world[6].

History of Pakistan: Pakistan is a country with low expenditure, established in South Asia at the junction of Middle East and

Central Asia, having an area of 770880.0 sq. km. Pakistan is the 6th most populated country along with population of 199 million. It is anticipated that the population of Pakistan may be increase 254.7 million by 2030 and 344million by 2050. The percentage of population living in urban areas is 38% and the percentage of population living in rural areas is 62%[7]. Pakistan is the emerging country with the GDP (gross domestic product) rate of 4.24% in 2014-2015. However, the GDP rate may be varied with the time. According to the resources of World Bank the GDP rate between 1961 and 2014 is considered to be 5.18% with a minimum value of 0.47% in 1971 and maximum value of 11.35% in 1970. In 2014 the rate of underemployment of country was to be 5.2%. Pakistan strictly pursued the health system established by the British between 1947 and 2011[8]. Nowadays, the healthcare system consists of three phases including primary, secondary and tertiary care. Primary care was provided by the lady health workers (LHW), the basic health units (BHUs) and rural health centers (RHCs). The tehsil headquarters hospitals (THQH) and district headquarters hospitals (DHQH) stated the secondary care. Tertiary care is usually stated by the hospitals located in the areas where the population rate is usually high. Pakistan is basically the emerging country so a lot of attempts and principles are developed to make the health system in Pakistan better[9]. A latest report released by Asian bank development said that GDP rate of Pakistan will shrink to 2.6% to 3.3%, while in 2020 expansion will be around 11.5%. Latest GDP data is represented in graph in figure 2[10].

Figure 2: GDP rate of Pakistan from 2018-2021

Startup of pharmaceutical industry in Pakistan: In Pakistan pharmaceutical industry established after many years. At the time of Independence, traders of Pakistan usually import medicines from different countries as there is no pharmaceutical industry in Pakistan (11)The main reasons behind that were having no knowledge about the techniques used in pharmaceutical industry, shortage of material, and deficiency of quality control. After understanding and acknowledging the importance of this industry Pakistan Government developed two units under the instructions of Pakistan Industrial Development Board (PIDB) namely Khurram Chemicals Limited near Islamabad and Antibiotics Private Limited in Mianwali[12]. The pharmaceutical industry history comprised of three stages. The first stage started from 1948 to 1971. The pharmaceutical industry made a lot of progress during that time period. The second stage started from 1972 to 1991, because of restriction polices the pharmaceutical industry faced a great loss and lost its position in the market. The drugs and medicines related to genes were less effective and having low quality. Due to all these reasons the industry lost its rank in the market[13].

Establishment of pharmaceutical industries in Pakistan: In Pakistan, pharmaceutical industries emerged in a long way. At the time of independence, there is no pharmaceutical industry and most of the medicines are imported by the traders of that time. This is because of no quality control, absence of most of raw materials and mainly the lack of technical knowledge[14]. Once the government recognized the importance of pharmaceutical industries, under the supervision of Pakistan Industrial Development Board two units were established:

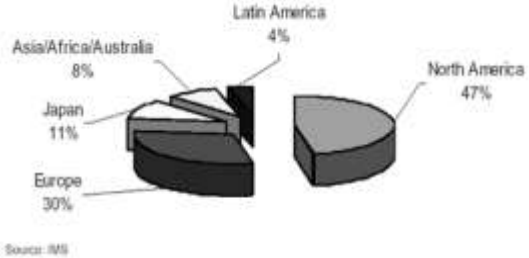
- Khurram Chemical Limited near Islamabad.
- Antibiotic Private Limited in Mianwali.

Three phases can be observed in the history of establishment of pharmaceutical industries in the Pakistan. The first phase is started from 1948-1971. It continuously grows up to 1971. Due to its capabilities industry arrived to its top at that time and had influence position in Asia[15]. The second phase is from 1972-1991.In 1972 drug generic act came into being. Due to this companies bear the more because of poor efficiency of generic drug.1991 is the start of the third phase and still is present. The command of multinational companies in pharmaceutical market of Pakistan was brought out in 1996 by Mehdi and Kalani[16]. In 1993 rates of drug increased about 400% due to deregulation policy that is under the supervision of government. In 1990s prices were reduce by the federal government. Prices of imported material were fixed by the government under a policy. It produce a rapid development in national companies and they compete the multinational companies[17]. Below is the timeline of pharmaceutical industry of Pakistan.

Figure 3: Establishment of pharmaceutical industry in Pakistan

Global pharmaceutical industries: In the world, pharmaceutical industry is ruled by multi-national corporations which includes America, Canada, Japan, Europe and Latin America. Research and development in the field of pharmaceutics is mostly done in North America[18]. Prior to a brief overview to pharmaceutical market in Pakistan, have a look in this field world-wide. The whole global Pharmaceutical market has a value of 650 billion US dollars (2008-09), along with growth rate of 8% annually and continue with this rate it will certainly surpass the value of 1.1 trillion US dollars by the year 2014. Globally, the market is ruled by USA, EU and Japan with a share of 48%, 28% and 12% respectively1[9].

Figure4: Pharmaceutical global sales (%)



Pakistan pharmaceutical market: As most of the industries in Pakistan are ruled by private sector, the pharmaceutical industry also depends on many factors. These factors may be political, social or economic level[20]. These factors can be used as fortuneteller of the situation of the industries dominated by private sectors. Pharmaceutical industry is also one of them. This industry faces many challenges and competitions. Among 750 registered pharmaceuticals units in Pakistan, 400 produced active finished drugs which also include those 24 units run by multi-national companies[21]. In Pakistan, multi-national (MNC) and national units are working with a ratio of 2:3. GSK, a multi-national with 11.60% while among national Getz has a market share of 3.75%[22]. Here are the top ten pharmaceutical companies of Pakistan.

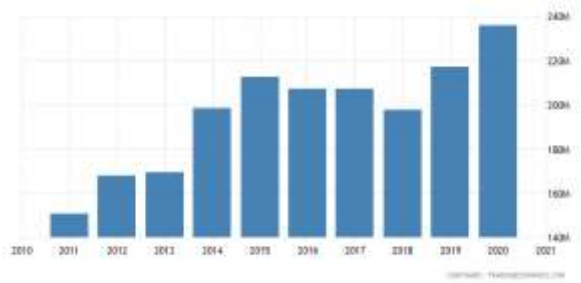
Figure 5: Top 10 pharmaceutical industries in Pakistan

Although 80% of local market demand is fulfilled by Pakistani industries, however about 90% active ingredients used for manufacturing of medicines is imported[23]. The picture has completely changed in terms of pharmaceutical industries in Pakistan in comparison to past history. In times of early nineties, MNCs are leading the Pakistan pharmaceutical industries with 30 out of 386 units are multi-national. But now the rate is 45% and 55% for MNCs and national companies. It is a point of hope for local investors[24]. Today, total volume of the Pharmaceutical market of Pakistan is 1.64 billion US dollars, with growth of 11% annually, more than the growth of the Pharmaceutical industry globally[25]. Pakistan's US dollar 1.64 billion pharmaceutical market is the 10th largest in Asia Pacific, behind the Philippines (US dollar 2.58 billion) and ahead of Vietnam (US dollar 1.53 billion). Per-capita spending on medicine is US dollar 10 annually, which is far less than the regional average of US dollar 14[26]. The registration of new medicines and new manufacturing sites is controlled by The Drug Regulatory Authority of Pakistan (DRAP). It also works to determine the Maximum Retail Price (MRP) of all medicines marketed in Pakistan[27]. The Pakistani Pharmaceutical market is mainly an out-of-pocket market means that healthcare spending mainly comes from personal savings of individuals, however the government is providing free or low cost treatment in government hospitals and clinics[28]. Top five trading brands of medicine are representing in figure 6.

Figure 6: Top 5 using brand of medicine

Pakistan export of Pharmaceutical products: Pakistan Exports of pharmaceutical products was US$235.75 Million during 2020, according to the United Nations COMTRADE database on international trade. Pakistan Exports of pharmaceutical products - data, historical chart and statistics - was last updated on October of 2021[29].

Figure 7: In Pakistan year wise export of pharmaceutical products



Pakistan's exporters:

Table 1: Pakistan's exporters of pharmaceutical products

Countries	Million US dollar
Germany	96,888.63
Switzerland	81,188.31
Ireland	52,547.34
United states	52,537.48

Pakistan imports of Pharmaceutical products: Medicinal and Pharmaceutical product was reported at 507,230.454 USD in Dec 2020. This records a decrease from the previous number of 544,918.220 USD for Dec 2019. Imports data is updated on yearly basis, averaging 279,917.508 USD from Dec 1995 to 2020 after 26 observations. This data reached an all-time high of 568,548.231 USD in 2018 and a record low of 95,863.192 USD in 2002. Medicinal and Pharmaceutical product data remains active status in CEIC and is reported by United Nations Conference on Trade and Development[30].

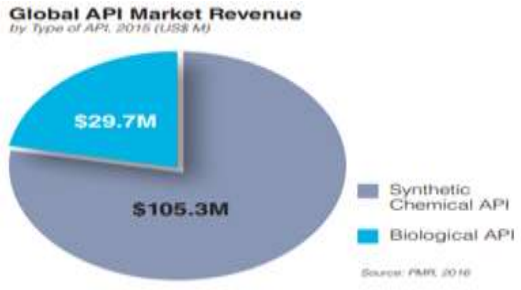
Figure 8: Year wise imports of pharmaceutical products in Pakistan

Active pharmaceutical ingredients: "Any substance that is used in final pharmaceutical product that is active biologically and it is aimed to provide activity to the drug"[31]. APIs are generated in the market by two ways.

1. Biological API
2. Chemically produced API

Biological method is the common one because most of the companies produce API by this method. Both of these processes are quite different in such a way that in chemical process reaction is started by the chemical ingredients and biological process is started by the seed cell that is picked by the cell culture[32].

Figure 9: Global API market interest



The single largest pharmaceutical market is the US, according to the report collected from the IQVIA institute for science of Human data , US consider to approximately 485 billion dollar or 38%, in 2018 of the global pharmaceutical market of 1.205 trillion dollar.US has the large share in market in spite of this it chase the other countries who supplies active pharmaceutical ingredients to the US market[33]. About 28% of the constructing facilities required for making APIs were present in US till August 2019. The rest of the API that is about 72% are imported by US in which China is one of the main country that supply 13% of API to them[34]. API manufacturing industry of China plays a vital role in global pharmaceutical market. About 40% of API are exported the China[35].

Figure 10: The major APIs imported from China

Factors on which APIs depend

APIs formation is depended on many different factors like reagents, intermediate ,catalyst ,key starting materials, biosimilar and peptides , quality excipients , solvents and on chemicals[36].

Formulation of drug: In pharmaceutical formulation series of steps are involve in which all the components of drug are mixed with the active drug. During this size of the particle, solubility, PH and polymorphism of the particles are considered and we get the final advantageous medicinal product (37) To get the favorable outcome of pharmaceutical formulation the four main factors are involve that are active pharmaceutical ingredients, associated interactions, synthetic procedures and precious excipients[38]. As a result of formulation we get a variety of dosage forms. Dosage form is the mixture of active and inactive ingredient and it is the product of drug that come in market for use. It has a specific presentation just like in the form of tablet , capsule and divided into a specific dose[39]. In fruitfulness of medicinal treatment not only chemical characteristics are involved but it also depends on the procedure that how drug is formulated and distributed[40]. The aim of research and evolution of drug formulation is to completely utilize all the beneficial characteristics of already available active drug also evolve drug molecule as a result of this many undesired properties are avoided[41]. As early as possible success of drug molecules on of the main is to do research and development on formulation. Pharmaceutical industry consider it to be very beneficial[42]. Formulation is the main part of this scheme in which discovery of drug , development and synthesis are involved . That is why formulation should confirm that drug that is pharmacologically active can be produce and drug can be synthesize, administered and delivered into a specific amount through the route by which it reaches to its target site in a specific time with a specific therapeutic effect while it reduces the unnecessary adverse effects[43].

Pharmaceutical formulation needed no contamination either it is chemical contamination or microbial contamination. Physicochemical as well as therapeutic characteristics of formulation are changed by the microbial attack. Drugs are stable in dry solid form when they are present individually but when drugs are mixed with other reagents stability issues are develop in them. To regulate the sterility for a specific time and to lengthen the mean life of formulation preservatives are added to them[44].

Different forms of drug formulation: A drug can be formulated in different forms like solid, liquid and in the form of semi liquid just like creams. Which type of formulation is given to the patient it depends on the age of the patient, sex, the route by which the drug is administered and it also depends

on health condition of the patient[45]. Drugs that are taken orally its formulation must be precisely controlled. But when they are taken orally in the form of solution in water then important things are of its viscosity and osmolerity. Sometimes due to cosolvents structural changes are observed in gastrointestinal mucosa as well as some functional changes are also produce (46)Drug formulations come in different form a brief overview on them is given below.

Figure 11: Formulations of drug

Solid formulation

Tablets: It is a disc shaped drug that is produce in a suitable machinery by squeezing a granular powder. As the drug is break in the digestive tract of the human so it is coated with a chemically inert substance just like a starch. To make the tablet eatable different flavors, binding agents as well as lubricating materials are added[47].

Tablets with enteric coating: These tablets are coated with specific material that disintegrate in the basic PH of intestine but does not break in the stomach with acidic PH. These are only swallow but we cannot chew them.

Tablets with controlled release: The tablets in which active ingredient is released in a particular amount over a particular interval of time. Drug is released gradually on the whole day and it is independent of the PH of gastrointestinal tract of the patient. So the drug is distributed in a constant amount at a constant rate[48].

Sustain release tablets: In this case drug is released in a fixed amount over an elongated time period. Treatment compliance is improved in it.

Capsules: Capsules can be hard or it can be soft. Drug is present in solid form in hard capsule so that it easily dissolved in water. Liquid or semi solid form of drug is present in soft capsule and it is not dissolve in water but soluble in glycol[49].

Liquid and partial- solid formulation: They are rapidly absorbed in the body and distributed by different routes like:

Oral preparations: It is easy to swallow for children and aged patients. To make them tasty sugar and different flavors are added to them. They are available in market in the form of solution, suspension and before use we must shake them.

Topical preparations: It is the direct application of the drug to the body is known as a topical application. Different forms are included in this section that are eye drops, ear drops, it may be in the form of cream, gel, inhaler, nasal drops and nebulizer are also included in them.

Administration through buccal cavity: Drugs which are active in blood in very low quantity, it is used for them. In this case drug is dissolved by putting it under the tongue in the middle of the cheeks. In this case drug act very vastly because it is directly absorbed in the blood after passing the digestive tract[50,51].

Rectal Administration:

Suppositories: They are used for those drugs that are given through the rectum. Drug is directly entering to the blood by absorbing through the rectal mucosa. It is a very useful method in

case when patient is not in senses and cannot swallow the medicine.

Enemas: A liquid mixture is preparing for given through rectal. They are used for bowel motion and for topical therapy[52].

Parental drug distribution: In this case absorption of drug takes place out of the gastrointestinal tract of the patient. Injections are used to insert the drug.

Intradermal administration: Drug is absorbed into the blood through the skin.

Subcutaneous injection: Drug is absorbed into the blood by inserting it through the subcutaneous tissue of the skin. It is used for those drugs that cannot be intake via mouth[53].

Intramuscular injection: Drug is absorbed in to the blood by inserting it through the muscle. In this case drugs having low molecular weight are easily distributing into the blood.

Intravenous injection: It is the faster method for the absorption of drug in which drug is directly inserted into the vein[54].

Reformulations studies are carried out to know whether the drug is solid, liquid or in semi-solid form. Reformulation studies helped us to estimate the physical and chemical characteristics of the drug as well as its stability and its relationship with other substances[55].

Limitations and strength: Each pharmaceutical industry suffers from several limitations of increased risk of competition from generic products, legal liability for addiction to opium, product, counterfeit and spurious drugs and keeping it up with modified technology and patent clips. The strength of each pharmaceutical industry based upon quality goods, providing values, services excellence. The internal industry components can include physical resources, human capital or features the industry can control. For example, the pharmaceutical industry strengths could include low operating overhead, firm fiscal management, low staff turnover, high return on investment (ROI), state-of-the-art laboratory equipment and an experienced research staff.

CONCLUSION

The medical system in a country is crucially dependent on the pharmaceutical sector.This study's goal was to shed light on Pakistan's entire pharmaceutical sector, including startups, imports, exports, and detail of APIs.The pharmaceutical industry in Pakistan is still in its early stages, but it has managed to establish a small presence in Asia-Pacific market.The study's findings show that there are concerns about the current rules in Pakistan for evaluating the quality of pharmaceuticals raw materials (APIs). These require immediate attention that patients in Pakistan have access to high-quality generics, and better your prospective export prospects. The pharmaceutical business has a strong capacity for innovation, and governments should conduct studies and encourage discussion on how to improve this capacity without endangering public health.

Conflict of interest: No conflict of interest arises throughout this work.

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