Welfare Impact of Generic Drug Shortages in Pakistan

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CERTIFICATE

This is to certify that this thesis entitled **"Welfare Impact of Generic Drug Shortages in Pakistan"** submitted by **Ms. Kainat Yousaf** is accepted in its present form by the School of Economics, Pakistan Institute of Development Economics (PIDE), Islamabad as satisfying the requirements for partial fulfillment of the degree in Master of Philosophy in Health Economics.

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Author's Declaration

I, Ms Kainat Yousaf, hereby declare that my MPHIL thesis titled 'Welfare Impact of Generic Drug Shortages in Pakistan' is my work and has not been submitted previously by me for taking any degree from the Pakistan Institute of Development Economics, Islamabad or anywhere else in the country/world.

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Dedication

Every challenging work needs self-efforts as well as guidance of elders especially those who are very close to our heart. I wholeheartedly, dedicate my work to my supportive Mother and Father; and my grandparents, whose affection, love, encouragement and prayers of day and night make me able to accomplish such success and pride.

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Abstract

The availability of life-saving drugs and healthy lives share a strong bond that impacts not only health but also aggregate economic outcomes. Pakistan, however, suffers from persistent drug shortages whose negative repercussions remain rarely discussed. This first ever attempt delves into the welfare impact of drugs shortages on the consumers in terms of the loss that accrues to them monetarily due to non-availability of generic drugs. Calculations indicate that the quantum of monetary losses inflicted upon the masses due to drug shortages over the last six years alone came to Rupees 78.5 million. Research further delved into the factors propagating these shortages. Qualitative results indicated Government regulations to be the main culprit behind these shortages, with quantitative results affirming these findings.

Keywords: Generic Drugs, Drug Shortages, Welfare Impact.

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List of Abbreviations

DRAP	Drug Regulatory Authority of Pakistan
WHO	World Health Organization
API	Active Pharmaceutical Ingredient
OOP	Out of Pocket
LMIC	Lower- and Middle-Income Countries
SOP	Standard Operating Procedure
NHA	National Health Accounts
HIES	Household
NEML	National Essential Medicines List
DTL	Drug Testing Laboratory
BE	Bioequivalence
FDA	Food and Drug Administration
FDI	Foreign Direct Investment
ARV	Antiretroviral
INN	International Non-Proprietary Names
TNCP	The Network for Consumer Protection
MNC	Multinational Companies
PPMA	Pakistan Pharmaceutical Manufacturers' Association
PB	Pharma Bureau
FBR	Federal Board of Revenue
GST	General Sales Tax
DVT	Deep Vein Thrombosis
GMP	Good Manufacturing Practice

GP	General Practitioners
SAPM	Special Assistant to Prime Minister
MNHSRC	Ministry of National Health Services, Regulation and Coordination
CEO	Chief Executive Officer
OTC	Over the Counter
SRO	Statutory Regulatory Orders

Chapter 1

Introduction

Drugs[1] and healthy lives share a strong bond, and health has a direct link with economic growth, an assertion backed by credible research! Georgieva, for example, estimated a GDP increase of 1.5 percent each year due to a healthy workforce. (Georgieva, 2019). Poor health, in contrast, has been linked with reducing global GDP growth by 15 percent per year. (Remes et al., 2020)

It follows, then, that drug shortages can create difficulties in terms of achieving the goal of a healthy, disease-free workforce. Such an adverse situation, in turn, tends to not only manifest itself in poor health indicators, but financial and economic cost to the individual and the country.

Unfortunately, drug shortage is a global problem that affects low, middle, and high-income countries, although the level of severity in terms of shortages differs by countries. Drugs, especially the one categorised as essential life-saving drugs such as oncology drugs, antimicrobial drugs, palliatives, opioids, cardiovascular drugs, radiopharmaceutical, and parenteral products, etc., tend to suffer shortages, especially in the developing world. As pointed out above, such a state of affairs not only has personal but also aggregate repercussions for the country and the economy.

1.1 Background

Drugs are essential components of health-care, and access to drugs has been considered as a fundamental human right. (Hogerzeil, 2006) The World Health Organization (WHO) labels essential drugs that "satisfy the population's priority health care needs". However, persistent drug shortage problems make it exceptionally difficult to meet these goals. (De Weerdt et al., 2015)

[1] Drug' is the name ascribed to allopathic medicines, which are the subject of this research effort. 'Medicines' covers a wider category, including Homeopathic, Ayurvedic and other such products.

Despite having around 100,000 registered drugs[2] , essential live-saving drugs suffer frequent shortages in Pakistan, both in markets and in public plus private hospitals – thus putting lives in danger. Persistent shortages imply that drugs have to be either imported or are found in black market at astronomical prices. (Wire, 2019)

In this regard, with a substantial portion of individuals in Pakistan living below the poverty line, generic drugs are the favoured drugs among them since branded drugs are unaffordable for major portion of the population. (Abbasi, 2014) An implication, in terms of the poor gaining access to critical drugs, is that policies to ensure the cost-effective generic[3] alternatives be implemented since they tend to be cheaper in price, and provide the same therapeutic outcomes, resulting in significant savings for consumers and the healthcare systems. According to US Food and Drug Administration (FDA) statistics, generic drugs are 80-85% less expensive than the originator branded drugs. (FDA, 2016)

The urge to pursue increased use and availability of generics comes in context of various factors, one of the most pressing one's being the increasing cost of healthcare (including drug use and consumption). Increasing healthcare costs, of which drug consumption costs are a substantial portion[4], are a global phenomenon, as depicted by the graphs below that reflect total healthcare costs in the US over the long-run. (Kurani et al., 2022)

[2] Source: DRAP officials. Though registered drugs have shown a healthy growth from around 55,000 in 2014-15, not all registered drugs get produced. Sources within industry claim that hardly 20,000 registered drugs are being produced at the moment.

[3] Generics, in general, are local, cost-effective copies of branded medicines that do not carry any IP protection for a specified period of time. In other words, they are close bio-equivalent alternatives (if not 100 percent similar) of originator brands.

[4] As per the various Pakistan National Health Account (NHA) surveys, drug usage cost is almost half of total healthcare costs in Pakistan

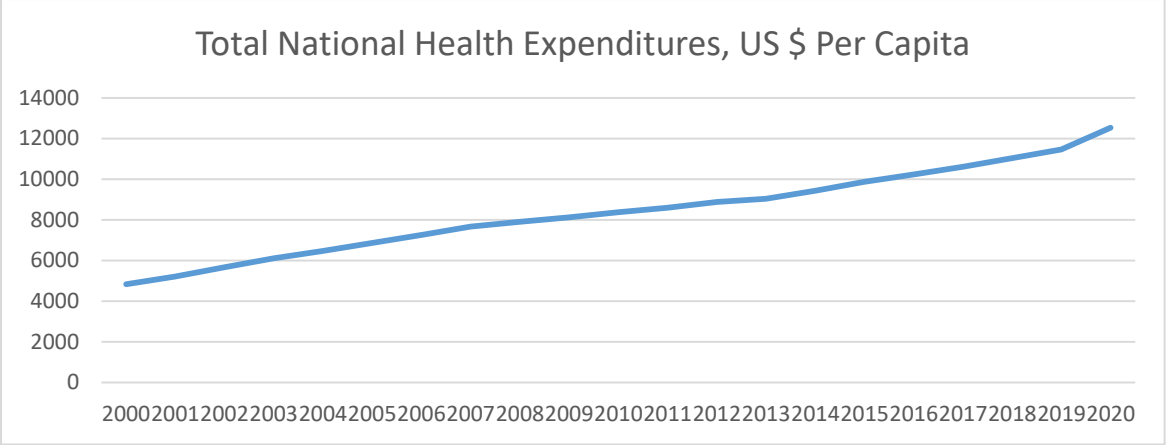
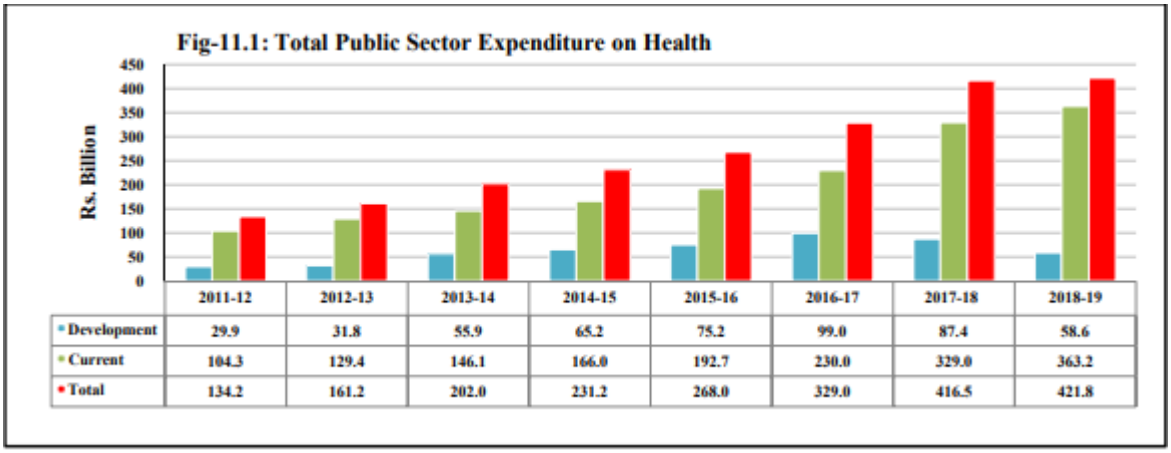


Figure 1.1: Total National Health Expenditure – US

We witness a similar pattern in Pakistan's case, reflected in the graphs reproduced below. (PRSP Expenditures, 2019-2020)



	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
Development	29.9	31.8	55.9	65.2	75.2	99.0	87.4	58.6
Current	104.3	129.4	146.1	166.0	192.7	230.0	329.0	363.2
Total	134.2	161.2	202.0	231.2	268.0	329.0	416.5	421.8

Figure 1.2: Total Public Sector Expenditure on Health

Table 11.3: Federal and Provincial Governments Health Expenditure

Fiscal Years	Public Sector Expenditure (Federal and Provincial) Rs Million			Health Expenditure as % of GDP
	Total Health Expenditures	Development Expenditure	Current Expenditure	
2011-12	134,182	29,898	104,284	0.7
2012-13	161,202	31,781	129,421	0.6
2013-14	201,986	55,904	146,082	0.7
2014-15	231,172	65,213	165,959	0.7
2015-16	267,953	75,249	192,704	0.9
2016-17	328,962	99,005	229,957	1.0
2017-18	416,467	87,434	329,033	1.2
2018-19	421,778	58,624	363,154	1.1

Source: PRSP Expenditures, (EF-Policy Wing), Finance Division

Figure 1.3: Federal and Provincial Health Expenditures

From a health policy perspective, given the above, it is important to ensure that generic varieties of drugs (especially the essential, life-saving drugs) are available throughout the year, which will not only save lives but also save precious financial resources. Unfortunately, that is not the case!

1.2 Financial Constraints

In Pakistan, various sources (like WHO) have reported that consumers of drugs have had to incur up to 80 percent rise in Out of Pocket (OOP) expenditure due to escalating healthcare expenditure. In case of Pakistan, the OOP expenditure as a share of health expenditure was 53.8 percent in 2019. (Worldbank, 2022) As stated Thus, what is needed is to maintain healthcare expenses as low as possible without compromising access to high-quality treatment. (Bakthavathsalam, 2006) Without access to affordable generics, such a goal cannot be realized.

In Pakistan, the overall dismal state of affairs in healthcare provision is reflected in the high burden of infectious and non-communicable diseases, as well as high mortality rates for mothers, new-borns and infants; as shown in the Table – 1. (Organization, 2018) This kind of a situation calls for provision of quality healthcare, of which provision and timely availability of needed drugs is a must, which sadly is not the case.

Table 1: Burden of Diseases

Disease Category	Disease Burden
Communicable Diseases	42-44%
Non-Communicable Diseases	56-58%
Source: WHO. Non-communicable Diseases Country Profiles. (2018)	

This state of affairs is partially reflected in the accompanying table (Table-2) that tabulates rise in per capita medical expenses over time, compiled using statistics from NHA. (Mehmood, 2022).

Table 2: Percentage wise expenses on drugs and per capita expense

Years	**Expenses on Drugs, as percentage of total health expenses**	**Per Capita expense on drugs**
2004	25	
2008	56	PKR 900
2010	56	PKR 920
2012	50	PKR 822
2014	53	PKR 1,338
2016	50	PKR 1,440
2018	51	PKR 1,580
Source: National Health Accounts and Household Income Expenditure Survey. Mehmood, S. (2022) 'Regulating the Pharmaceutical Industry: An Analysis of DRAP', PIDE, Islamabad.		

And the repercussions of non-affordability reach far beyond the poor health. Datta, Hussain, and Fatehin (2020), for e.g., found that drug expenses had a 'crowding out' effect on food consumption, with the effect being significantly stronger in impoverished households who are already food insecure. (Datta et al., 2020)

1.3 Generics and Branded Drugs

WHO defines generic drugs as a pharmaceutical product, generally interchangeable with an innovator product that is made without obtaining a license from the innovator firm and promoted after the patent or other exclusive rights have expired. (WHO, 2012)

The chemical composition of a branded and generic drug is the same. Generic drugs need to have the similar active ingredient, strength, identity, administrative method, quality, purity, effectiveness, as well as the identical intended use of the brand name drugs. (FDA, 2012) Having said that, small variations in inactive components (e.g., preservatives, tastes), colour, shape, and packaging might exist between generic and brand name preparations of the drugs. (FDA, 2014)

Generic drugs can provide the same clinical outcomes as brand name medicines at a considerably cheaper cost, reducing the burden on the community who are reluctant to purchase expensive branded drugs, thus leading to realized savings. (Fischer & Avorn, 2004)

Given Pakistan's on-ground realities like growing population and a low per capita income, the use of generics is a cost-effective approach to improve drugs access and affordability across the country. (Jamshed et al., 2009)

Additionally, generics can be helpful in enhancing exports and bringing in Foreign Direct Investment (FDI). For these to happen, Government will have to improve its capacity in terms of regulation, focusing on quality infrastructure (especially Bioequivalence or BE labs), of which there are only two in the public sphere (under Bio-Study Rules 2017), supervised by DRAP.

1.4 Generic Drugs in Global Scenario

The ever-increasing healthcare expenses are one of the key issues facing the healthcare workforce and policymakers throughout the world. (Borger et al., 2006) (Steinwachs, 2002) Increased pharmaceutical spending might be due to a number of reasons, including an increase in illness occurrence, a rise in population risk factors, variations in clinical treatment thresholds, and the introduction of novel medicinal therapies. (Thorpe, 2005) (Thorpe, 2006)

The situation is getting worse in low-income and middle-income countries where the household expenditures especially on health surpass the comparative total spending in high-income countries. (Hopkins, 2010) Likewise, poor nations have highly inefficient and unfair healthcare systems marked by limited resources, availability of ineffective drugs, economic instability, income disparity and meagre infrastructure.

There are number of studies available on the perception and acceptability of generic medicines among healthcare workers in the West. According to a research carried out in France, prescription having International Non-Proprietary Names (INN) is generally well received by individuals in the health field, with some concerns about side effects. (Biga et al., 2005) (Lagarce et al., 2005) Similarly, generic medicines are well-known in Brazil, although not many take them. (Bertoldi et al., 2005) Likewise, general practitioners in Slovenia have shown willingness to expand the use of generic drugs being worried about the expense of prescription medications. (Kersnik & Peklar, 2006) In Australia, it’s a common practice to use generic medicine to save healthcare expenses. In several countries, healthcare administrations significantly encourage

generic replacement, generic prescriptions, and generic distribution. (Hassali et al., 2004)

In developed nations such as Canada, Germany, Denmark, Holland, UK, and USA, a substantial body of data supports various policy strategies to encourage generic drugs. These include both demand and supply sides policies that are critical for generic promotion and use.

In a survey conducted by Lopes (2013), a substantial percentage of doctors felt that generic medications are an essential strategy for lowering total healthcare costs. (Lopes, 2013) The cheaper cost of generic medicines is a big benefit. In India, the price of generic medicines is found to be up to 91 percent cheaper than the cost of brand-name original innovator drugs. Broader use of generic medication has the capacity to lower the price of other brand-name drugs by increasing competition.

1.5 Pakistan Pharmaceutical Industry

Currently, with 700+ pharmaceutical production units (22 MNCs included), 100,000+ registered medicines and 1100-1200 drug molecules, Pakistan's pharma sector meets roughly 70 -80percent of the country's demand for finished drugs.[5] There used to be more than 40 Multi-National Corporations (MNCs) working in Pakistan, bringing with them repute, experience and FDI. Now, there are hardly 20 left, and quite a few of them have divested away from manufacturing drugs to other products (like dry milk, baby food, etc.) (Mehmood, 2020)

Historically, the price of drugs has been strictly regulated by the federal government, although in recent years there has been some laxity in the pricing regulations. Many of the country's APIs are imported, with hardly 40 manufactured domestically, shown in figure 1.4.

[5] Talks with Industrial officials and Statistics from DRAP

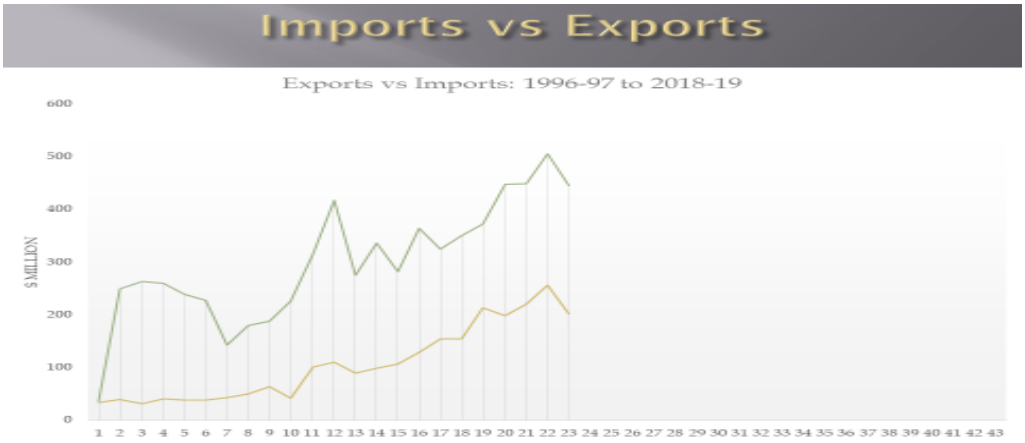


***Figure 1.4*: Pakistan's Pharmaceutical Imports Vs Exports**

In terms of regulating pharma industry – Drug Regulatory Authority of Pakistan (DRAP) being the official supervisor, some major considerations for regulating the industry come in the form of assuring drug quality, consistent supply of life-saving therapies, affordability, and access to drugs. (Aamir & Zaman, 2011)

But despite having more than 700 pharmaceutical firms, Pakistan regularly experiences drug shortages, many of them categorized as 'critical' (or lifesaving) drugs, compelling us to import them on astronomical prices or with consumers ending up buying it in black. We do have domestic manufacturing capability of imported medicines as well as those local medicines whose production has been discontinued, yet we are unable to manufacture them, primarily due to government's regulation concerning prices of drugs, that have to be approved first by DRAP and then by the federal Cabinet. Simply put, proper management and the incentives are absent. Examples abound! We had a failed attempt to produce APIs using '*ephidra sinica*' plant, which is abundant in Baluchistan. This is a common ingredient in cough syrups and low blood pressure drugs during spinal anaesthesia. An attempt was made to set up a factory for its extraction, but it was finally shut down, owing in part to regulatory obstacles. (Mehmood, 2022c)

Similarly, another example is Pakistan's domestic non-production of medications to cure cutaneous '*leishmaniosis*,' a deadly skin disease that has persistently plagued the country, particularly in rural regions. (MSF, 2018) Despite this, there has been no incentive from the regulators, as well as no coordination with the industry, to produce this drug domestically. As a result, it's only available in black at an exorbitant price, and even then, its quality is often questioned in many instances. (Mehmood, 2022c)

These are just few examples of how regulations prove to be a disincentive for domestic production.

1.6 Status of Generics in Pakistan

Pakistan's formal policy on the usage of generic drugs goes back to 1972, when the 'Generic Drug Act' was implemented. The major goal was to encourage use of generic medication use by making them affordable and accessible. This statute advocated the use of generic or International Non-Proprietary (INN) names rather than brand names while prescribing medicines. It also offered local industries an opportunity to compete against multinational corporations. The program came to an end in 1975, when 38 local medicine manufacturers were charged for manufacturing poor quality drugs. (Babar et al., 2013) In 1976, the government revoked the regulations governing generic branding and prescribing, and enacted the 1976 Drug Act which provided local manufacturing incentive. (Quraeshi et al., 1983) Since then, the generic market has grown to the extent that the market segmentation is now in favour of local manufacturers, at 70:30. In the hospitals, especially public hospitals, drugs are usually prescribed by their generic names.

The market for pharmaceutical products in Pakistan's is estimated to be $3.1-3.2 billion. The majority of marketed innovator brands and generic medicines are produced locally by subsidiaries of multinational or local generic manufacturing companies by utilizing imported raw materials. Price controls might have kept prices artificially low, but there are substantial costs associated with it too. The production of many domestically produced drugs[6] has been discontinued over time, resulting in production loss at local level, potential investment loss, potential job loss, foreign exchange rate loss, and black market for high-demand drugs has increased, etc. This suggests that policies still have a lot of potential for improvement.

The Pakistani government has emphasized the usefulness of generic medications in the context of promoting and selling pharmaceuticals under their generic identities in order to keep drug prices in check and thus control price hike in drugs. (Dawn, 2007b) (Dawn, 2007a) But despite the efforts, the production of critically required, in-demand generic drug still suffers shortages from time-to-time.

[6] Opium patches, Ropinirole, Epival, etc.

Also, as DFID points out, there is no legislation or authoritative rule both in the private or public sector regarding generic prescription or alternative, and hence, generic prescription or substitution is completely at the prerogative of the dispenser or prescriber. Not only are there no financial incentives for prescribers and dispensers, there are also no rebates for innovators or generics in either the private or public sectors. (DFID) This might lead to lower use of generics despite availability.

1.7 Justification/Significance of Current Research

This importance of current research rests in narrowing down the knowledge gap regarding potential savings and welfare impact of generic drugs among masses as the use of generic drugs increases (given its availability). Critically, for the policymakers, the study is intended to bring to light the monetary costs due to non-availability of local generic substitutes (against costly branded drugs), a situation in which adverse regulations play a central role.

Additionally, the study will be useful for policymakers in terms of understanding the issues surrounding non-production (or ceasing of production) of generic brands. If such outcomes can be prevented in the future, drug shortages are highly unlikely to occur.

1.7.1 Research Gap

Except for a brief attempt by Mehmood (Mehmood, 2015), there exists no study that delves into the welfare and monetary impact of government policies due to adverse pharmaceutical sector regulations i.e., what government regulations do to working of the pharmaceutical industry and its probable impact upon the consumers. This paper is first of its kind in terms of it evaluating the welfare impact-based calculation of probable monetary losses inflicted upon the consumers due to generic drug shortages. Moreover,

research would further analyse the factors that impact the availability of critically needed generic drugs.

1.8 Research Question

What's the monetary loss inflicted upon consumers due to non-availability of generics? What factors contribute to it?

1.9 Research Objectives

1. To assess the welfare impacts of drugs experiencing persistent shortages in Pakistan over the period of last six years
2. To evaluate the potential savings linked with broad substitution of generic drugs (through calculating estimated loss)
3. To find out the determinants of drug shortages

1.10 Hypothesis

Monetary losses inflicted upon the consumers due to shortages are significant, and that various government regulations drive these shortages.

1.11 Organization of Thesis

Chapter 1 consists of the Introduction, Chapter 2 gives Overview of the Scholarly Literature, Chapter 3 discusses the Regulatory framework of pharmaceutical industry of Pakistan, Chapter 4 highlights the data and methodology adopted in this study, Chapter 5 delves into results and analytical discussion and Chapter 6 contains Conclusion and Policy Recommendations.

Chapter 2

Literature Review

This section of the study primarily reflects upon the previously published scholarly articles on generic drugs, both in Pakistan and foreign countries, so that after a detailed and in-depth analysis, the research gap and significance of the study could be established. The timeline for the evaluation of literature ranges from 2003-2021. In general, the literature addressing the welfare impact of various commodities is pretty common, but there is dearth of literature measuring the welfare impact of drugs, especially in terms of monetary losses incurred due to drug shortages. From a global perspective, there has been limited research in addressing the welfare impact of generic drugs in monetary terms, while extensive research is available on its broader aspects such as generic drugs prescription, its substitution to innovator drugs, the knowledge, belief and perception of generic drugs usage among health practitioners, students, pharmacists and patients, etc. Critically, there is no such study in Pakistan that measures the monetary impact of drug shortages, a gap that this study aims to fill! Therefore, this research effort is the first of its kind in Pakistan.

2.1 Generic Drugs Analysis in Pakistan

The shortages of drugs have had a long history in Pakistan; On 30th March, 1954, the then Health Minister informed the Constituent Assembly session highlighted the severe shortages of drugs in the country. Again, in 1976, a US health expert, Mr. Arthur Homer Furnia noticed the same shortages of drugs, particularly in public facilities. The crux of above two is that drug shortages are nothing new for our country. (Mohmand, 2022)

The literature on Pakistan's pharmaceutical sector is extensive, but studies on persistent shortages or even non-availability of drugs is comparatively scarce. It's tough to locate a peer-reviewed publication of significance on this subject in a reputable journal. Whatever information there is about the availability of drugs is mainly found in news articles that randomly report on instances of drug shortages and the ensuing difficulties in sourcing the required medication. However, aside from frequent mentions of drug shortages as an aspect of the pharmaceutical and health sector (mostly reported in newspapers), there has never been a concise study on drug shortages that takes up this particular aspect as the sole aim of research.

Mehmood (2017) carried out a survey of drug shortages in twin cities of Islamabad and Rawalpindi, arguably the first focused study that specifically addressed this particular aspect. Other than this, there has been piecemeal discussion on drug shortages and their implications in various research papers. (Mehmood, 2017)

Rashid, H. (2015) examined the DRAP via the lens of three policies (regulation of the industry, encouragement of its growth and ensuring accessibility of the drugs). She believes that serious inadequacies in the regulator's effectiveness are impeding the industry's progress. (Rashid, 2015)

Rashid et al. (2019) conducted the second study that just examined the performance of DRAPs, with the major topic of their research being the regulatory framework of the pharmaceutical sector in Pakistan. They discovered major inadequacies in the regulator's effectiveness in terms of assuring prescribed pharmaceutical quality. They also recommend that the broader framework for assuring quality be improved, for example by increasing GMP inspections (GMPI). (Rasheed et al., 2019)

Further, almost every type of drug has been reported as being in short supply, it includes antibiotics, antiretroviral drugs, anti-protozoal, antineoplastic agents, cardiovascular drugs, painkillers, etc. Essential and emergency medicines are more liable to suffer shortage. Such shortages have been reported in several newspapers persistently. DAWN (2017) (2020) (2021) has been regularly reporting the drug shortages along with the underlying causes. Reported drugs experiencing shortages includes more than 60 drugs categorized by WHO as 'essential medicines' that are not available in the Pakistani market or are in short supply (Junaidi, 2020b) ; instances include Panadol/paracetamol, drugs (particularly hydrocortisone) for rare but most common type of genetic disorder – congenital adrenal hyperplasia (Dawn, 2017); a variety of life-saving biological products are in short supply that are used to treat cancer, angina (Angised tab (0.5mg), diabetes as well as vaccines, actemra for critical Covid patients; and ibuprofen, etc. (Dawn, 2020). Another dawn article (2020) reported the drug prices hike up to 250% (mainly due to lower supply and non-availability of drugs), thus compelling many to delay or quit treatment.

These news articles primarily state that the underlying causes of drug shortages are related to the pricing issues (Junaidi, 2021), delays in approval to buy controlled raw material, delay in the issuance of the certificates by national control lab or international alerts to stop using the drugs, the delay by sole manufacturer of the drug (for e.g., Actemra manufactured by a Multinational manufacturer) (Chaudhary, 2021), and imposed tax on raw material, etc. Furthermore, there is probable low demand for some drugs that no company wants to make due to fear of financial losses. Various vaccines are a prime example. In short, governments around the globe enter into a contract with drug manufacturers to produce a certain number of vaccines every year, which they then use to inoculate their citizens from various viruses. Put in other words, the vaccine

manufacturers are assured of demand by the government. However, there's always persistent shortages of vaccines in Pakistan because manufacturers do not get any persistent orders from the federal or the provincial governments! Similarly, we are incapable to manufacture raw materials needed for essential drugs in Pakistan primarily due to faulty regulations which provide no incentive for manufacturing APIs domestically.

Such a state of affairs, whereby essential, life-saving drugs are unavailable, encourages the influx of smuggled and sub-standard products into the country. For instance, DAWN (2020) stated the case of acetazolamide, a drug being used for the treatment of glaucoma, was being sold at the price of Rs.2/tablet. However, as government refused to allow a slight price increase, the drug experienced shortage and price rose to Rs.100/tablet from Rs.2/tab! This created untold misery as glaucoma is the second leading cause of blindness and we have 2 million glaucoma patients in Pakistan. Although later negotiations resulted in agreement to manufacture it with maximum retail price of Rs.7.30/tab, the resulting in between must have inflicted substantial losses upon consumers who were buying it in black at an astronomical price. (Junaidi, 2020a)

Similar severe drug shortages have been reported by Express Tribune as well. For example, a 2016 report pointed out the prevalence of low-quality, spurious and ineffective drugs whose sales increase in the backdrop of shortages, whereby production of quality generics is discontinued because the government does not agree to grant price increases, thus perpetuating shortages. (Siddiqi, 2016)

Tribune (2020) reported shortage of paracetamol and ibuprofen with the same reason as mentioned in dawn i.e., we lack the capabilities to produce raw materials that are used in locally manufactured drugs. The producers mainly rely on cheaper imported raw material. (Merchant, 2020) The same paper (2020) reported the struggle faced by

Punjab government with drug shortages amid pandemic, including drugs used in treatment of common cold (antibiotics), antivirals, sedatives, asthma inhalers, and anti-inflammatory drug tocilizumab, probably due to a sudden uptick in their demand during the pandemic. (Abbasi, 2020) A 2021 report noted the surging prices of Actemra vials, whereby NAB intervened to control prices of drug as its black market price rose up to Rs. 500,000/vial due to severe shortages, making it totally unaffordable for major portion of consumers within the country. (Tribune, 2021)

Business Recorder (2020) acknowledged the Pricing issues being the main culprit behind the country facing severe shortage of life-saving drugs. Citing locally manufactured nitrofurantoin, with approved retail price of Rs. 1.44/tab (approved by DRAP), it became financially unfeasible to be manufactured locally anymore as its costs of production moved above its retail price. Consequently, the manufacturers stopped its production. Only smuggled drug was available in the market which was costing Rs 3,400 per 30 blister pack. Moreover, Business Recorder also observed pneumonia vaccines, influenza vaccines and, Angised (0.5mg) are in short supply in the market – all due to pricing issues. (Azad, 2020)

Pricing dispute also hit the supply of tuberculosis drugs in Pakistan, Novartis – a renowned pharmaceutical company stopped the manufacturing of TB drugs due to indeterminable dispute over the pricing, as reported by Aaj TV (2016). This highlight putting the health at stake due to a shortage of drugs in a country with the world's fifth-highest TB rates. (Zuberi, 2016)

Likewise, shortages of paracetamol at the beginning of this year had been reported widely. Again, the main issue revolves around Government led regulations, especially pricing. As Cabinet failed to give the requested price raise by the pharmaceutical industry, the drug’s production was curtailed to save on costs that had increased

substantially due to rise in import cost of raw material, owing to decline in the exchange. (Mehmood, 2022a)

Recently, an attempt (qualitatively) was made by Sumaira Omer et al. (2021) to explore the management of Drug shortages in the Community Pharmacies of Pakistan. The goal of this study was to look into the strategies and resources used by community pharmacists to address a common shortage problem that has been reported across the country. Purposive sampling was used to conduct face-to-face interviews with 31 community pharmacists from Lahore, Multan, and Dera Ghazi Khan. This study looked into current scenarios of drug shortages in a community setting and found that shortages were common; they ran into roadblocks during the shortage management process and discovered that corrupt activities such as black marketing, hoarding, biased distribution, and bulk purchasing were at the top of the list; and in terms of influences of drug shortages, they found them to be negatively impacting the pharmaceutical sector. (Omer et al., 2021)

A qualitative study was conducted by M. Atif et al. (2021) to explore the influence of drug shortages on patients in Pakistan. Between July and September 2019, they conducted in-depth interviews with 13 physicians, 12 pharmacists, and 10 patients to learn about their experiences and the perspectives of healthcare professionals. Drug shortages have a major clinical and budgetary impact on patients, according to their findings. The main negative consequences due to drug shortages were compromised treatment, medication safety issues, and risk of mortality due to treatment failure. As a result, patients choose a variety of risky tactics to minimise treatment disruptions during shortages. A variety of pharmaceutical market concerns, medicine quality, and patient-related factors prevent physicians from switching from brand-name to generic drugs, resulting in inefficient drug shortage management. To mitigate the impact of drug

shortages on patients, promotion of generic prescriptions, the implementation of disciplinary laws, and proper patient consultation were recommended. (Atif et al., 2021)

Research into other aspects related to generics have been carried out by many scholars as well. Some of the studies are jotted down here regarding the effectiveness of generics, registration, usage perceptions and the regulations. Shahnaz, Bano, and Arshad (2009) conducted a technical analysis of six generic products of a particular drug (Cefixime 400 mg). They discovered that all six kinds are helpful at relieving symptoms and may be swapped out. (Shahnaz et al., 2009)

Baber et.al (2016) commenced a technical assessment of API's in drug registration processes. They came to the conclusion that the registration procedure for generic pharmaceuticals in Pakistan needed to be improved immediately as unnecessary delays may lead to shortages of needed drugs. (Babar et al., 2016)

Jamshed et al. (2010) highlighted the need for cost-effective approaches in a time when healthcare costs are rising and the population is ageing. The goal of this exploration was to learn more about community pharmacists' understanding, perceptions, and attitudes to generic medicines. The study used a qualitative approach. Eight community pharmacists were identified using a snowball sampling approach. The pharmacists were interrogated using semi-structured interviews until saturation was reached. Thematic content analysis was used to analyze the audio-taped and verbatim transcribed interviews, which was then confirmed by additional authors' analyses. The study found that all pharmacists had a good understanding of generic medicines and a favorable attitude toward them. When it came to dispensing locally made medicines, there were mixed reactions. The low cost was recognized as a key factor in their distribution. The survey also revealed that community pharmacists in Karachi, Pakistan, had a strong understanding and perspective of generic medicines. (Jamshed et al., 2010)

A qualitative study performed by Malik et al., (2013) in Pakistan with the goal to learn more about hospital pharmacists' attitudes about drug management and the reasons for antimalarial drug stock outs in Pakistan. Semi-structured/in-depth interviews with 16 hospital pharmacists were done in two major cities in Pakistan (Islamabad and Rawalpindi) for this study. They discovered that pharmaceutical companies' unethical promotion of the drug Artemether/Lumefantrine caused Sulphadoxine/Pyrimethamine (Fansidar) and Chloroquine to run out of stock. Furthermore, this study confirmed that all pharmacists agreed that irrational prescribing practises, ineffective drug management, lack of implementation of the essential drug list, and anti-malarial drug stock-outs were the major factors contributing to irrational malaria treatment practises in Pakistan's public and private sectors. (Malik et al., 2013)

Asif et al. (2018) analysed the OOP healthcare spending that required the prescribing of generic medicine. The purpose was to evaluate medical and pharmacy students in Lahore, Pakistan, on their knowledge and attitudes towards generic medication. A convenient sampling approach was used to conduct a cross-sectional study with a sample size of 295 students from third, fourth, and final year of studies, involving 185 pharmacy students and 110 medical students. Students' understanding of generic medication was assessed using a pre-validated questionnaire. The findings revealed that the majority of pharmacy and medical students understood the difference between brand and generic drug, with 86 (29.7%) students believing that generic medicine is substantially similar to brand name products and 108 (36.5%) students agreeing that using generics will reduce the cost burden. When compared to brands, there were reservations concerning generic medicine's quality ($P \leq 0.05$) and side effects ($P \leq 0.005$). (Asif et al., 2018)

An attempt was made by Mehmood, S. (2015) to estimate the effects of Government Regulations on Pakistan's pharmaceutical market and how it might affect welfare. He determined the loss/gain in terms of welfare on the country due to counterfeit medicines, lower level of investments, government procurement and lastly, due to resource underutilization. He concluded that government-imposed rules, particularly the unwillingness to allow price increases for pharmaceutical items, had detrimental impacts on the industry and the general welfare. It includes not only total withdrawal of firms from the market, but also drug smuggling. Overall, the effects on welfare were extremely negative. The calculations on the chosen criterion reveal annual losses are estimated to exceed Rs. 100 billion. Hence the government involvement in the pharmaceutical industry has only worsened the problems rather than ameliorating them. (Mehmood, 2015)

2.1 Generic drugs analysis in foreign countries

The shortage of drugs has had a long history on a global scale as well, continuing to the present date. We can, for example, find writings on insulin shortages of the early 1920s. Multiple studies have been conducted to cite the reasons as to why drug shortages occur. Quality production challenges, insufficient raw material supplies, regulatory issues, product discontinuation of products from the market, procurement issues, business decisions, and natural disasters are among them. (Mori et al., 2012) (Walker et al., 2017) (FDA, 2017) (Tan et al., 2016)

Hornecker, J. R. (2009) conducted a study to review history of generic drugs, its approval process and challenges faced during its utilization among the consumers. He found the positive welfare impact of generic drugs on consumers regarding the significant improvement not only on direct costs but also on the indirect costs with

respect to compliance, adherence to the drugs, thus leading to enhanced productivity. He concluded generic drugs to be a low-cost alternative to branded drugs in order to justify the needs of consumers in an affordable manner. (Hornecker, 2009)

Berndt, E. R., et al. (2007) outlined the issues related to generic drugs, its price competition in the market and consumers' welfare. For this purpose, they reviewed the data on generic drugs entry between 1999 to 2003, and case studies of authorized generic drugs from 2003-2004 in order to access the welfare impact of generic drugs entry on consumers under different market conditions. They found probable patterns of welfare impact on consumers through short run prices, that has positively impacted the welfare of drug consumers. (Berndt et al., 2007)

In order to make healthcare affordable, Indian government initiated a step to prescribe generic drugs only, after getting enough evidence regarding the equivalency of generic drugs to that of branded ones. There had been serious concerns about generic drugs quality and its availability in India. To explore the scientific aspects of initiating this generic prescription, Dixit, A., et al. (2018) analyzed the challenges and the benefits of generic drugs practice in the country, along with entertaining the concerns regarding its quality and availability. They also found positive impact of consuming generic drugs, which is in accordance with the previous researches, thus favoring generic drugs in order to limit healthcare expenditure both by the government and the consumers. They found increased availability of drugs at the affordable costs, thus contributing to the reduced poverty while progressing to achieve health objectives in the country. (Dixit et al., 2018)

Hassali, M. A., et al. (2014) analyzed the vital role of generic drugs in healthcare system. They reviewed different policies, adopted by 8 different countries, to promote generic drug as a cost-effective alternative to the branded drug. They found variable

utilization of generic policy among different countries; the main reason being the negative perception about the quality and efficacy of generic drugs. After getting insights from the selected countries, they learnt that there must be rigorous scientific based registration system for registering generic drugs in order to ensure quality, efficacy, safety and bioequivalence of generics. They suggested there must be well-designed promotion programs that address the utilization of generics; there must be cooperation between healthcare professional to ensure quality use of generic drugs and its successful implementation. Negative concerns regarding its quality, safety, efficacy are needed to be addressed to make its acceptance among consumers, i.e., healthcare professionals and patients. They also highlighted that there must be sound financial incentives for doctors and pharmacists to encourage its utilization; and the main policy adopted by particular country to promote generic drugs utilization needed to be facilitated by some complementary policies to overcome all the challenges that hamper its effective implementation. (Hassali, Alrasheedy, et al., 2014)

Branstetter, L., et al. (2016) estimated the welfare effects of generic drugs entry by using the data for hypertensive drugs in US (2000-2008). They analyzed the data by using random coefficient logit model. They calculated consumer gain to be $42 billion whereas producer loss of $32.5 billion from generic entry, thus estimating a $9.5 billion gain in social welfare; thereby shifting the demands from branded drugs to generic drugs. (Branstetter et al., 2016)

Conti, R. M., & Berndt, E. R. (2018) estimated the influence of generic entry on the prices and utilization of prescription drugs during the course of six years (2001-2007) in U.S., utilizing the data from IMS health for the drugs used for the treatment of cancer. They observed the extent to which estimated prices of these drugs undergoing loss of patency fall with the generic entry, and observed substantial price erosion after generic

entry. They concluded that in response to loss of exclusivity and upon the entry of generic drugs, there was rise in prices of branded drugs and fall in the prices of generic drugs, thus having positive impact on consumers with its increased utilization. (Conti & Berndt, 2016)

Hassali et al. (2006) looked at the factors that affect generic medicine prescribing among GPs in Melbourne, Australia. In a qualitative approach, a convenience sample of GPs practising in Melbourne were questioned using a semi-structured interview guide. Seven significant themes emerged from the content analysis of the interviews: drug prescribing trends, generic drug knowledge, patient compliance of generic drugs, difficulties with 'pseudo-generics' and drug labelling, drug marketing, brand substitution by community pharmacists; and lastly, generic drug prescribing methods. To speed up the present rate of generics prescribing general practitioners need to be convinced about the efficacy and safety of generic medicines, along with educating senior medical students and patients about generic drugs and their prescription. According to this study, practitioners in Melbourne had mixed opinions towards prescribing generics. The study also revealed that some physicians still have misunderstandings regarding the safety and effectiveness of generic medications. Unless they are properly educated, this will have a detrimental influence on generic drug use in the future. (Hassali et al., 2006)

Hassali et al. (2014) conducted a narrative review focusing on the perceptions of physicians working in low- and middle-income countries towards generic medicines. The goal of the study was to compile existing literature on physicians' awareness, attitudes, and opinions of generic medicines in low- and middle-income countries (LMICs) and compare the results to those in high-income countries. The approach was based on a systematic search of publications in peer-reviewed journals between January

2001 and February 2013. The findings revealed that the primary difference between high-income and low- and middle-income countries is that physicians in high-income countries have a more favourable attitude toward generic medications, whereas physicians in LMICs have a mixed attitude toward generic drugs. The authors found that physicians in LMICs have conflicting feelings about generic medications. This might be related to variations in health-care systems, pharmaceutical funding systems, medicine regulations, educational initiatives, and drug information sources. (Hassali, Wong, et al., 2014)

James et al. (2018) used a "Comparative Cross-Sectional Approach" to stress the utility of generic medications in healthcare. The purpose of this study was to assess final-year undergraduate medical, pharmacy, and nursing students in Sierra Leone's knowledge and awareness about generic drugs. At the University of Sierra Leone's College of Medicine and Allied Health Sciences, they conducted a questionnaire-based cross-sectional study of these students. Only two (3.2%) of the 62 participants were aware of the acceptable bioequivalence criterion. In all three groups, at least half of respondents agreed that all generics are medically comparable to the originator brand. In comparison to pharmacy students (5/11, 45.5 percent), at least half of medical (21/42, 50 percent) and nursing (6/9, 66.6 percent) students thought that unique medications require greater safety requirements than generic drugs. The majority of them felt that greater information on generics' safety, quality, and efficacy is needed (59/62, or 95.2%). Despite differences in responses, all three groups of healthcare students showed a lack of understanding and misperception about generic medications. Future healthcare practitioners in Sierra Leone require extensive training on generic drug at healthcare training institutes. (James et al., 2018)

An extensive review was carried out by Jonathan Minh Phuong et al. (2019) in which they used internet search engines such as Medline, Embase, Global Health, PsycINFO, and International Pharmaceutical Abstracts to look into the effects of drug shortages on patient outcomes, using the two crucial themes of medicine scarcity and patient outcomes. Drug shortages were mostly reported to have negative economic, clinical, and humanistic consequences for patients. During times of shortage, patients reported higher out-of-pocket expenditures, rates of drug faults, adverse events, mortality, and frustrated complaints, as well as a sense of being a burden to themselves and caregivers. The findings of this study add to our understanding of how drug shortages affect patient outcomes. The majority of research found that pharmaceutical shortages had unfavourable clinical, economic, and humanistic consequences for patients. (Phuong et al., 2019)

Milena McLaughlin et al. (2013) presented a study that delved into the impact of drug shortages on patient outcomes, clinical pharmacy operations, patient complaints, and institutional costs. Demographics, adverse events, prescription errors, patient outcomes, patient complaints, and institutional cost were all covered in this survey. The poll was given to 1,516 pharmacy directors. They discovered adverse events that were most likely or possibly linked to drug shortages, medication errors such omission, wrong dose dispensed/administered, wrong drug dispensed/administered, alternative medicine use, and delayed/cancelled care. The majority of respondents cited rising institutional expenses as a result of drug shortages, implying that medication errors and adverse events are still occurring as a result of drug shortages – often resulting in poor patient care, high institutional costs, and patient complaints. (McLaughlin et al., 2013)

Sonia Romano et al. (2021) conducted research in Portugal to examine the impact of drug shortages in community pharmacy on patients and the health system. They came

to the conclusion that drug shortages in community pharmacies are a national issue with severe repercussions for patients and the health system and it must be addressed and mitigated. (Romano et al., 2022)

Chapter 3

Pharmaceutical Regulatory Framework

This chapter provides an overview of the regulatory framework of Pakistan's pharmaceutical sector, its organizational structure and the drug policies.

3.1 Overview

The pharmaceutical sector in Pakistan is governed by the Pakistan's government, with the federal government in charge of drug licencing, manufacture, registration, pricing, imports, and exports, and the respective provincial governments in charge of distribution and sales of the drugs. The registration of new drugs and manufacturing facilities is controlled by DRAP, which is an autonomous regulatory organisation. It also establishes the MRP (Maximum Retail Price) for all drugs being sold in Pakistan. DRAP operates autonomously and independently to implement national drug and drug regulatory policy, reporting to the Secretary of Health and Minister of Health. Under the Drug Act, DRAP was instituted in 2012 to govern the manufacture, storage, distribution, sale, import, and export of beneficial commodities in Pakistan with the major goals to assure the safety, efficacy, and quality of pharmaceutical goods for Pakistan's citizens, patients, and customers. DRAP issues drug manufacturing licences and drug registrations (market authorization), regulates drug pricing, authorises drug imports and exports, and imports raw materials, as well as publicises and manages quality and compliance issues. Provincial health departments are responsible for drug marketing and sales, drug storage, distribution, and transportation of drugs as well as the management of other issues at the provincial level. The DRAP Chief Executive Officer (CEO) is the authority's leader and a pharmacy, regulatory affairs, and drug

policy expert. Under the supervision of the CEO, DRAP has the following 13 divisions and 4 administrative boards, run by 13 directors, who lead different divisions reporting to the CEO. The organizational structure is illustrated below in Fig. 3.1: (DRAP)

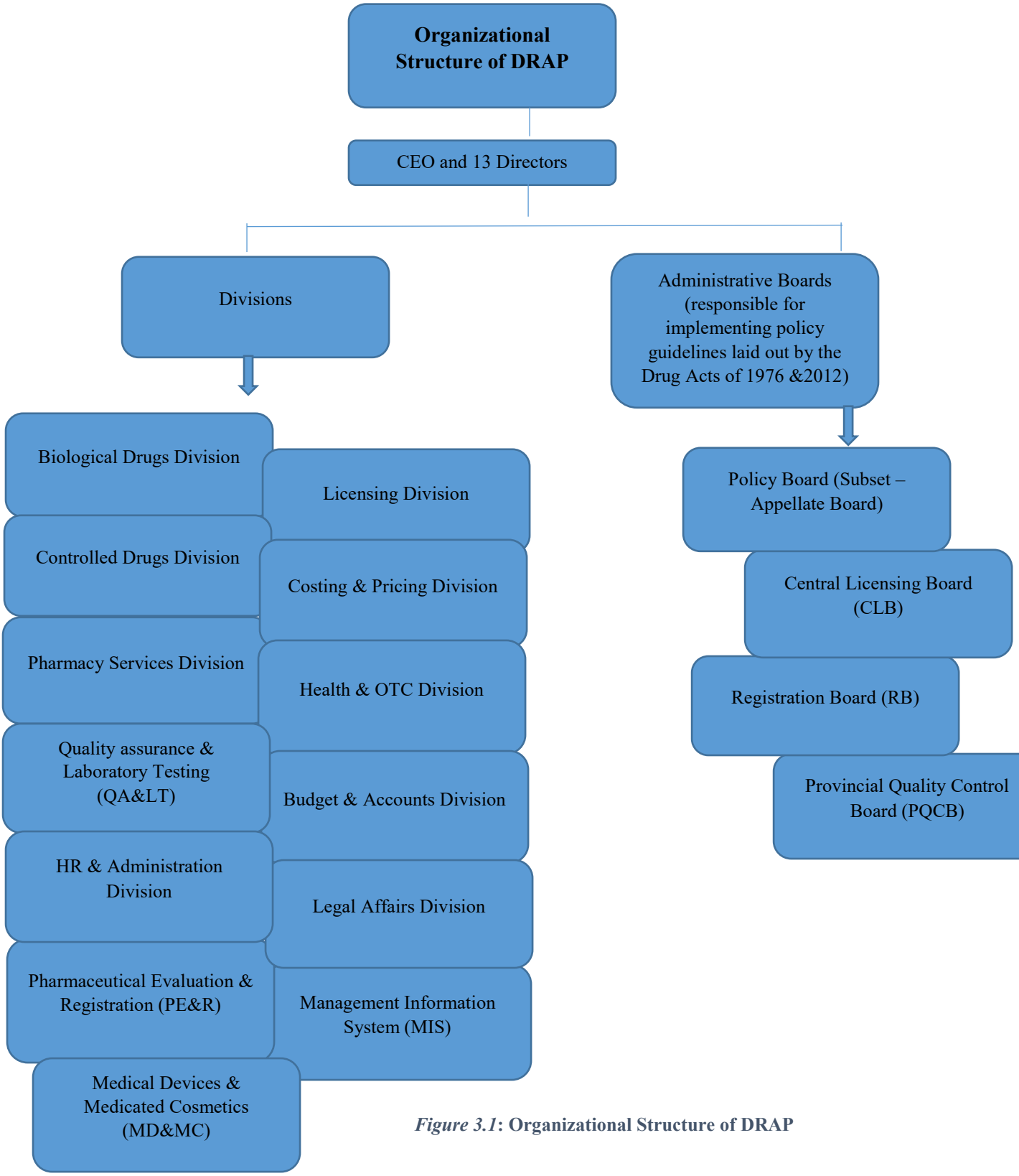


***Figure 3.1*: Organizational Structure of DRAP**

3.1.1 New Modification in Organizational Structure:

The new organizational structure of DRAP includes eight technical divisions and five support divisions. Federal drug inspectors, assistant drug controllers, and an appellate board support the department of quality assurance that further has five field offices. Registration, medical equipment, biological drugs, controlled drugs, pharmacy services, health & over-the-counter, costing, and pricing are the other seven technical divisions. (DRAP, 2018) Pharmacovigilance, clinical trials, contract research organisation regulation, and research are all covered by the pharmaceutical services section.

3.2 Regulatory Infrastructure

Regulatory framework of the Pharmaceutical sector is administered both by Ministry of National Health Services Regulations & Coordination (NHSR&C) and the DRAP, along with Pharmacy Council of Pakistan (Regulator for Pharmacists). (Dawani & Sayeed, 2019) The following major functions are carried out by Regulatory Affairs: (ICAP)

1. Registration and renewal of license for manufacturing and sale of Pharmaceutical products – All pharmaceutical firms that import, manufacture, or sell drugs in Pakistan must get a government licence. Every five years, these permits must be renewed. For the application and renewal of licences, Regulatory Affairs coordinates with all key stakeholders within the organisation.
2. Registration of newly launched drugs and application for pricing – A pharmaceutical company's new drugs cannot be marketed unless they have been registered under the Drugs Act and their prices have been decided by DRAP.

The Regulatory Affairs division ensures that new drugs are registered in a timely manner and that the most favourable pricing is received from DRAP based on underlying market and cost data.

3. Pricing and inflationary indexation – In Pakistan, DRAP sets the prices for all pharmaceutical items, which cannot be adjusted unilaterally by the pharmaceutical firms. The DRAP must approve any new prices or increases in price.
4. Hardship cases – In certain cases, when the cost of manufacturing a drug rises to the point that it is no longer economically sustainable for the Company to continue to produce and market the drug, it can be up to DRAP to raise the price of the product. DRAP evaluates these hardship instances and decides whether to accept or reject the application.
5. Post registration variations and approvals of Pharmaceutical products – After the launch of products, Pharmaceutical firms must renew their permits every five years. In some situations, if the firm's particulars change, such as its brand name, company name, or source of import, firm can apply to DRAP for a revision in the registration documents.

The Regulatory Framework of the Pharmaceutical Sector in Pakistan is illustrated in figure 3.2 below:

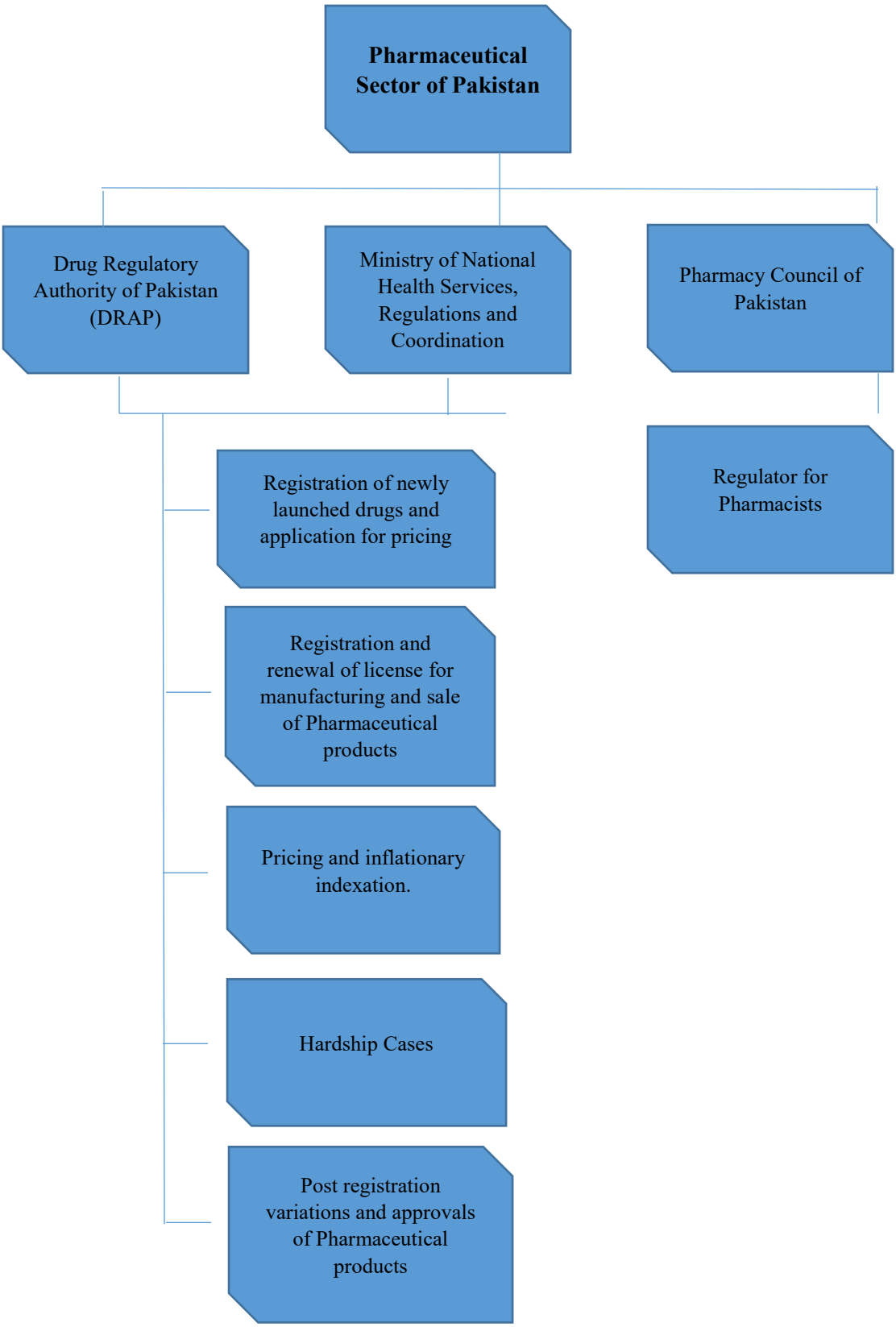


Figure 3.2: **Regulatory Framework of the Pharmaceutical Sector in Pakistan**

3.3 Drug Acts and National Drug Policy

Since the country's establishment, there have been two major Drug Acts –the Drugs Act of 1976 and the DRAP Act 2012, which was construed as a continuation of the 1976 Act. It extends to the whole of Pakistan.

The Drug Regulatory Authority of Pakistan Act of 2012, as well as the Drugs Act of 1976, lay out the legal framework for the manufacture, import, export, storage, distribution, and sale of medicinal commodities in Pakistan. The DRAP Act 2012 is authorised to provide effective coordination and execution of The Drugs Act, 1976 and to bring harmony in inter-provincial trade and commerce of therapeutic goods. (DRAP, 2022)

National Drug policy - sanctioned by Federal Cabinet of Pakistan – has the objectives aiming at rationalizing prices, promoting the "essential drug" concept and the rational use of drugs, and encouraging local production, especially the basic manufacture of active ingredients. The policy is also aimed at effective quality control, the elimination of "spurious" drugs, the development of systematic drug supply and distribution and the encouragement of R&D. The Health Ministry is to prepare a "comprehensive master plan" indicating targets and resources needed to fulfil the policy, and identify resources and technical support that could be generated from international and other sources. (letter, 1997)

3.4 Policies Review

Uncertainty in policy can have severe consequences for an economy. It can be difficult to prepare for the future, especially in long-term investments, when firms are unsure

whether a policy will be maintained or not. Governments of Pakistan have a reputation for being inconsistent in their policies throughout the time. We usually see either the same government making regular modifications to existing policies or a new government introducing a set of new policies. The Statutory Regulatory Offer (SRO) is the preferred tool for implementing these frequent modifications in policies.

Since decades, Pakistan's pharmaceutical sector, like many other sectors, has been subjected to periodic legislative changes. And the situation has not improved in the post-DRAP age. The following is a partial list of occasions in which the government has overturned its own regulations in various areas under its jurisdiction.

1. An April 2020 notification notified that the holders of valid Drug Manufacturing Licenses (DML) were allowed to manufacture hand sanitizers according to the approved formulae, but only for three months! On the 10th, 14th, and 17th of April 2020, similar notifications were issued enabling the manufacture of hand sanitizer. But, on the 21st of May 2020, per Cabinet directive, all four notices were withdrawn in less than a month! The decision was made without any explanation.
2. The Alternative Medicines and Health Products (Enlistment) Rules, 2014, were adopted by SRO 412 (I)/2014 (named 'Alternative Medicines and Health Products (Enlistment) Rules, 2014'), dated 27th May 2014, which was revised by another SRO in 2016.[7]
3. While SRO No. 28(1)2013, issued on 22nd January 2013, and SRO No. 334(1)2010, dated 18th May 2010 (and similar SROs) were intended to discourage imports, SRO No. 577(1)2016, dated 15th May 2016, allowed for a five-year exception for the import of drugs intended for donation. However,

[7] F-3-5/2013-DDC (Alt. Med.), dated 10th June 2016

there is no fool proof mechanism in place to prevent individuals or organisations, particularly informal market participants, from abusing this exception.

4. The rule for applying for 'hardship' cases was adjusted under SRO No. F.11-2/2020-DD (P) dated 15th July 2020, reducing the number of days from 180 to 120, which are eventually accepted by the federal government after being provided by DRAP. Part 'b' is crucial, as it allows the federal government to cancel agreed-upon price rises in line with the Consumer Price Index (CPI) provided it has a 'cogent' justification, thereby keeping the window open for the government cancelling agreed-upon price increases.
5. Importing much-needed COVID-19 vaccines was recently hampered by policy inconsistencies. The Drug Regulatory Authority of Pakistan (DRAP) issued SRO No. 113(I)/2021 on February 2, 2021, permitting unrestricted import of vaccines from abroad and enabling the importer to sell them at market prices. However, on March 18, 2021, another SRO (No. 308(I)/2021) revoked the earlier SRO, depriving the public of the opportunity to receive more immunizations vaccines.
6. COVID-19 vaccines are covered under SRO No. 307 (I)/2021, issued on March 18, 2021. According to SRO, the vaccine must first be approved by DRAP. However, new vaccines arrived in Pakistan recently (purchased by the federal government) without DRAP's knowledge.
7. Between the 6th and 17th of April 2020, four SROs were issued, all of which were revoked by SRO (F. NO 4-2/2017-DD (H&OTC) in lieu of the Cabinet's decision on the 5th of May 2020.
8. SRO No. 1002(1)/2013, dated November 27, 2013, was issued to abolish the 'prize freeze' policy, which had been in place for more than a decade. It was

cancelled within two days after the Prime Minister ordered to withdraw drug price increases.

The above were just a few examples of how the government and its regulator's policies are inconsistent.

Aside from the issue of policy inconsistency, there's also the reality that, like its predecessor DRO, DRAP takes a reactive rather than proactive strategy in many instances. This is another factor that leads to policy/regulatory changes. For instance, SRO No.F.296-DRB/2020 (PE&R) (ft.), dated 4th February 2021, directs manufacturers to reveal 'gluten/lactose' on labels/packs. But this happened only after persistent complaints reported by patients suffering from Celiac disease. Similarly, DRAP requested that manufacturing licences for Fludrocortisone tablets (for Congenital Adrenal Hyperplasia) be cleared on a priority basis in Pakistan via notification No. F.1-21/2019-Add; Dir. (PE&R) as devastating shortages began to emerge in Pakistan. However, DRAP only came to know about it after complaints from PM Citizen's Portal.[8]

[8] F. No 4-2/2017-DD (H&OTC) (Pt), 6th April 2020

Chapter 4

Data and Methodology

This section covers in detail the data sources and methodology that we adopted in the paper for analysing the welfare impact of generic drugs in Pakistan. This chapter will discuss all the variables that have been used in the research followed by the methodology adopted for the data collection and its further analysis.

4.1 Data

4.1.1 Data source

For the current study purpose, the data was collected from:

1. Primary sources
    a) Four Federal drug inspectors (information about drugs experiencing shortages and local drugs whose production has been discontinued)
    b) Ten Pharmacists from all over Pakistan (information about drugs experiencing shortages)
    c) Ten Industrial officials from all over Pakistan (information about drugs experiencing shortages and local drugs whose production has been discontinued)
    d) Leading retailers in leading cities of the country (Islamabad, Rawalpindi, Lahore, Karachi, Peshawar)
2. Secondary sources

a) Four leading newspapers (Dawn, The News, Express Tribune and Business Recorder, that have been frequently reporting on drugs experiencing shortages)
b) National Health Accounts (Statistics about out-of-pocket expenditure, total health expenditure, per capita expenditure on health, and percentage of drug expenditure out of total health expenditure)
c) Drug Regulatory Authority of Pakistan (DRAP, which issues the National Essential Medicines List)

4.1.2 Data Description

This study utilizes the mixed research methods (qualitative and quantitative). For qualitative analysis, a in-depth interviews were conducted out among the pharmacists, DRAP, PPMA[9] and PB[10] officials, complemented by questionnaire. For quantitative analysis, both the primary and secondary data sources were utilized.

Monthly and annual time series data related to drugs experiencing shortages over the last six years i.e. 2015-16 to 2020-21, were chosen for inquiry into drug shortages (upon which we base our monetary calculations) as well as econometric analysis.

4.1.3 Study tool/Study Design

For execution of thesis, both primary and secondary data has been collected. The primary data collection was done through survey using the structured interviews complemented by a self-designed structured questionnaire. The interview questions started out with general questions, and then condensed down to the study's main objectives. The questionnaire consists of three areas/domains. The first part consisted of queries related to sociodemographic factors such as, age, locality, level of education

[9] Representative of 237 Pharmaceutical companies in Pakistan
[10] Representative of 22 Multinational Pharmaceutical companies

and years of working experience in the pharmaceutical sector. The second part of questionnaire inquires about company information and the respondents'

designation in particular company. And the third part comprises of questions related to our research objectives inquiring about the drug shortages, the reasons behind it, some queries related to APIs, Drug policies, black markets and impact of that shortage on patients. We opted for this approach as it is suitable to explore untouched issues and effectively translate the interviewees' viewpoints and experiences. The response was more than we expected, as PPMA (comprising more than 300 domestic manufacturers) and PB (comprising all the MNCs) forwarded a combined reply, reflecting the industry wide answers to the questionnaire. The names of pharmacies and retailers have been anonymized as per ethical considerations.

On the other hand, the secondary data sources like was newspapers articles, Pharmapedia and other published sources on drug shortages have also be optimized upon. NEML from DRAP has been evaluated in accordance with the categorization of different diseases and analysed correlating to our variables.

4.1.4 Study Setting

This study was primarily conducted in Islamabad, with some travel to nearby Rawalpindi for the purpose of interviews and data gathering. In this study, four Federal drug inspectors, ten Pharmacists working in different hospitals and leading pharmacies and ten Industrial officials (PPMA and PB members) from all over Pakistan were interviewed for our study. The ones present in Islamabad and Rawalpindi were interviewed in their presence, while interviews from persons in Karachi, Peshawar and Lahore had to be conducted over the phone. Wherever optimization opportunities in terms of resources and time saved beckoned, they were employed. For example, in terms of retailers, D-Watson's main branch in Blue Area Islamabad offered one such

opportunity since it had drug sales and availability data from all its branches in major cities of Pakistan, making it easier to confirm or deny the shortage of a particular drug without the need for physically travelling to other cities. Similarly, pharmacies of major hospitals also offered similar advantage, whereby similar nature data was present in their systems. However, they do not share their data with other pharmacies or with other hospitals. Every unit of interview seems to have maintained its own, unique database.

4.1.5 Selection of Study Participants

Purposive sampling accompanied by the convenience sampling was used to engage the study participants. In the first stage, all the pharmacists either working in hospitals or in leading pharmacies, residing in twin cities (Rawalpindi and Islamabad) were purposively approached during working hours through telephonic calls and personal visits, and invited to participate after briefly explaining the intent of the study. The pharmacists residing in other cities were approached through telephonic calls only. Further information regarding the study was provided to them on demand. PPMA and PB were also approached to participate in the study. Questionnaires via email were sent to these officials as they are representatives of 300 domestic and MNC pharmaceutical companies in Pakistan. In the next step, those who agreed to participate in the study were interviewed face-to-face at their offices in hospitals and pharmacies. These interviews were complemented by structured questionnaires. To ensure the reliability and quality of data gathered, the pharmacists having work experience of at least 10 years were included in study.

4.1.6 Sampling Procedure

This study sampled out those generic drugs that have experienced shortages over the period of last six years, either due to discontinuation of production, or the drugs which

are available from black market during shortages, using both primary as well as secondary sources. The study concentrated on the National Essential Medicines List (NEML), which contains government mandated list of drugs that are considered essential for human health.

Initial input was taken from the seminal work done by Mehmood who carried out a survey of drug shortages in twin cities in 2017. (Mehmood, 2017a) This work and the list of drugs have been further updated in this study. Data related to the generic drugs experiencing shortages has been obtained from Federal drug inspectors, pharmacists, and producers all over the country using structured interviews complemented by structured questionnaires; through purposive sampling. The reason behind opting for this was that the pharmacists specially practicing in hospitals are well aware of the shortages issue since they face this situation frequently. Besides these primary sources, secondary sources like newspapers articles and other published sources on drug shortages have also been optimized upon. NEML from DRAP has been evaluated in accordance with the categorization of different diseases. All drugs – categorized as essential ones by DRAP, have been classified into 30 categories. Each category has been segmented further to delve into the determinants of drugs experiencing shortages.

4.2 Methodology

This section discusses the methodology (both monetary and econometric), unit of our analysis, theoretical basis for drug shortages, issues encountered in data accumulation and usage, model description, procedure and steps involved in analysing the welfare impact of generic drug shortages.

4.2.1 Unit of Analysis

Our unit of analysis is the list of drugs that have experienced shortage in the market over the last six years, or are available in black market during shortages. The drugs can be further subdivided into categories:

1. Imported drugs that can be manufactured locally given the right incentives, and
2. Local drugs whose production has been discontinued
3. Drugs available in black market at higher prices during their shortages

4.2.2 Methodological Framework

4.2.2.1 The theoretical basis of drug shortages

The theoretical underpinning of this research into drug shortages, as well as shortages in general, is provided by the theory of price controls! This theory can easily have demonstrated by a standard supply-demand diagram (on the left side). (Neely, 2022) The supply and demand diagrams intersect at a point where quantity supplied is QE

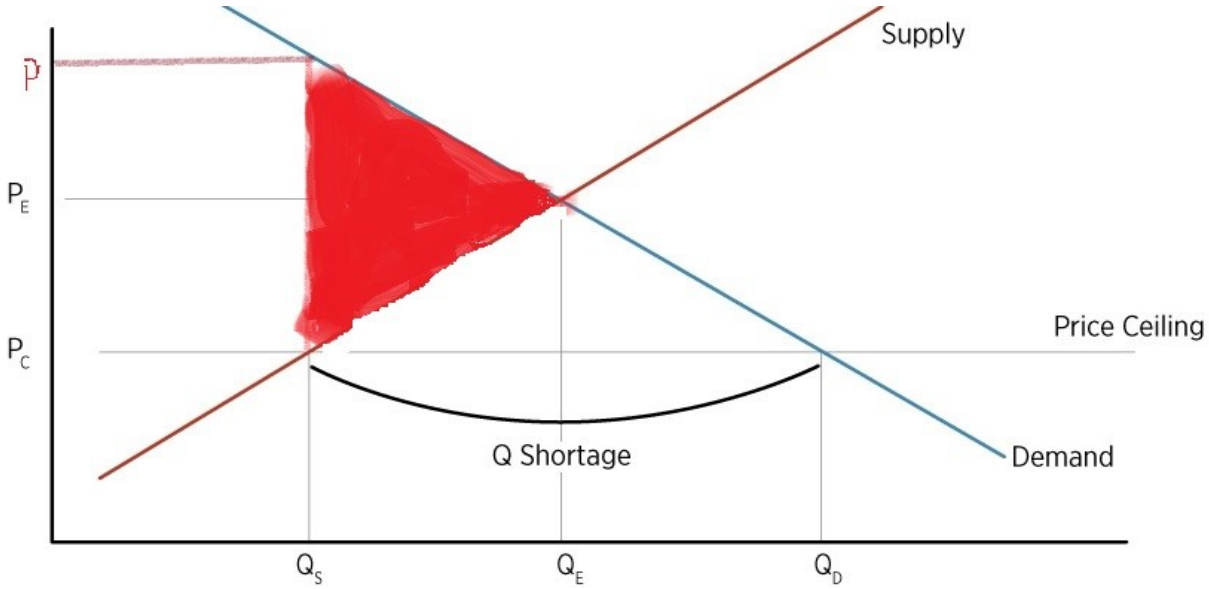


Figure 4.1: **Standard Supply-Demand Curve**

while product price is P_E. But if a

price ceiling is forced upon the market by the regulator/government, the quantity demanded settles at Q_D, but the supply is much lower than the equilibrium level, with

manufacturers only willing to provide up till point Q_S, thus creating a shortage between demand and supply (marked as 'Q Shortage').

This shortage is a 'black market' price, above the equilibrium price P_E. (shown at point 'P'). The end result of government's efforts to keep price down is a higher price of a product, inflicting a loss upon the consumer who has to spend more. In the diagram, the loss is shown as the shaded area between P_C and P, labelled as 'welfare loss' in textbook lingo. Simply put, evidence from economic history goes squarely against such interventions since they create more problems than solutions.[11] However, it continues to be a go-to policy in many countries.

This diagrammatic representation and the interpretation of its implications is a classic reflection of what has been happening in Pakistan in terms of drug shortages- the Government believe that pricing should be left to its discretion, which it has used with fervour under the guise of welfare of the poor people. As described above, this policy saw its extreme in the case of 'price freeze' policy between 2001 and 2013, whereby drug prices were not allowed to increase. Yet, suppressing drug prices below the market price has only resulted in debilitating and persistent shortages of critically needed drugs.[12]

4.2.3 Issues in data accumulation and usage

As state above, this is the first of its kind of exercise in Pakistan, aiming to come up with a monetary loss, inflicted upon the consumers that result due to drug shortages.

[11] The most damning indictment of price controls as a policy comes in the form of 'Forty centuries of wage and price controls: How not to fight inflation' by Robert Scheuttinger and Eamonn Butler, which details the ineffectiveness of such policies. For a more recent example, see 'Price controls are disastrous. Just ask South America', by Alex Horenstein and Noah Williams

[12] An exception to the situation depicted above in the diagram would be a shift in demand curve ('Demand' in the diagram) that may cause drug shortages. Such a case occurred in the immediate aftermath of COVID-19 as demand for certain drugs short up considerably. But in Pakistan's case, it is the exception rather than the norm!

Suffice to say, this exercise/research threw up exceptionally difficult challenges that are unique in their nature! These challenges arose due to:

1) Absence of any centralized database that counts the instances of drug shortages while also keeping a record by their names and nature/reason for a particular drug's shortage
2) The geographic non-linearity in instances of drug shortages. In other words, presence or absence of a certain drug in a certain geographic locality is no assurance that the same situation would persist in another geographic locality; and
3) The very complex nature of drugs and their usage. For example, two different brands may contain the same API, yet their reaction and effect upon a patient may differ. Moreover, the opinion regarding the substitutability of drugs with similar APIs remains divided among the medical community, pharmacists and pharmaceutical business

The absence of any centralized database meant that the instances of drug shortages had to be collated from various sources and then confirmed through pharmacies in leading hospitals during the in-depth interviews and leading retailers in various cities. Arguably the most surprising revelation was that the main regulator, the DRAP, has little or no information upon this critical matter. In fact, their policy in this particular matter has followed a reactionary path rather than being proactive, amply demonstrated by the recent events surrounding shortage of Panadol across Pakistan. Briefly put, despite warnings and letters by the industry and other sources that the drug may suffer shortage given the issues surrounding price increase, the regulator turned a deaf ear until the shortages became rampant and debilitating. (Mehmood, 2022a) Except for a few particular instances, like an extreme surge in demand for certain drugs during COVID-

19, DRAPs reaction always follow a reactionary path. In other instances, its Standard Operating Procedure (SOP) has itself been a cause of shortages, aside from the usual issue of granting price increases. A recent example came in the form of manufacturing the generic version of anti-COVID drug 'Remdisivir', whose demand had skyrocketed after its approval as an anti-COVID 19 drug. In May 2020, the manufacturer of the drug (Gilead) gave approval to the local manufacturer (Ferozesons Ltd.) within a week after inspecting its facilities. However, despite the fact that Gilead's product (and the firm itself) is a Federal Drug Authority (FDA) approved, meaning it has attained the international gold standard for drug manufacturing, DRAP took over two months to let the domestic manufacturer start manufacturing the same drug locally. (Usman Khan, et al., , 2021) In the meantime, imported Remdisivir were sold at astronomical rates within Pakistan.

4.2.4 Methodological strategy

Given the absence of any central database, the seminal survey by Mehmood (2017), containing a list of 115 drugs that suffered shortages, was used as a starting point. (Mehmood, 2017) Further drugs, in terms of recurrence of shortages, were added after visits to pharmacies, hospitals and retailers. Moreover, various newspapers (specifically DAWN and Express Tribune) report drug shortages randomly. The reported drugs from them were added in case they were not in the compiled list.

Data on drug shortages from all these sources was gathered, and finally a list of 278 drugs was compiled that reflects the instances of reported shortages since 2015-16. A very helpful trick, that not only reduced the time spent on interviews but also confirming/negating the reported shortages of drugs, employed during the interviews was to access the records of a large retailer! In our case, as stated above, it was D-Watson's main branch in Blue Area Islamabad. The advantage was that the Islamabad

branch had drug sales and availability data from all its branches in major cities of Pakistan, making it easier to confirm or deny the shortage of a particular drug without the need for physically travelling to other cities. Similarly, pharmacies of major hospitals also offered similar advantage, whereby similar nature data was present in their systems.

However, in terms of calculating the probable monetary losses inflicted upon the users due to shortages, all the drugs in the list could not be used for two reasons: a) the shortage was not geographically uniform. A drug available in Karachi at a certain time, for example, may have been unavailable in Rawalpindi, Islamabad and Peshawar. Similarly, a drug available in major cities of the country may not have been available in peri-urban and rural area retail outlets and pharmacies; and b) not all the drugs suffering shortage were non-substitutable! In other words, there were many drugs which had a substitute, meaning that their absence did not cause much discomfort (financial or physical) to the end-user.

Therefore, keeping in view these two important considerations, the list was filtered down by drugs whose shortages were geographically uniform (whether in major cities or outside of them) and those that have no generic substitute. In the end, the final list used for calculating the monetary losses after (applying the filters) was shortened to 50 drugs. It is important to note that this list was compiled only after thorough discussion/query with leading pharmacists, retailers and industrialists who confirmed that the drugs in question had no substitute.

One very surprising aspect, though, that propped up during the interviews related to the quality of drugs. Sometimes, a shortage may be caused when hospitals or retailers find out that the drugs being used had some shortcoming (like the API not performing according to its specifications, or ‘spurious’ API). But hospitals and retailers were tight-

lipped about naming the manufacturers or drugs. Their reason for not divulging such details was that in case they name the manufacturer, it could invite retaliation by the manufacturer in the future, thus jeopardizing the supply of a certain drug, which could be very bothersome especially if the drug is manufactured by only a single manufacturer[13].

The third issue that made these interviews very challenging, especially in terms of finalizing the list of drugs to be used for monetary estimates, is the complex nature of drugs and how they tend to react within a patient/user. Suffice to say, every person is different in terms of physical characteristics, which implies that the same drug may have very different effects upon different users. The following are few examples-

a) Nalbuphine and Fentanyl are both categorized as 'narcotic analgesics'. They both are administered pre and post-operations to lessen the pain. However, when the pain is extreme, Fentanyl is the preferred go-to drug because it has been found to be 80 times more potent than morphine and more result yielding in terms of immediate relief. Therefore, in cases where the post-operation discomfort is severe, Fentanyl becomes a non-substitutable drug because Nalbuphine takes time to ameliorate the pain
b) Different types of Typhoid vaccines are available in the market, majority of them assembled domestically by local manufacturers. These are usually interchangeable/substitute. However, Pakistan has been experiencing a new, dangerous strand of drug resistant typhoid (XDR typhoid). This particular form cannot be treated through the normal typhoid vaccines and needs a special formulation. Thus, in this case, there are two types of typhoid vaccines that are not substitutes

[13] Which is mostly the case in terms of vaccines

c) There are a number of anti-blood clotting drugs available in the market that can be used interchangeably, with brands like Loprin used extensively across the country. However, when it comes to preventing blood clots in patients during major orthopaedic surgeries, there is no substitute available for Fondaparinux Sodium injection, a synthetic pentasaccharide that inhibits the clotting factor during surgeries (available under brand name 'Arixtra', manufactured by a sole manufacturer)

d) In patients undergoing chemotherapy for various types of cancers, there is little or no substitute for Fentanyl based injections which provide the most potent and immediate relief from pain

e) Clexane (enoxaparin) and Heparinol (Heparin) are both classified as anti-coagulants used in treatment of Deep Vein Thrombosis (DVT), with medical practitioners finding it equally effective in treatment. However, in dialysis of kidneys, Heparin is the preferred drug of most practitioners as it has been found to be more effective

f) Etoposide injections are chemotherapeutic injections used to treat ovarian cancers. All of them are imported. However, physicians across Pakistan prefer the ones imported from India as they are within financial reach of most patients. The ones imported from Europe, for example, cost substantially more. A shortage of these injections, as in the aftermath of Balakot episode which led to import ban from India, put patients under tremendous stress since other imported varieties were simply out of reach for most of them

g) Penacillamine and Azathioprine can both be used for Rheumatoid arthritis, but Azathioprine is further used for Lupus nephritis while penicillamine is used for kidney stone removal. Thus, despite being from the same class of drugs, patients using one of these are advised against using the other due to different reactions

h) The drug ‘Paineze’ is of the same category as other Paracetamol containing drugs (analgesic and antipyretic). However, the addition of codeine to its final formulation renders it useless in a number of patients who carry a certain genetic mutation

The above stated examples explain/clarify the assertion of cases whereby drugs not being good substitute of each other despite belonging to the same category. It is these kinds of considerations that were kept in view while finalizing the list upon which monetary calculations are being based, i.e., drugs that have no good substitute (or no substitute at all), are categorized as ‘essential drugs’ whose absence can put lives at risk of death or life-long disability.

4.3 Monetary calculations

This was arguably the most challenging part of the research work after accumulation of data. Part of the reason, as explained above, is the non-availability of data on drugs maintained in a central database that can be accessed by the public. Even more challenging was to search for the sales data and prices by years. To the astonishment of the researcher, even major retailers and hospital pharmacies keep varied data on drugs, and not all of retailers tabulate the sales information. The reason varies by place and by retailers/hospitals, and is out of the scope of this research effort, but suffice to say, it created considerable hurdles in calculations. Multiple sources were used for this purpose, including sales data since 2015-16 from industry officials, retailers and pharmacies.

Both the Pharmaceutical Manufacturers Association (PPMA, representing domestic drug manufacturers) and Pharma Bureau (PB, representing MNCs) did not have any central record of sales data. The sales data on selected drugs was accumulated through

two sources- firms that manufactured the drugs (finalized for calculations), and the firm IQVIA.[14] The sales figures (units sold and total sales price[15]) helped countercheck it against Government mandated prices, revealing the difference (if any) between the official and the sales price (in case of higher sales price than the official price, the sales price is the black market price). The difference between official and black market prices was further verified from retailers and pharmacists in surveyed hospitals. The variation in responses regarding unofficial/black market prices was found to be minimal among respondents, almost converging upon a specific value, helping us calculate the monetary losses inflicted upon the consumers due to drug shortages.

The complete list of the 50 drugs selected for the purpose of monetary calculations is presented in Table-3 below.

[14] It should be noted here that PPMA, PB and the firms manufacturing the selected drugs were extremely reluctant to provide the required data. It required persistent requests, assurance that the research in question is not aimed against firms or the industry, personal contacts through a PIDE staff member and a guarantee not to share sales data with anyone else that finally led to provision of required data

[15] Per unit/per pack price could be gauged by dividing units sold by total sales

Table 3: Final List of Selected Drugs

Amphotericin B (Amfotericina)	**Infliximab (Remicade)**
Anagrelide (Thromboreductin)	**Interferon Alfa-2b (Leveron)**
Azathioprine (Imuran)	**Measles, Mumps, Rubella and Varicella Vaccine (MMR Vaccine and Varivac)**
Benzyl Penicillin (Benzibiotic)	**Methyldopa (Aldomet)**
Botulinum Toxin (Botox 100U)	**Methylphenidate (Ritalin)**
Busulphan (Busulf)	**Milrinone (Milron)**
Cladribine (Cladrim)	**Morphine (Magnus MR/Morfscot/Qonza/Morphine)**
Clidinium and Clordiazepoxide (Librax)	**Nitrofurantoin (Nitrofurantin)**
Clobazam (Frisium)	**Otilonium Bromide (Otomin)**
Codeine and Paracetamol (Codogesic)	**Papilloma Virus Vaccine (Human)**
Codeine, Caffeine and Paracetamol (Napadoc)	**Paracetamol (Panadol)**
Croconazole HCl (Pilzcin)	**Paracetamol, Mepyramine and Pamabrom (Femistar)**
Dactinomycin (Dactinomycin)	**Penicillamine (Vistamin)**
Diazepam (Valium)	**Pilocarpine (Medicarpine)**
Dilfunizal (Dolobis)	**Estradiol And Norgestrel (Progyluton)**
Etomidate (Etomidate Lipure)	**Protamine Sulphate (Protamine)**
Etoposide (Lastet)	**Rabies Vaccine (Veroreb)**
Factor VII Recombinant/Eptacoglpha (Novoseven)	**Remdisivir (Remdisivir)**
Fentanyl (Fent)	**Rotavirus Vaccine (Rotarix)**
Fondaparinux Sodium (Arixtra inj)	**Nitroprusside (Nitrop)**
Glycopyrolate (Pyrolate)	**Tetanus Vaccine (Tritanrix)**
Haemophilus Influenza type B (Hib) Vaccine (Hiberix)	**Tibolone (Livial)**
Hepatitis A Vaccine (Havrix/Avaxim)	**Tocilizumab (Actemra)**
Hyaluronidase (Viscoat)	**Topotecan (Hycamtin)**
Hydroxyprogesterone Caproate (Proluton Depot Inj)	**Vecuronium Br (Norcuron)**

4.4 Quantitative Query

With most of the drugs tabulated, queries revealed that the primary reason for shortages can be traced to the way government regulates the pharmaceutical industry. In other words, regulations are responsible for majority of shortages, especially of critically required drugs with no substitutes. Take, for example, Morphine based drugs, which face persistent shortages majority of the times of any given year. Former Special Assistant to Prime Minister (SAPM) on Health, Dr. Faisal Sultan, talking in context of severe morphine based drug shortages in cancer hospitals across the country (thus putting lives at severe risk), confirmed that the main reason for these shortages was that the government 'approval process' that was 'lengthy'[16]! It is to be noted that this situation has been persisting since decades for the same reason (government administered regulation), clearly reflecting upon the failure of government and its regulator to tackle this issue that puts lives at risk.

The above is confirmed by a simple bifurcation of the drug shortages by their source (from our sample of 278 drugs), as reflected in the pie chart (reproduced below which shows bifurcation by percentages)[17] shown in Fig 4.2.

[16] 'Morphine crisis deepens as cancer patients across the country suffer'
[17] Further clarification as to which category falls under Government induced regulatory burden and which ones don't is clarified in the following lines

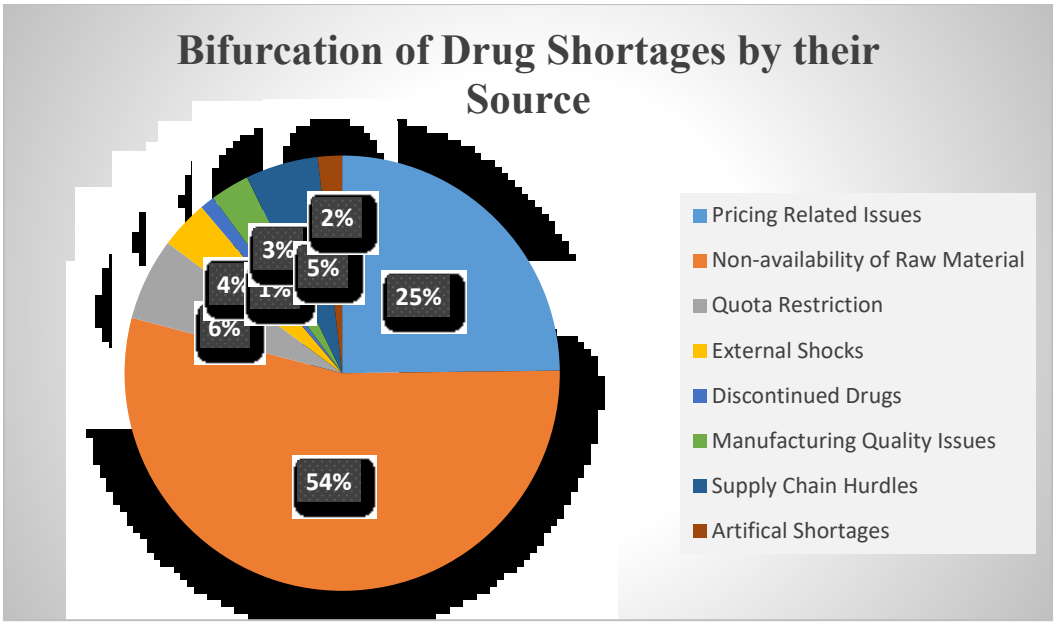


Figure 4.2: **Bifurcation of Drug Shortages**

From a quantitative point of view, though, we want (for example) to establish that the effects of government regulations are related to drug shortages and the predictive power that each factor yields in terms of the shortages. For this, given the number of variables that can contribute to drug shortages, we use a multiple regression method which offers several advantages over the simple linear regression. For example, multiple regression allows us to see the effect of a particular independent variable upon the dependent variable while controlling for other variables! A typical multiple regression model is written as-

$$\boldsymbol{E(Y_i/X1_i = x1, X2_i = x2, X3_i = x3, \ldots Xk_i = xk) = \beta 0 + \beta 1 x1 + \beta 2 x2 + \beta 3 x3 + \cdots + \beta k x k}$$

---Eq1

To determine the main factors that are significant in influencing the welfare impact due to drug shortages, we incorporated simple multiple linear regression. It is referred to the analysis when two or more independent variables are required for a prediction. In other words, it is a statistical technique that can be used to study the relationship between a single dependent and numerous independent variables.

Dataset was constructed according to the frequency of shortages (by 12 months of a year) and also separated by the factor that gave rise to shortages. In terms of factors that have led to shortages of drugs over the timeframe taken, there are two major categories- shortages propagated by regulations and shortages propagated by non-government, non-regulatory intervention, as summarized in Fig 4.3 below. These were further divided into sub-categories to distil the effects of each factor separately, e.g., in terms of shortages that can be trace to government imposed regulatory matters is one major category, which contains the following three sub-categories-

1. **Regulatory burden** (due to DRAP, Health Ministry or Cabinet decisions). Pricing of drugs is the most prominent example, while others include issues like imposition of 17 percent GST or issues related to refund/rebate by FBR
2. **Non-availability of raw material**. Only those instances are counted under this head whereby a specific government regulation makes it impossible to import certain raw materials, as in the case of 'controlled substances' like Morphine (mentioned above)
3. **Quota restrictions**. Again, Morphine and other APIs used in psychotropic drugs provide a good example, since they cannot be exported beyond a government determined quota despite higher demand.

Other than the Government's regulatory interventions, there are other factors that affect the availability and manufacturing of drugs. These include

1. **External shocks** - COVID-19 is a vivid example, as the demand shock instigated by it made the demand for vaccines and certain medicines (like Remdisivir) short through the roof
2. **Discontinued drugs** - Manufacturers, in many instances, decided to discontinue a certain drug as it decided to move towards production of a more financially

feasible drug, or due to emergence of a low cost alternative by a competitor or zero sales due to poor marketing

3. **Manufacturing quality issues** - Regulator may stop the production the production of a certain drug if inspections reveal some shortcoming in Good Manufacturing Practices (GMP)
4. **Supply Chain Hurdles** - Again, COVID-19 is a vivid example, as the supply of raw materials by foreign producers became restricted due to non-availability of shipping
5. **Artificial shortages/Hoarding** - Distributors or retailers resorting to hoarding of a particular drug in anticipation of its shortage in near future, which increases the price of drug (then mostly sold in black).

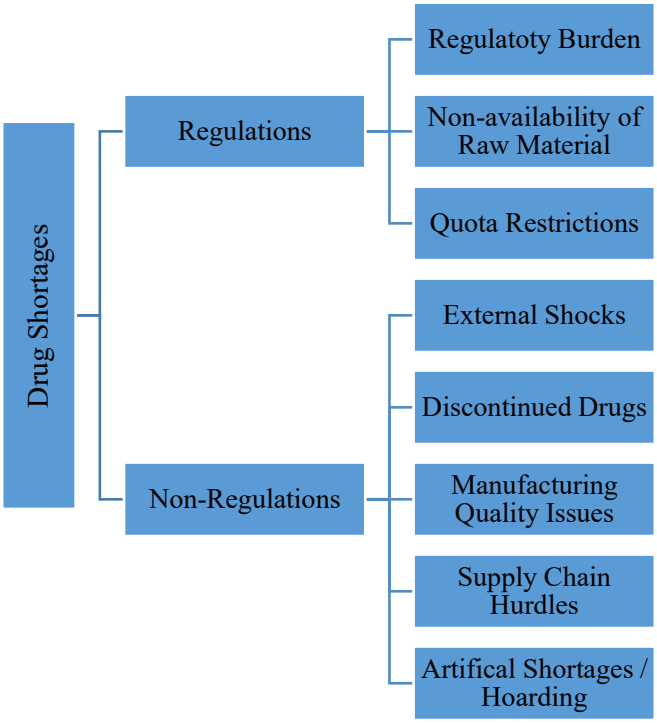


Figure 4.3: **Drug Shortages Determinants**

Based on the above stated division by factors that influence drug shortages, multiple regression equation is written as follows-

$$Y = \alpha + \beta x_1 + \beta x_2 + \beta x_3 + \beta x_4 + \beta x_5 + \beta x_6 + \beta x_7 + \beta x_8 + \mu_i, \ldots where\ i = 1, \ldots, 8 \quad \text{---Eq2}$$

x_1= Regulatory Burden; x_2= non-availability of raw material; x_3= Quota restrictions; x_4= External shocks; x_5= Discontinued drugs; x_6= Manufacturing quality issues; x_7= Supply chain hurdles; x_8= Artificial shortage/hoarding; and μ= error term

Chapter 5

Results and Discussion

All the results of statistical test i.e. multiple linear regression analysis to support the objectives of this study have been analysed, interpreted and discussed in this chapter.

5.1 Welfare loss in monetary terms

Based on all the gathered information, the calculated loss inflicted upon the consumer due to the unavailability of these drugs over the selected time-period came to Rs. 78.5 million.

5.2 Results of analysis

The results of the analysis are as follow:

Table 4: Regression Co-efficient

Standardized Co-efficient			
	Beta	**t Value**	**p Value**
Intercept		-4.079	0.000
Regulatory Burden	0.734	5.397	0.001
Non-availability of Raw Material	0.431	3.969	0.005
Quota Restrictions	0.346	2.104	0.004
External Shocks	-0.054	-0.686	0.221

Discontinued Drugs	-0.021	-0.916	0.173
Manufacturing Quality Issues	-0.130	-1.077	0.251
Supply Chain Hurdles	-0.123	-1.057	0.201
Artificial shortages	-0.157	-1.308	0.334

Table 5: **Multiple Regression Results Predicting Drug Shortages**

R	**R Square**	**Adjusted R square**	**Std. Error of the Estimate**
0.912	0.853	0.822	1.1312

Table 6: **ANOVA Results**

	Sum of Squares	**D*f***	**Mean Squares**	***F* Value**	**p Value**
Regression	28.37	7	4.05	35.086	0.000
Residual	218.794	257			
Total	247.164	275			

5.3 Discussion of results

In hindsight, the results throw up a surprise as well as conform to what we have known about the pharmaceutical industry and the role of regulations in its functioning! The surprise comes in the form of the quantum of monetary losses inflicted upon the masses due to drug shortages and the complementing apathy of policymakers to ameliorate this very pressing issue! Since this is the first attempt of its kind, many might feel astonished at the quantum of calculated monetary losses. But this is primarily due to the fact that, as stated before, this is the first attempt to calculate such a loss. Almost everyone who has had taken recourse to drugs or needed it for some family member would endorse that they have encountered shortages of critical drugs one time or the other[18].

Moreover, while the calculated amount of loss may sound substantial, it pales in comparison to total sales of drugs by the Pharmaceutical industry. Calculations indicate that the total quantum of sales for the time period under consideration exceeds Rs. 1,500 billion.[19] However, this in no way lessens the pain of consumers (especially the patients who need the drug most) who had to suffer due to shortages. During interviews, almost every physicians and pharmacists confided that innumerable deaths have occurred over the years due to non-availability of critically needed drugs. Moreover, mere figures cannot hide the fact that there exists a substantial black market in drugs in the country, and that Government regulations have played a huge part in this situation, as affirmed by both the qualitative and quantitative query.

[18] Industry officials, in fact, were quiet confident in suggesting that the quantum of losses is actually much bigger. However, they accepted, were satisfied with the calculated figure in context of strict filters applied and the need to exercise caution as it is the first attempt of its kind

[19] The total sales data of the pharmaceutical sector are easy to find. It is reported through various sources, with slight variation amongst the reported sales data. For example, the publication Profit reported FY 2019-20 sales at Rs. 453 billion with annual CAGR of 13 percent over several years. These kinds of stats were used to calculate total sales over the selected time period

An important question that may prop up in readers' mind- who gets to enjoy the spoils from customers'/patients' misery? In other words, who get the better part of the Rs. 78.5 million? In essence, this is another story that would require another major research effort. There is no harm, though, in pointing out what this research found in this regard- that it's the large retailers and importers of drugs who end up making the most of this situation.

But apart from the monetary losses, the quantitative results threw up no surprises! Research into the issues confronting the pharmaceutical sector has pointed out since long the issues encountered by the industry due to irrational, suffocating regulations. The quantitative results only affirm what has been known. Not only do the results show correlation between the independent and dependent variables, but also tend to support the assertion that various forms of government regulations (and its outcomes) are main cause of shortages by displaying practical as well as statistical significance (in 'Variance Explained' table). This statistical significance is further affirmed by the ANOVA table through F- value of 35.086. Finally, in the table ('Regression Co-efficient'), results under Standardized measurement again affirm that government regulations are fairly close in strength of relation to the dependent variable.

Although the quantitative results affirm to what has been known since long, there might be an argument that given the nature of the data, more robust results could have been obtained through application of PROBIT and LOGIT models. While this may be true, it is important to remember the fact that the main concern of the paper was to estimate a monetary cost born out of persistent shortages! Proving assertions (like regulations being a prime contributor) through quantitative methodology was a secondary concern. Even then, the quantitative results fit nicely with the stated narrative. However, in case of future queries that probe deeper into the issue, and where quantitative rather than

qualitative results are a primary prerogative, Probit and Logit type models definitely need to be considered.

Here, a few considerations need to pointed out that might be useful in terms of further research. First, given the very challenging nature of data and its accumulation in terms of shortages of drugs, the study had to be limited to shortages over a time-frame of five years. If long-term data becomes available in the future (of which there is a very low chance), quantitative studies would probably show an even greater magnitude of government regulations in perpetuating drug shortages. For example, drug shortages started to become rampant and debilitating since 2001, when the government experimented with the 'price freeze' policy, which continued till 2013. Under this policy, drug prices were kept frozen till 2013 (except for a few cases under the 'hardship' category) while the production prices went through the roof. Resultantly, almost half of MNCs left Pakistan, mainly over the issue of refusal to grant price increase! It is pertinent to remember that many of the critically needed medicines (like vaccines) are manufactured by MNCs. As they left, it led to a critical supply gap of critically needed drugs that would make for a good study in the future. Of further interest, in this regard, would be inquiry into how those drugs were replaced by local manufactured generic versions (if they ever were) and whether the local versions were reliable substitutes to the ones manufactured by the MNCs that left Pakistan?

Another query that merits more research is the vexing (and technically complex issue) issue of substitutability of drugs! This is not limited to the question of whether locally manufactured generic versions are good or excellent substitutes for originator brands, but also to whether the locally manufactured drugs are good substitutes of each other? This query is logical in the context of the final list of drugs upon which monetary calculations were based. A number of readers, and even medical practitioners and

retailers, may query the logic behind this reduction, from 278 drugs to only 50 because of customer loyalty to a particular brand. A number of stakeholders interviewed during the course of research pointed to 'brand consciousness' among Pakistani consumers, implying that despite presence of viable alternatives, they tend to stick to a particular brand, something that makes the shortages even more debilitating. A common example pointed out during interview was that of brand Panadol (containing paracetamol as API). There are over 20 brands being manufactured in Pakistan that contain the same paracetamol as ingredient, and pharmacists consider majority of them as excellent substitutes for Panadol. Yet, a major portion of consumers remain stuck on Panadol usage, refusing to use the alternatives (a primary reason why it was included in the list of final calculation).

In hindsight, this kind of brand consciousness has considerable monetary repercussions too, as witnessed in the recent case of Panadol shortages. But given that this research effort was first of its kind to address a unique question, inclusion of all such drugs suffering 'brand fetishism' in the list for monetary calculations would have raised unnecessary controversies (besides taking a lot more time for completion of the research effort, given the tremendous difficulties encountered in terms of collecting pricing data, especially of black market prices).

Chapter 6

Conclusion and Policy Recommendation

This chapter comprises of two parts. The first part addresses the conclusion of the study based on the findings and results, while the second part discusses the policy recommendations.

6.1 Conclusion

To the best of my knowledge, this effort is the first of its kind to probe deeply into the repercussions of persistent drug shortages, especially those drugs that are geographically uniform (shortages wise) and have no good substitute (or no substitute at all). There exists no other study that has accumulated data of drug shortages over a span of six years, filtered the data (out of 278 drugs, 50 drugs were filtered out for monetary calculations), verified it from the most relevant sources, and then estimated a monetary cost that befalls the hapless consumer due to these shortages. The calculated loss inflicted upon consumer welfare due to unavailability of drugs in market over the selected time span come to Rs. 78.5 million. Moreover, quantitative methodology complements the results of the study. Worryingly, this inquiry into drug shortages revealed that there were severe shortages, especially of the essential drug that had severe impact on quality of patients' life, even resulting in deaths due to non-availability. Further, the drivers for drug shortages were complex and multifaceted, with the study dividing these into eight categories. There was, however, no doubt that government led regulations had a primary role to play in these persistent drug shortages,

especially of critically required drugs with no substitutes at all, as affirmed by both the qualitative and quantitative query.

As our interviewees reported, the number of drugs in short supply was substantial and quite a few of them were essential drugs with no other substitute, thus seriously impacting livelihoods of the patients. The low availability of essential drugs has become the most critical point for care of patients that not only leads to delay in their treatment, but also poses a serious threat to public health in Pakistan. It seemed that the shortage of antimicrobials, biologicals, and anticancer drugs were more prominent in leading pharmacies and tertiary hospitals because they reported more shortages.

As our interviewees reported, following factors indicated as the determinant of drug shortages – Regulatory Burden (Pricing/Taxation/Registration/Licensing), Non-Availability of Raw Material, Quota restrictions, External shocks, Discontinued drugs, Manufacturing quality issues, Supply chain hurdles, and last but not the least, Artificial shortage/hoarding. Another aspect that also came forward is the compromised quality of drugs i.e. drugs containing the spurious APIs, thus impacting the quality of treatment. Our quantitative query also shows the significant correlation among the drug shortages and their various drivers behind these persistent occurrences.

It also concludes that provided the right incentive, almost all the imported drugs can be manufactured within Pakistan since the Pharmaceutical industry has the capability to do that. Consider the graph of imports and exports of drugs, depicted below in figure 6.1

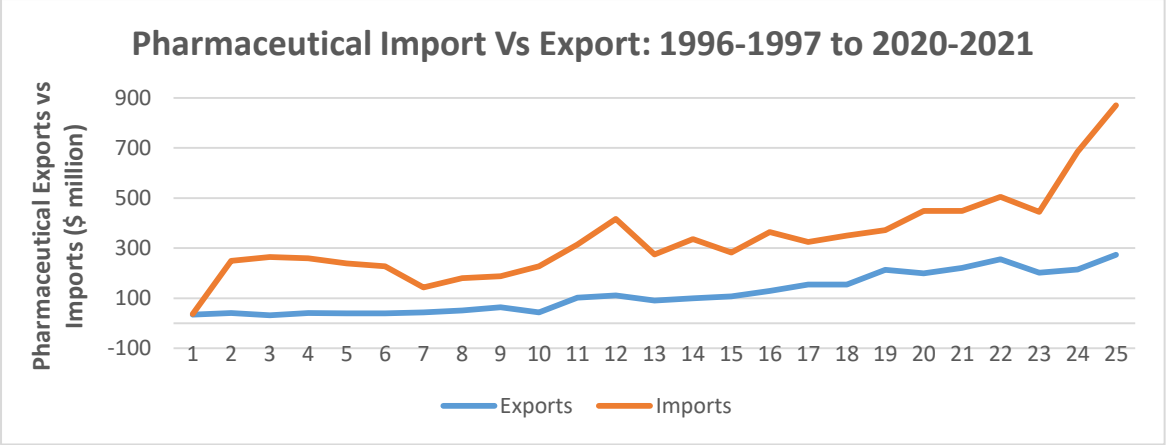


Figure 6.1: **Pharmaceutical Sector Imports Vs Exports**

The most striking feature of the graph is the increasing distance between the imports and exports of the drugs i.e. imports of drugs are outpacing the exports by a significant margin. Various factors perpetuate this situation, but there is unanimity in views of experts that the major reason has to do with the non-availability of generic substitutes in Pakistan despite firms in Pakistan having the ability to manufacture almost all of imported drugs (given the right incentives).

6.2 Policy Recommendations

After identifying the factors propagating drug shortages, it is important to come up with policy recommendations to ameliorate future occurrences of these episodes. Important policy recommendations are listed below-

First of all, Government should not administer drug prices because it has proven to be a failed strategy, causing ample difficulties to the industry and inducing drug shortages. The practical solution would be to let the market forces of supply and demand determine the drug price and to foster more competitive environment between the pharmaceutical firms. For essential drugs, strict price control may easily lead to them vanishing from the market as the manufacturers would find it difficult to obtain profits. When the price

is to be decided by the market, drug price may rise. Moreover, the drug price would not increase too much because of the market competition.

Second, the government needed to play a leading role in the management of drug shortages. There is an urgent need to develop a national task force to estimate the local pharmaceutical reserves in the country and a list of essential drugs needed to fight the crisis. Government should optimize upon its regulatory framework (through DRAP and Health Ministry at Federal and provincial level) to maintain a repository of drugs suffering shortages so that the situation can be ameliorated in time. They also need to monitor if there are any artificial shortages/hoardings, so that strict administrative and legal action can be taken in time.

Third, although respondents indicated that despite the fact that information about drug shortages was exchanged amongst the various partners in the supply chain, the information was not delivered in advance. As a result, creating an information platform where pharmacists and hospitals may communicate drug scarcity information will improve collaboration between hospitals, pharmacies, and suppliers. Furthermore, if distributors and manufacturers started disclosing information, healthcare personnel would be able to predict a drug shortage at the early stages. As a result, the negative consequences of medicine shortages can be mitigated.

Fourth, preserving an amount of drugs that were frequently in shortage, especially for emergency drugs, would considerably lessen the clinical consequences of drug shortages. However, because reserving medications necessitates significant investment in the health sector, supply chain participants should exercise caution when selecting drugs and determining the reserve quantity. Wholesalers are also crucial in the management of drug shortages. Information can be communicated more easily in the supply chain and most drug shortages can be avoided if they can be more active in

fostering contact between manufacturers and hospitals. Pharmacies and hospitals also needed to boost their awareness of efficient inventory management, which can help, which can not only decrease drug shortages in hospitals, but also reduce their inventory costs and improve their competitiveness. Pharmacies can provide timely and real-world data about the drugs sales and shortages.

Fifth, there should be education and training of the consumers as well i.e. more awareness about usage and availability of generic drugs/awareness about therapeutic alternatives to the patients)

Last, but not the least, local manufacturers should be encouraged and provided with the best incentives to manufacture the drugs and even APIs. Such incentives have largely been absent till now.

Other than price adjustments, some other actions are needed to increase demand for low-cost generics and enhance access to medications as both the public and prescribers appear to favour brand goods, i.e.

1. The competent authorities must ensure the quality of all marketed generic goods so that prescribers and patients build faith in generic medicines.
2. Educating the public about safe and effective low-cost generic products.

The availability and use of generic medications will grow as a result of a well-thought-out strategy that includes:

Evaluating and identifying latent factors and situations for pharmacists and physicians in prescribing and distributing generic medicines.

1. The estimation of cost savings with usage of generic drugs and its influence on economy.

2. The promotion of generic prescription and dispensation in terms of cost and accessibility.
3. Sensitivity of consumers in terms of accessibility and satisfaction.
4. Educational engagement to buyers, future physicians and pharmacists.
5. To ensure higher standard for generics, the registration procedure for drugs needs to be streamlined.

Annexure – A: Interview Questionnaire

Name of Respondent Age

Level of Education Years of Working Experience

Pharmaceutical Company Designation

Locality

Pharmacist/Industrial Official

Kindly answer the following:

1. Has the approval and implementation of 2015 and 2018 Drug policies helped resolve issues surrounding pricing of drugs (between government and industry)?
2. Do companies still require DRAP and Government's permission to increase prices of drugs (especially the ones on the NEML), or companies increase it automatically as per the formulae/methodology agreed according to which prices can be increased by half percentage of CPI?
3. The number of drugs produced is usually far below he number of drugs registered. Why? Has the lag/time in drug registration/approval process improved?
4. How many or which drugs have companies stopped producing over time due to pricing issues?
    a. Name of Drug
    b. Yes, non-production was due to issues of pricing
    c. No, non-production was due to other issues (non-availability of API, distributors and retailers, etc.)
5. What was the effect upon local market in terms of shortages?
    a. minute or small effect because good substitutes are/were available
    b. Since no good substitutes are/were available, it led to issues for patients/users
6. What's the normal difference (percentage wise) between a normal, market price of a drug and the same drug being sold in black (when its short)?
7. Why are APIs only sourced from China and India? Why couldn't we develop API production on our own?
8. What percentage of drugs produced locally (generics) are good substitutes of imported drugs? Are the 5 DTLs and Bio-Equivalence labs in the country

credible enough that their conclusions in terms of equivalence of generics be accepted with confidence?

9. Has DRAPs functioning been helpful to industry compared to its predecessor?

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