Growth Potential of Biosimilar Products in Bangladesh

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Table of Contents

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Certificate of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material published or written by another person nor material which to a substantial extent has been approved or accepted for the award of any other degree or diploma of a university or other institution of higher learning, except where due acknowledgement is made in the acknowledgement.

Md. Abu Zafor Sadek
Registration Number: 27/2014-2015

Certificate of the Supervisor

This is to certify that the thesis entitled "Growth Potential of Biosimilar Products in Bangladesh" is an original research work submitted by Md. Abu Zafor Sadek for the award of Doctor of Business Administration at the Institute of Business Administration (IBA), University of Dhaka under my guidance and supervision.

The results embodied in this thesis have not been submitted to any other university or institute for the award of any degree or diploma.

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Abbreviation

API	: Active Pharmaceutical Ingredients
BAPI	: Bangladesh Association of Pharmaceutical Industries
BLA	: Biologics License Applications
BSMMU	: Bangabandhu Sheikh Mujib Medical University
BCSIR	: Bangladesh Council of Scientific and Industrial Research
BGE	: Biotechnology & Genetic Engineering
CAGR	: Compound Annual Growth Rate
CEO	: Chief Executive Officer
COO	: Chief Operating Officer
COO	: Country of Origin
CDIP	: Chancellor's Doctor Incentive Program
CME	: Continuing Medical Education
CKD	: Chronic Kidney Disease
CII	: Confederation of Indian Industry
DGDA	: Directorate General of Drug Administration
DNA	: Deoxyribonucleic acid
EBL	: Eastern Bank Limited
EU5	: European Union 5 (France, Germany, Italy, Spain, United Kingdom)
EMA	: European Medicines Agency
EPO	: Erythropoietin
EPB	: Export Promotion Bureau
CETP	: Common Effluent Treatment Plant

GaBi	: Generics and Biosimilars
GDP	: Gross Domestic Product
IMS	: Intercontinental Marketing Services
IFPMA	: International Federation of Pharmaceutical Manufacturers & Associations
ICDDR, B	: International Centre for Diarrheal Disease Research, Bangladesh
KOLs	: Key Opinion Leaders
LDCs	: Least Developed Countries
MABs	: Monoclonal Antibodies
MNCs	: Multinational Companies
MR	: Medical Representative
NCBs	: Non-Comparable Biologics
NCDs	: Non-Communicable Diseases
NME	: New Molecule Entity
PwC	: PricewaterhouseCoopers (a multinational professional services network)
ppd	: Pharmaceutical Product Development
PTMs	: Posttranslational Modifications
R&D	: Research & Development
SRM	: Social Research Method
SEBs	: Subsequent Entry Biologics
TNF	: Tissue Necrosis Factors
TGA	: Therapeutic Goods Administration, Australia
TRIPS	: Trade-Related Aspects of Intellectual Property Rights
UKMHRA	: The Medicines and Healthcare Products Regulatory Agency of UK
USFDA	: United States Food and Drug Administration
USD	: United States Dollar

WTO : World Trade Organization

WHO : World Health Organization

List of Tables

List of Figures

This DBA thesis is dedicated to my father Md. Shirajul Islam and mother Most. Hajera Khatun with love and gratitude.

Abstract

In view of the global changes in disease pattern, reduced health budget in developed countries, increasing health budget in developing countries, patent expiry of some high valued products, transformations in R&D productivities and side effects of chemical drugs global pharmaceutical giants are concentrating on biologic products among which anticancer, antidiabetic, antiarthritic, cardiovascular products are especially important. However, developing a biotech product involved huge cost which is possible only by research based top companies. Realizing the fact, many pharmaceutical companies tried to imitate the original biotech products after patent expiry and became successful which bring a breakthrough in terms of health cost. These imitated products are termed as biosimilar products. Although the history of biosimilars started at European Union (EU) in 2006 with single product but currently it has been recognized everywhere in the world and EU have highest 19 biosimilar products. United States Food & Drug Administration (USFDA) was little conservative with biosimilars; nevertheless, they approved the first biosimilar 09 years after EU approval and presently they have three biosimilars which are playing significant role in price cutting of branded biologics. They also have so many biosimilars in pipelines. Emerging economies especially South Africa, China & India are very aggressive with biosimilars. Under Pharmaceutical Benefits Scheme Australian government is promoting biosimilars and they already approved 09 biosimilars. Japan, Korea, Canada are also encouraging biosimilars. Bangladesh is the only Least Development Countries (LDCs) that have very strong pharmaceutical sector; there are so many manufacturing facilities with global standard and approved by USFDA and UKMHRA. Bangladesh pharmaceuticals industry worth $ 2 billion and have a long history success in both domestic and international markets with generic products. Unlike global giants very few Bangladeshi companies are putting concentration on biosimilars. Till to date one pharmaceutical

claimed them as true biosimilar company without any product in the market. 08 other pharmaceutical companies are offering Non-Comparable Biologics (NCBs) which is below 5% of the total domestic revenue although biologics accounts for more than 22% of the global total. Considering huge number of patients with chronic diseases, increasing access to biologic treatment due to changes in income level, improving access to medical services and diagnostic facilities, easy regulations, cheap labor and related cost factors, geographical location, availability of trainable manpower, raising patient awareness, price sensitivity, strong entrepreneurial skills Bangladesh is in little advantageous position with biosimilars. However, success of biosimilars in Bangladesh is mostly depends on the acceptance by the physicians, reduction of treatment cost, increasing life expectancy, easy availability at the drug stores, trust on manufacturers, various promotional and disease awareness campaigns, dissemination of proper information towards doctors and patients, monitoring by the regulatory bodies, government patronization, drug substitution, efficacy and safety of the individual product, technical collaboration with the experts, export possibilities etc. Therefore, this study identifies the growth potential of biosimilar products in Bangladesh.

1.1 Background

In view of the global changes in disease pattern, reduced health budget, patent expiry of some high valued products and side effects of chemical drugs, global pharmaceutical giants are concentrating on biotech products among which anticancer, cardiovascular, antidiabetic, antiasthmatic, antiarthritic and other personalized products are especially important.

However, developing a biotech product involved huge cost which is possible only by research based top companies. Realizing the fact, many pharmaceutical companies tried to imitate the original biotech products after patent expiry and became successful which bring a breakthrough in terms of health cost. These imitated products are termed as biosimilar products.

Almost one decade back the first biosimilar was launched in Europe. Now they have 15 biosimilars and all are well accepted since high price branded biologics were tough to reach by many patients. Recently biosimilars has been endorsed everywhere in the world starting from underdeveloped to developed countries. United States Food & Drug Administration (USFDA) approved the first biosimilar in 2015 and currently they have “03” biosimilars which are playing pivotal role in price cutting of branded biologics. They also have many biosimilars in pipeline which will be launched shortly. Australia, Canada, Africa and Asia are also aggressive with biosimilars; especially India, Korea and China made remarkable efforts in biosimilars.

Considering huge number of population, rising health awareness, recent economic growth, success history of some biologic companies, dependence on generic items, price sensitivity, relax regulation, growing health budget, very low production cost and other relevant factors Asia is an important hub for biosimilars.

However, in view of present stumpy growth (7.84%) in pharmaceuticals (IMS 4Q, 2018), sharp positive growth of Non-Comparable Biologics (NCBs), price sensitivity, geographical location, sharp economic advances, increasing purchasing capacity, rapid rise of non-communicable diseases, recent biosimilars guideline by Directorate General of Drug Administration, Bangladesh, development of expertise, marketing and technical capabilities of the local manufacturers, government patronization etc. Bangladesh is an impressive hub for rapid growth of biosimilar products.

1.2 Research Gap

Still now biosimilars are the hot topic across the world as cost towards healthcare, expenses, time and uncertainty of new product development, strict regulations are getting increased attention. The big pharma market place like Europe and America are looking for the ways to reduce health budget by cost effective medicines whereas developing world like Asia and Africa are increasing healthcare budget to get access to presently untouched specialized costly biologics. (Henriette Jacobsen, 2013 & WHO, 2018). Therefore, biosimilars are important for both developed and developing countries. Leading generic exporters India, China and Korea are giving keen attention to biosimilars as they noticed huge opportunity in both developing and developed countries (Ranjit & Divya, 2019). There are numerous market researches on growth potential of biosimilars in global arena but there are very few academic researches on biosimilars.

Historically, Asia has led in generics adoption with approximately 40% of global generics spending coming from this region. With more than 300 biosimilars under development in Asia; hence, the region positioned itself as the center for global biosimilars manufacturing and adoption. (Zafar Momin et. al., 2018). Few studies analyzed how the biosimilars industry would evolve in Asia, examining the industry growth drivers, enablers and challenges it will likely face and how industry players can ride the growth waves. (Mordor, 2019).

Bangladesh is a successful model of generic pharmaceuticals in meeting both local and global demand. (The Dhaka Tribune, 2019). However, still now there are very few studies on growth potential of biosimilars in Bangladesh (Raquibur et al., 201& Eva Rahman Kabir et. al., 2018) although our expertise, success history, rapidly expanding local market, entrepreneurship, competitive production cost, skilled manpower, government patronization, supportive regulatory guidelines etc. are in favorable state with biosimilars.

1.3 Justification of the Research

Biosimilar medicines offer great potential for increasing access to biologics. In global context, some literature suggests that use of biosimilars may positively impact on the financial sustainability of healthcare systems, addressing the unmet need for broader access to biologic therapies, without compromising patient outcomes. However, despite more than ten years' experience with biosimilars in Europe, considerable skepticism & misunderstandings around biosimilars are observed amongst healthcare professionals. Indeed, surveys have shown that many physicians and pharmacists have little or no familiarity with recent biosimilar developments. (Joan-O-Callaghan et al., 2013).

If Bangladesh perspective is considered, then it is seen that due to changes in disease pattern many patients need treatment with biological products which are very costly. In view of the socioeconomic condition many patients don't get access to those high cost biologics; for these patients biosimilars may be blessing as they are almost 40% less cost than that of the original one.

Although the concept of biosimilars is familiar with the doctors of some developing and developed countries but in Bangladesh this concept is almost unknown among the practitioners. Therefore, this study will give an opportunity to be familiar with biosimilars.

Many companies in Bangladesh are still in dilemma with biosimilars since it involved with high investment cost (Survey among the MD/CEOs). If biosimilars industry grows in Bangladesh, then it will give a sudden boost to entire pharma-industry which will secure smooth growth in both domestic as well as export market. Also, there is very few or no market study on biosimilars in Bangladesh perspective. Therefore, it is extremely important to know the growth potential of biosimilars in Bangladesh.

1.4 Contribution of the research to the literature

It is noted that globally biosimilars are getting huge attention both from academic as well as industry perspective. (European Pharmaceutical Report, 2015). Research conducted reveals that the market for biosimilars is expected to reach a value of $61.47 billion by 2025. The report suggests that it is expected to rise at a compound annual growth rate of 34.2 percent over the period, as some major biological drugs are fast approaching their patent cliff. This area is the most significant driving factor for the biosimilars market and in 2016, the market for biosimilars was valued at $4.6 billion. (Arshad Ahad, 2018). However, being one of the very potential destinations for pharmaceutical investment there are very few study on biosimilars in Bangladesh. Nevertheless, this study will also propose a biosimilars marketing model which will be unique.

1.5 Contribution of the research to the industry

Currently total biologics market in Bangladesh is aprroxiamately $ 80 mln/year. (IMS, 4Q, 2019 & Internal Data). The growth rate of biologics is almost three to four times compared to conventional pharmaceutical products. (IMS, 4Q, 2016-2018). From available research it is noted that biosimilars are usually 30% less cost than that of original brand. Therefore, considering present market growth it is assumed that if biosimilars are offered at 30% reduced cost in Bangladesh then the total saving will be around $20-30mln in next 5 years. (Internal Analysis). Also, this study will give a 12 years sales projection of biologics in Bangladesh based on present market size, current growth trend, increasing trend of market share etc. Apart from the above the study will figureout the changes of the landscape of insulin market due to launching by the local manufacrurers like Incepta Pharmaceuticals, Square Pharmaceuticals, Popular Pharmaceuticals, ACI Pharmaceuticals and Aristopharma Limited. It is worth mentioning that before 2013 the insulin market was fully captured by MNCs like Novonordisk, Sanofi, EliLily etc.

1.6 Scope of the Research

For marking changes in disease pattern the researcher shall mostly target chronic diseases like cardiovascular, diabetes, arthritis, hepatitis, cancer and kidney diseases considering our resources & time constraint. However, use of biosimilar products in these diseases is comparatively higher than other groups.

Lots of issues related with biosimilar products but considering time and resource constraint and our area of interests the researcher will be focusing on marketing and export related issues.

There are more than 2 lacs qualified & non-qualified doctors in Bangladesh. For our study we shall limit our access only to qualified specialist doctors as other have very few scope to prescribe biosimilar products. Considering the earlier mentioned diseases the researcher shall target Cardiologists, Diabetologists/Endocrinologists, Orthopedists, Hepatologists, Oncologists and Nephrologists for our responses. There are so many doctors in the above categories but the researcher shall limit study only to specialist doctors. For selecting specialist doctors the researcher shall follow some criteria which are discussed below.

A medical practitioner whose practice is limited to a particular class of patients (as children) or of diseases (as skin diseases) or of technique (as surgery); especially*:* a physician who is qualified by advanced training and certification by a specialty examining board to so limit his or her practice. For our study they are group of doctors who have completed at least one post-graduation degree in a specific area of medical science from any government endorsed institution and usually prescribe any of the above selected biologics.

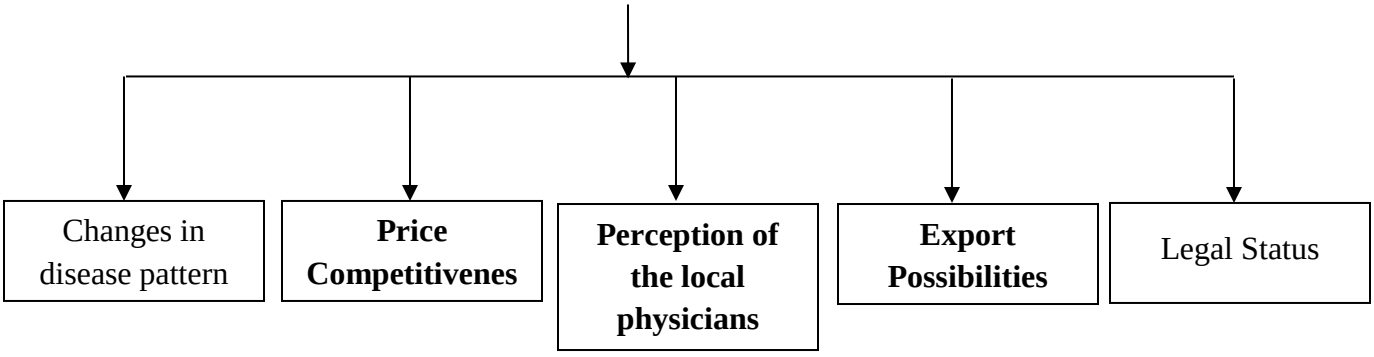
For survey response the doctors have been selected from renowned institutions where post-graduation medical degree is offered and all divisional cities/city corporations/Old district towns

like Dhaka, Chattogram, Khulna, Rajshahi, Sylhet, Rangpur, Mymensingh and Barishal as the above said specialist doctors mostly practice in the mentioned places and represents the entire specialist community. Also, more than 80% of the total pharma sales come from these regions.

There are around 200 pharmaceutical companies in Bangladesh who have registration from Directorate General Drug Administration (DGDA). The researcher shall concentrate his study only to top 15 companies as they represent almost 85% of the total market and others are not still equipped enough to launch biosimilar products.

There are lots of biosimilar products available in the global markets but considering the Bangladesh context the researcher shall consider Insulin, Interferon, Monoclonal Antibodies, Erythropoietin, Filgrastim and Streptokinase for study as they are the leading used drugs among different biologics. The researcher has excluded vaccines as many of them are supplied by the government to different hospitals and health centers where there is little or no scope to choose certain brand other than the supplied one.

Growth Potential of Biosimilar Products in Bangladesh



Considering time and resources constraint the researcher shall study with the above marked three issues only.

1.7 Limitations

This study identifies market potential of biosimilars; therefore, this is a descriptive research. (Kotler & Gary Armstrong, 2011). The population size of this study is 1700; hence, the selected sample size for the quantitative part of the research was 330 (by using Daniel's Equation, level of confidence 95%, margin of error 5%). (L. Naing et al., 2006); however, the researcher could collect data from 217 respondents. It is worth mentioning that all the listed respondents are very busy practitioners and it was very difficult to get their appointment and time. It also needs to be mentioned that the respondents must have at least one post-graduation degree in relevant field. (Derek Silva, 2019).

For in-depth interview the researcher approached Chairman/Managing Director/Chief Executive Officer/Chief Operating Officer/Director, Marketing of top "13" companies by value sales; however, Chairman, Radiant Pharmaceuticals Ltd. Chief Operating Officer, Beximco Pharmaceuticals Ltd., Chief Executive Officer, Eskayef Pharmaceuticals Ltd., and Country Manager, Roche Bangladesh were unable to manage their time and it is worth mentioning that all of them are highly experienced and eminent in their field, also very potential source of information.

1.8 Definitions

Biologics: A biologic drug (biologics) is a product that is produced from living organisms or contain components of living organisms. Biologic drugs include a wide variety of products derived from human, animal, or microorganisms by using biotechnology.

Biosimilars: A biosimilar is a biologic medical product that is almost an identical copy of an original product that is manufactured by a different company. Biosimilars are officially approved versions of original "innovator" products and can be manufactured when the original product's patent expires.

Biosimilars Interchangeability: Under the Biologics Price Competition and Innovation Act (BPCIA), an interchangeable biosimilar is defined as a biosimilar that is expected to produce the same clinical result as the reference product in any given patient.

Biosimilar Substitution: Substitution describes the practice where a pharmacist elects to change a product, dispensing an equivalent (generic small molecule) or highly similar (biosimilar) product without the prescribing physician's prior consent.

Biotechnology: Biotechnology is the broad area of biology involving living systems and organisms to develop or make products, or "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use".

Biotherapeutic Agent: A “probiotic” or a “biotherapeutic agent” (BTA) is a living microorganism administered to promote the health of the host by treating or preventing infections owing to strains of pathogens.

Biobetter: Biobetters are improved versions of originator biologics. Although there are varying interpretations of the term biobetter, according to Andrew Merron, therapy lead in oncology and biosimilars at healthcare research and consulting company Decision Resources Group, the improvements in these products often lie in efficacy, safety or delivery. (The Pharma Letter, 2017)

Competitiveness: Company competition, or competitiveness, pertains to the ability and performance of a firm, sub-sector or country to sell and supply goods and services in a given market, in relation to the ability and performance of other firms, sub-sectors or countries in the same market.

Continuing Medical Education (CME): It is consisting of educational activities which serve to maintain, develop, or increase the knowledge, skills, and professional performance and relationships that a physician uses to provide services for patients, the public, or the profession.

Cold Chain/Cool Chain: A cold chain or cool chain is a temperature-controlled supply chain. An unbroken cold chain is an uninterrupted series of refrigerated production, storage and distribution activities, along with associated equipment and logistics, which maintain a desired low-temperature range.

Efficacy: The word efficacy is used in pharmacology and medicine to refer both to the maximum response achievable from a pharmaceutical drug in research settings and to the capacity for sufficient therapeutic effect or beneficial change in clinical settings.

Emerging Markets: An emerging market is a country that has some characteristics of a developed market, but does not satisfy standards to be termed a developed market. This includes countries that may become developed markets in the future or were in the past.

Freedom of Choice: Freedom of choice describes an individual's opportunity and autonomy to perform an action selected from at least two available options, unconstrained by external parties.

Generic Drugs: A generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

Growth Potential: Growth potential is an organization's future ability to generate larger profits, expand its workforce and increase production.

Immunosuppressant: Immunosuppressant drugs are a class of drugs that suppress, or reduce, the strength of the body's immune system.

Interferon: Interferons (IFNs) are a group of signaling proteins made and released by host cells in response to the presence of several pathogens, such as viruses, bacteria, parasites and also tumor cells.

Immunogenicity: It is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human and other animal. In other words, immunogenicity is the ability to induce a humoral and/or cell-mediated immune responses.

Monoclonal antibodies (MABs): Monoclonal antibodies are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have

monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody).

Non-Comparable biologics: They are those biosimilars that do not meet the requirements of similarity to the original medicinal product since they have not been through the strict requirements including comparability studies among other requirements, as stipulated by the relevant bodies, such as the EMA, the World Health Organization.

Non-Communicable Diseases (NCDs): Non-communicable disease is not transmissible directly from one person to another. NCDs include autoimmune diseases, strokes, most heart diseases, most cancers, diabetes, chronic kidney disease (CKD), osteoarthritis, osteoporosis, Alzheimer's disease, cataracts and others.

Potency: In the field of pharmacology, potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity.

Patent: A patent is an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something, or offers a new technical solution to a problem. To get a patent, technical information about the invention must be disclosed to the public in a patent application.

Perception: Perception is the organization, identification and interpretation of sensory information in order to represent and understand the presented information, or the environment.

Quality: The standard of something as measured against other things of a similar kind; the degree of excellence of something.

Specialist Doctor: Doctors who have completed advanced education and clinical training in a specific area of medicine (their specialty area). Examples of medical specialists include the followings: Addiction psychiatrist. Adolescent medicine specialist. Allergist (immunologist).

Seminar: A seminar is a form of academic instruction, either at an academic institution or offered by a commercial or professional organization.

Therapeutic Class: A drug class is a set of medications and other compounds that have similar chemical structures, the same mechanism of action (i.e., bind to the same biological target), a related mode of action, and/or are used to treat the same disease.

2.1.1 Global Pharmaceutical Industry

The modern pharmaceutical industry, as we know now it, is barely 60 years old. From modest beginnings, it has grown rapidly, reaching an estimated value of US$100 billion by the mid-1980s. There are well in excess of 10,000 pharmaceutical companies in existence, although only about 100 of these can claim to be of true international significance. The companies manufacture in excess of 5000 individual pharmaceutical substances used routinely in medicine (Walsh, 2007).

The global pharmaceutical market harvested revenue of $989 billion in 2013 and was forecasted to reach $1.3 trillion in 2018 at a compound annual growth rate (CAGR) of 4%-7%. Despite this healthy growth, the market incumbents face a wide variety of challenges from a more diverse and globalized economy, stringent government regulations, downward price pressure, and increased demand for better healthcare (Evaluate, 2015).

Over the last few years, generic drugs-low-cost copies of branded drugs-have been gaining in volume and market share. Typically priced at significant discounts (50%-70%) to their branded counterparts, health plans and governments around the world, which are dealing with rapidly increasing costs and aging populations, have actively encouraged and promoted their use. Today in the US, generic drugs account for 88% of all prescriptions filled and according to latest IMS report, generics may account for 91%-92% of prescription volumes by 2020. (IMS Health, 2014)

According to a report by IMS Health, from 2013-2018 generic drugs are expected to account for 52% of global pharmaceutical spending growth, compared to 35% for branded drugs. Overall, sales of generic drugs are forecast to increase from $267 billion in 2013 to $442 billion in 2017, an annualized growth rate of 10.6%. Major factors driving this growth include popular branded

drugs losing their patent protection (known as patent cliff), support for generics from governments, new complex generics coming into the market, and industry consolidation. (IMS Health, 2014)

The US has the largest pharmaceutical market in the world with a value of $339,694 million USD followed by Japan ($94,025 million USD) and China ($86,774 million USD). In Germany, the value of its pharmaceutical market is about $45,828 million USD and in France, it is about $37,156 million USD. In Brazil, the value of its pharmaceutical market is about $30,670 million USD. In Italy, the value is about $27,930 million USD. In the UK, it is about $24,513 million USD while in Canada it is about $21,353 million USD. In Spain, it is about $20,741 million USD (IMS, 2014).

2.1.2 Top market places for pharmaceuticals: The global pharmaceutical industry is an imperative driver of the world economy today, generating more than 1 trillion US dollars in revenues annually (IFPMA, 2017). The American pharmaceutical industry accounts for about 40% of these revenues. However, China is fast catching up as having the fastest growth in the industry. European pharmaceuticals have also shown high revenues in prescription sales. Top ten countries considering pharmaceutical consumption is contributing 72.3% of the total market. (Rolando Y. Wee, 2017). The following table shows top ten market places of pharmaceutical products with their share percentage.

Table-1: Top 10 pharmaceuticals market places in the world by values sales'2016

Sl #	Country	Value in mln $	% of Total	Cumulative %
1	USA	339694	33.9	33.9
2	Japan	94025	9.4	43.3
3	China	86774	8.6	51.9
4	Germany	45828	4.5	56.4
5	France	37156	3.7	60.1
6	Brazil	30670	3	63.1
7	Italy	27930	2.7	65.8
8	UK	24513	2.4	68.2
9	Canada	21353	2.1	70.3
10	Spain	20741	2	72.3

Source: Rolando Y. Wee, 2017, Arjun Datta, 2016 and compilation of the researcher

2.1.3 Leading pharmaceuticals exporting countries: Global sales from exported drugs and medicines by country in 2016 totaled US$ 318.6 billion. On the whole, the value of drugs and medicine exports were up by an average 0.4% for all exporting countries since 2012 when drugs and medicines shipments were valued at $317.3 billion. (Market Research, 2018). Year over year, there was a -1.5% decline from 2015 to 2016. Among continents, European countries accounted for the highest dollar value worth of drugs and medicine exports during 2016 with shipments amounting to $251.9 billion or 79% of the global total. In second place were North American exporters at 9.8% while 9.4% of worldwide drugs and medicine shipments originated from Asia. (Daniel Workman, 2017).

Table-2: Top-10 Pharmaceutical product exporters with their share percentage

Sl #	Country	Value in billion $	% of Total	Cumulative %
1	Germany	48.6	15.3	15.3
2	Switzerland	39.9	12.5	27.8
3	Belgium	26.5	8.3	36.1
4	France	22.8	7.1	43.2
5	USA	22.5	7.1	50.3
6	UK	22	6.9	57.2
7	Ireland	19.8	6.2	63.4
8	Italy	16.6	4.9	68.3
9	Netherlands	15.5	4.9	73.2
10	India	11.6	3.6	76.8

Source: Daniel Workman, 2017 and compilation of the researcher

Among the above and other countries, the fastest-growing drugs and medicine exporters since 2012 were as follows:

Table-3: The fastest growing (up/down) drug exporting countries

Sl #	Country	Growth %	Sl #	Country	Growth %
1	Canada	84.5	5	France	-17
2	India	38.2	6	Spain	-16.2
3	Switzerland	27	7	Israel	-11.8
4	Netherlands	17.5	8	Belgium	-10.9

Source: Daniel Workman, 2017

2.1.4 Top Pharmaceutical Product Importers: The pharma market is radically changing position, with traditional strongholds, such as Japan and Europe, flipping over and emerging

markets, such as China, becoming the head. The consequence is that healthcare investors need a fresh strategy; they need a way to keep an eye on emerging markets so they aren't left in the pitch because they don't understand the true engines for growth in their holdings. (Cheryl, 2017).

The following table shows top Pharmaceutical product importers of 2016 by value sales.

Table-4: Top Pharmaceutical product importers 2016 by value sales

Sl #	Country	Value in $ billion	% of total	Cumulative %
1	USA	92.5	17.4	17.4
2	Germany	49.1	9.2	26.6
3	Belgium	34.9	6.6	33.2
4	UK	32.7	6.1	39.3
5	Switzerland	24.7	4.6	43.9
6	Japan	24.4	4.6	48.5
7	France	22.1	4.1	52.6
8	Netherlands	22.1	4.1	56.7
9	Italy	21.3	4	60.7
10	China	20.7	3.9	64.6

Source: Cheryl Swanson, 2017and compilation of the researcher

2.1.5 Top pharmaceutical companies considering yearly revenue: The ten largest pharmaceutical companies in the world account for more than a third of the industry's total market share according to the World Health Organization (WHO). Here the researcher looks at who the current top ten companies are and some of their highlights.

Table-5: Top-10 pharma companies considering yearly value sales of 2016

Sl	Company	Origin	Revenue	Remarks
1	J&J	USA	71.89	Revenue has increased, in part, due to a 6.5% rise in pharma sales.
2	Pfizer	USA	52.82	The company focuses on a wide range of areas including oncology, neuroscience and metabolic diseases.
3	Roche	Switzerland	50.1	This year's success is owed to growing sales of best-selling drugs, Herceptin and Perjeta.
4	Novartis	Switzerland	48.52	Split their pharma unit in two, one being exclusively focused on oncology-which they hope to go forwards.
5	Merck	USA	39.8	Their anticancer drug Keytruda gained approval from the FDA and EMA and is expected to be a 'game-changer'
6	Sanofi	France	36.57	Gained FDA approval for once-daily insulin Soliqua, while blockbuster drug Lantus experienced a dip in sales
7	GSK	UK	34.79	Their increased sales can be attributed to the excellent performance of HIV drugs and strong vaccine sales
8	Gilead	USA	30.39	Antiviral drug sales accounted for 90% of total revenue, the amount accumulated from others has risen by 13.6%
9	AbbVie	USA	25.56	Owes much of its success this year to the usual range of global top selling drugs, such as Humira and Imbruvica.
10	Bayer	Germany	25.27	Joins the 2017 list of top 10 pharma companies due to a surge of sales from drug Xarelto (anticoagulant)

*Revenue figures are in $ billion

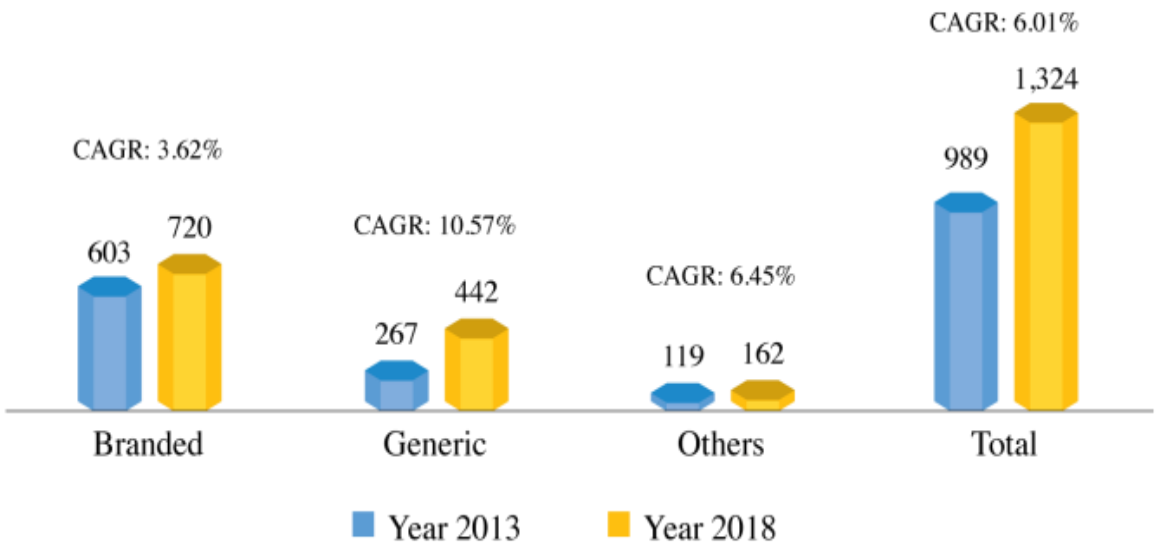
Source: Monique Ellis, 2017

2.2.1 Growth Pattern of Pharmaceutical Industries

Over the past decade every unit of pharmaceutical sector has experienced healthy growth. The global market for pharmaceuticals has doubled within a decade. It has reached a value of 1 trillion USD per year and expected to grow by 5-6% up to next three years (Deloitte, 2015). Recently this market faces major challenge from increasing investment & strict regulation. Changing lifestyles due to urbanization in both developed and growth markets globally are expected drive the demand. The ability to create new technology and innovative drugs is becoming the key driver for success in this market (PwC, 2013).

2.2.2 Increasing share of generics: The generics industry quickly put this setback behind it. In 1984, generic drugs were just 19% of prescriptions in the US; according to the market research firm IMS. By 2013, they had reached 86%. (Ann M. Thayer, 2014). Over the last few years, generic drugs have been gaining in volume and market share. Typically priced at significant discounts (50%-70%) to their branded counterparts, health plans and governments around the world, which are dealing with rapidly increasing costs and aging populations, have actively encouraged and promoted their use. Today in the US, generic drugs account for 88% of all prescriptions filled and according to latest IMS report, generics may account for 91%-92% of prescription volumes by 2020. (IMS, 2014 & Indxx, 2016).

Figure-1: Global pharmaceutical Sales ($ billion).



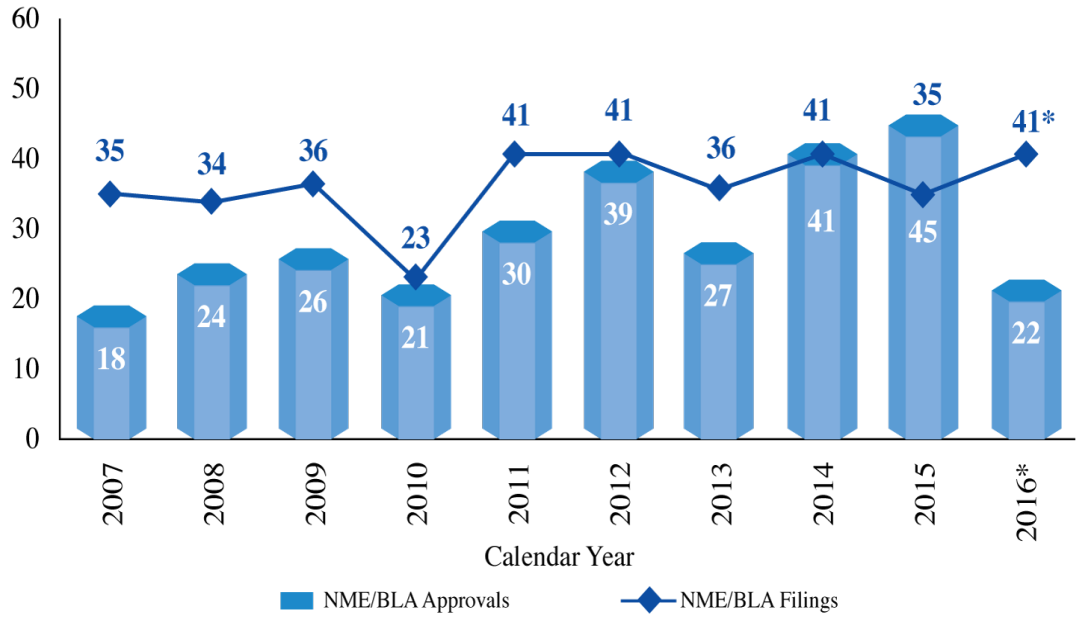
Source: IMS, 2014

2.3.1 Drug Discovery in Pharmaceuticals

The drug discovery process begins with the screening of thousands of compounds and modifying them to raise disease-fighting activity and/or minimize undesirable side effects for patients. Both laboratory and animal studies may be used to evaluate a drug's safety and efficacy during preclinical testing. Investigational new drugs go through a rigorous review by the FDA before moving to the clinical trials stage. Clinical trials of new medicines occur in three testing phases. Phase I includes drug tests in a small group of about 20 to 100 healthy volunteers to determine safety. During Phase II, 100 to 500 volunteer patients participate in controlled trials to determine whether the medicine effectively treats the disease. Phase III includes 1,000 to 5,000 patients taking the new drug and being monitored to confirm effectiveness and identify any side effects with comparison to patients in the placebo (inactive substance) group (Armantier et al, 2008).

2.3.2 Limited number of new molecules: Number of new molecule 2016 was a slow year for drug approvals. In this year, the FDA's Center for Drug Evaluation and Research approved 51% fewer new molecular entities (NMEs) than in the prior year. In the years leading up to 2016, NMEs were on an upswing. Although approvals were lower than average in 2016, the number of applications for approval has remained relatively stable. (Emily Walter, 2017). It is difficult to pinpoint the reason for a reduction in approvals, whether it is stricter guidelines or product-specific issues, so it is difficult to predict the outcome for 2017.

Figure-2: New Molecule Entity (NME) and New Biologics License Application (BLA) Filings Approvals



Source: official website of USFDA, 2017

2.4.1 Pharmaceutical Marketing

Marketing has been defined as "an organizational function and a set of processes for creating, communicating and delivering value to the customer and for managing customer relationships in ways that benefit the organization and its stakeholder" (Kotler et al. 2007, p.7). For decades there have been outcries that the consumer has been mistreated, but marketing concept, a marketing philosophy that evolved in the late 1950s, not only focuses on consumer requirements, but also protects consumers' rights (Bell & Emory 1971). However, different alternative marketing philosophies that have been followed in the real world; a) production concept, b) product concept, c) selling concept, d) marketing concept and e) societal marketing concept. The Marketing concept is crucial and contemporary among these concepts. Marketing management philosophy holds that achieving organizational goals depends on determining the needs and wants of target markets and delivering the desired satisfaction more effectively and efficiently than competitors. Broadly, Marketing concept (market orientation) is concerned with the processes and activities associated with creating and satisfying customers by continually assessing their needs and wants, and doing so in a way that there is a demonstrable and measurable impact on business performance (Uncles, 2000). Most of the literature of marketing concept concentrated on explaining the need of companies to devote more time and effort to the requirements for their customers. The extant literature also agreed with this concept because an adequate understanding of consumers' needs and wants by organizations could lead to better performance such as growth in resources, higher customer satisfaction, and growth in reputation (Gainer & Padanyl 2002; McClymont, Ogunmokun & Akbari 2004).

Pharma market is typical in the sense that the doctors are the one who decides therapy and drugs for the consumers (patients). So, marketers promote their products directly to doctors to influence

favorable prescription generation by them. Prescription behavior of doctors further increases peculiarity as doctors' choice is more logical for choosing a therapy & drug molecule but when it comes to selecting a particular brand their decision may be more inclined towards emotional and less rational (Blackett, 2001).

Mizik & Jacobson (2007) reported that marketing efforts by pharmaceutical companies to the doctor positively affect new prescriptions issued by a doctor, but the effect size was found to be modest.

Ingole & Dube (2010) explored how physician's drug prescribing is influenced by drug promotion done by medical representatives. Study revealed that the sales representatives of different Pharma companies are the commonest source of information and latest updates on drug developments.

Vakratsas & Kalyanaram (2010) studied the price sensitivity of physicians for select drugs in and attempted to distinguish between probability and frequency of prescription effects. They reported that physicians are price sensitive with respect to frequency but not probability of prescription. In other words, they would not exclude a drug from prescription due to its higher price, but would prescribe it at a lower frequency. Thus, physicians are selectively price sensitive, which we interpret as an effort to balance quality and cost considerations.

Many authors reported miscellaneous factors which would influence doctors' prescription choice of drug and the brand. Talgeri & Chiplunkar (2002) reported that easy and extensive availability of a particular product of a Pharma company has a strong positive influence over prescription behavior towards that particular product. Gonul et al. (2001) suggested that the doctors while prescribing medicine brand for a specific disease, consider the regular visits from the medical representatives very important.

Pharmaceutical companies have to primarily depend on personal selling to promote their medicines in the market as the target audience and customers are different, who are not the end users but merely influencers. The following factors influence them.

a) Product efficacy
b) Short & easy to remember names
c) Economical price
d) Attractive & safe packaging
e) Quality of medicine
f) Availability at all chemist shop
g) Long expiry dates
h) Easy to consume
i) Safety of drugs
j) Well accepted by the component authority like FDA etc. (Irfan Sharfoddin Inamdar and Dr. Malhar Jayant Kolhatkar, 2012)

Another identified the following influential factors for deciding medicine for a patient.

a) Quality of the product
b) Price of the product
c) Availability of the product
d) Image of the company
e) Regular visits of the representatives of the producing companies
f) Research in the molecular domain
g) The specialty literature/journals
h) The personality of the medical representatives
i) Sponsorships for participating in conferences

j) New combinations

k) Medical educational programs

l) Presentation way (package)

m) Obtained incentives

n) Personally received gifts

o) Samples of the products

p) Free campaigns for the identification of illnesses

q) Existence of the websites of the medicine producers (Nitin Girdharwal & Ajaypal Singh, 2007)

2.4.2 New Drug Selection

In 2014, Lubloy stated that early adoption of new drugs is not a personal trait, independent of drug type, but early adopters share both micro and meso-level characteristics. At prescriber level, doctors' interest in particular therapeutic areas, participation in clinical trials, and volume of prescribing-either in total or within the therapeutic class of the new drug increases the likelihood of early adoption. The marketing efforts of pharmaceutical companies and doctors' professional and social interactions leading to prescribing contagion are very powerful predictors of new drug uptake. At patient level, doctors with younger patients, patients with higher socioeconomic statuses and/or patients with poorer health statuses are more inclined to prescribe new drugs early. In contrast, the socio-demographic characteristics of prescribers and many practice-related factors play little role in the adoption process. (Agnes Lubloy, 2014)

2.5.1 Pharmaceuticals in total healthcare spending

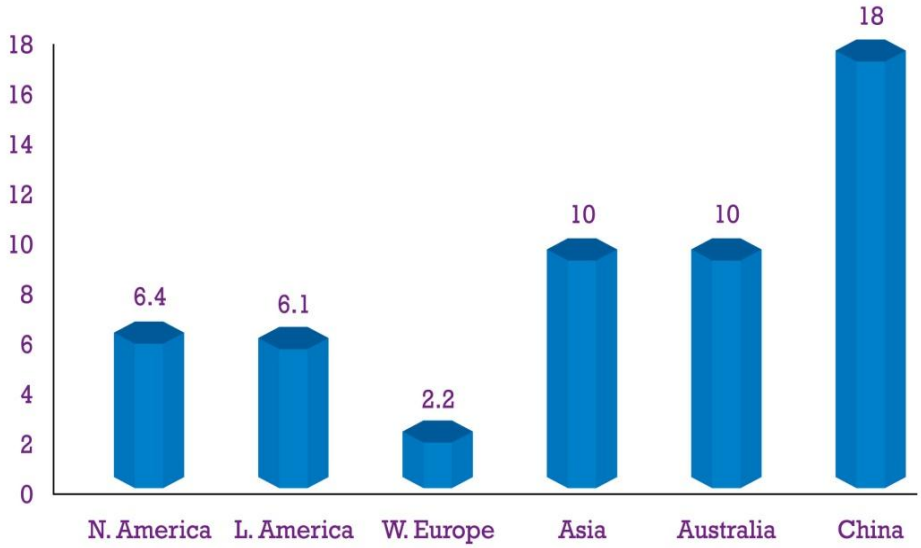
Pharmaceuticals as a percentage of total health care spending during 2002 comprised 12.8 percent in the United States, 14.5 percent in Germany, 15.8 percent in the United Kingdom, and 22.4

percent in Italy. Pharmaceutical spending in the United States grew at an average annual rate of 11 percent between 1970 and 2005. The industry is global and led all other industries in rent-seeking activities by spending nearly $1 billion from 1998 to 2004 on lobbying. Profit-seeking firms engage in strategic lobbying, a special case of rent seeking. Rent seeking is a selfishly motivated effort of one party (pharmaceutical firms) targeted at influencing another party's (government regulators) decision. Economic agents will decide to invest in rent-seeking activities, such as lobbying, if the expected net present value of the effort is profitable at the margin. Global pharmaceutical trade grew at an average annual rate of 23 percent from 2000 to 2003 and was valued at $200 billion in 2002. More than 80 percent of pharmaceutical production and consumption occurs in North America, Western Europe and Japan (Armantier et al, 2008).

2.5.2 Expected growth (%) in pharma spending in next few years

The global pharmaceutical industry is facing moderate growth over the next five years, marked by a rebound in US pharmaceutical growth and strong, but slower growth from emerging markets. At the same time, specialty products have and are expected to assume a greater role in new product growth, a trend that is shifting the balance of market share among the large pharmaceutical companies and mid-sized pharmaceutical companies. (Patricia Van Arnum, 2015)

Figure-3: Region-wise expected growth in pharmaceutical market (next 04 years)



Source: Why drug companies are betting big on pharmerging countries (2015) by Laura Lorenzetti

2.5.3 Emerging Pharmaceutical Market

Emerging markets have now overtaken the EU5 economies (Germany, France, Italy, the UK, and Spain) in pharmaceutical spending, with a total market size of USD 281 billion compared with the EU5's USD 196 billion in 2014. As developed economies continue to constrain or cut healthcare funding, governments in many emerging markets are making healthcare a priority. They are investing in infrastructure, funding services, encouraging the development of a domestic industry, and expanding health insurance to a broader population. As a result, emerging markets will be an important contributor to pharmaceutical sales growth over the next few years. Between 2015 and 2020, they are expected to account for USD 190 billion in sales growth, of which approximately 40 percent will come from innovative drugs. Much of this growth is likely to be driven by Brazil, Russia, India, China, Mexico and Turkey (Jan Ascher et al, 2015)

2.6 Changes in Disease Pattern

A special scenario in pharmaceutical sector is changing in disease pattern. In 2010 there were 10% people with more than 60 years of age and in 2050 this figure will be increased by 21%. Therefore, chronic care diseases like Asthma, Alzheimer's diseases, Bone related problems, Hypertension, Cancer & Diabetes is becoming the major health concern (PwC, 2012). Considering the above, developed countries already invested a huge amount on biotech product development as these products offer superiorities over chemical generics in these special diseases (Intellectual Property Watch: 2015).

Five Non Communicable Diseases (cardiovascular, cancers, diabetes, obesity & chronic respiratory) factors are the world's leading causes of death. They kill an estimated 35 million people each year-60% of all deaths globally-with 80% in low and middle income countries. WHO estimates that total deaths from non-communicable diseases will increase by a further 17% over the next 10 years. (WMD, 2016)

There is evidence of an increasing prevalence in developing countries of non-communicable diseases previously seen only in industrialized countries. This includes hypertension, coronary artery disease and atherosclerosis, and cancer. Many of these diseases result from poor adaptation to significant environmental changes. Habits those are not conductive to good health, such as smoking, drug and alcohol abuse, overeating, and a sedentary life style, have been adopted in many Third World countries. Industrialization and urbanization have created stress and social problems unknown in earlier societies. In addition, there have been changes in eating habits--less fiber and starch, as well as more fatty foods and refined carbohydrates such as sugar. Economic development tends to be accompanied by an increased incidence of cancers of the lung, large bowel, breast,

prostate, bladder and ovary. This trend is believed to result from environmental pollution, increased consumption of tobacco and alcohol, sexual behavior, personal and community hygiene, and high-fat diets. Given the experience in developed countries, the following changes can be expected in developing countries as industrialization intensifies: 1) fewer nutritional deficiencies and infections, with declines in mortality among infants and young adults; 2) more dental caries, obesity, hypertension, diabetes, and vascular diseases; 3) more gastrointestinal diseases such as large bowel malignancy, diverticulitis, and appendicitis; and 4) fewer cancers in some sites (e.g., liver) offset by more in others such as the lung. A thorough assessment of the disease patterns in developing countries is handicapped by a lack of reliable data. There is an urgent need for more facts and figures so that intervention programs can be designed to avoid epidemics of non-communicable diseases in the Third World. (World Health Forum. 1985)

2.7.1 Pharmaceutical Biotechnology

The word biotechnology was first used by Karl Ereky in 1919, featuring the use of living organisms on a given raw material for the purpose of obtaining a particular product and introducing the concept of genetic change.

Broadly, the history of pharmaceutical biotechnology includes Alexander Fleming's discovery of penicillin in a common mold, in 1928, and the subsequent development prompted by World War II injuries of large-scale manufacturing methods to grow the organism in tanks of broth. Pharmaceutical biotechnology has since changed enormously. Two breakthroughs of the late 1970s became the basis of the modern biotech industry: the interspecies transplantation of genetic material, and the fusion of tumor cells and certain leukocytes. The cells resulting from such fusion hybridomas replicate endlessly and can be geared to produce specific antibodies in bulk. (J. Pharm, 1998).

Amongst the earliest uses of biotechnology in pharmaceutical manufacturing is the use of recombinant DNA technology to modify *Escherichia coli* bacteria to produce human insulin, which was performed at Genentech in 1978 (Science News, 1978).

As its advantages have become ever more apparent, the pharmaceutical sector's interest in biotechnology has grown significantly. "Biotechnology has exploded across the industry. It started to emerge in the mid-1990s, incrementally gathering speed as more products were approved in the last ten years (Biotech effect, 2008).

There are 1,466 biotech firms in the United States (318 of them publicly traded), with some 200,000 total employees, the biotech industry is significantly smaller than the pharmaceutical industry. Still, this is a vibrant sector. Between 1992 and 2002, revenue for the industry more than tripled, from $8 billion in 1992 to nearly $30 billion in 2002. And while funding for biotech concerns dropped in the early 2000s, this remains one of the industries where investors are most likely to put their money (Industry Overview, 2012)

Following the phenomena all success of its information technology industry, India is fast emerging as an important player in the biotechnology sector in the Asia–Pacific Region. The large pool of scientific talent available at a reasonable cost, a wealth of R & D institutions, a rich and varied bio-diversity, a flourishing pharmaceutical industry, strong IT skills and an English speaking population have all placed India favorably in the global market. Biotechnology is the new sunrise sector in India and is poised to take the country into the next big league of internal and international investment. India is ranked among the top-12 biotech destinations in the world and is the third biggest in the Asia-Pacific region in terms of the number of biotech companies according to a

report by the Confederation of Indian Industry (CII) and the consultancy firm KPMG (UK Trade & Investment, 2010)

2.7.2 Recent Growth Status of Biotech Products

According to Brian Tempest, editor, Journal of Generic Medicines, "in the near coming years, biotherapeutic are going to take over the whole pharmaceutical industry and by 2016, 11 out of the top 20 pharmaceutical products will be biologics". In last five years more than 60 biotech products have been approved worldwide. More than 600 new biotech generics are in development and 370 generics are in different phases of clinical trials. In 2010 the market of biotech Pharmaceutical products grew at 135% which is one of the remarkable growths in the history. In 2014 the total biotech product market was almost $ 288.7 billion which is very significant compare to entire market (Moklesur, 2104).

The opportunity in biopharmaceuticals is big and growing too rapidly to ignore. Today, biopharmaceuticals generate global revenues of $163 billion, making up about 20 percent of the pharmaceutical market. It's by far the fastest-growing part of the industry: biopharma's current annual growth rate of more than 8 percent is double that of conventional pharmaceutical and growth is expected to continue at that rate for the foreseeable future. The efficacy and safety of biopharmaceutical products, combined with their ability to address previously untreatable conditions, allows pharmaceutical companies to command high prices for innovative drugs. Strong demand has driven significant profits, despite the high cost of goods sold. Biopharmaceuticals have set new standards for blockbuster drugs as well. Blockbusters are traditionally defined as drugs that have $1 billion or more in annual sales; the top 15 biopharma products each enjoy annual revenue of more than $2 billion, with some, such as the anti-inflammatory drug Humira, generating sales of more than $10 billion a year. For many players, the biggest challenge has been simply

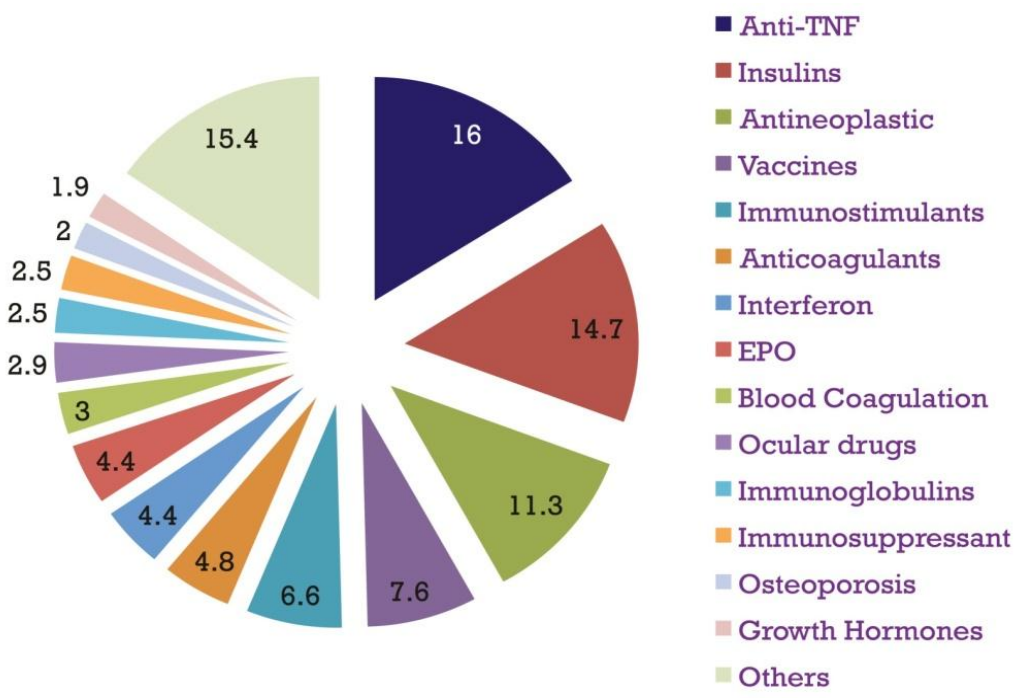
making enough products to sell. It's no surprise that major pharmaceutical companies around the world are increasingly shifting their R&D and sourcing focus to large-molecule products (Ralf Otto et al, 2014).

2.7.3 Market Segments (%) of Biologics

The global pharmaceutical industry has charted growth at an impressive rate in the past few years owing to a vast increase in research and developmental activities, development and launch of new product varieties, breakthrough progress in treatment options for chronic and rare diseases. A significant rise in big pharmaceutical companies' operational setups and funds directed towards novel and more effective drug varieties for complex diseases has also been observed across the globe in the past few years. The scenario has led to an increased focus on the development of biologics and a large number of international players are venturing into the global biologics market.

Transparency Market Research estimates that the market will tread along a healthy growth path in the next few years. The market is anticipated to exhibit a CAGR of about 10.9% over the period between 2016 and 2024. If the number holds true, the market is expected to rise to a valuation of US$479, 752 mln by 2024. (Transparency, 2016)

Figure-4: Market Segments (%) of Biologics



Source: IMS MIDAS, Q2, 2016; Rx

2.7.4 Interchangeability of biosimilar and biological reference product

Since 2006, biosimilars have been available in several countries worldwide, thus allowing for potential savings in pharmaceutical expenditure. However, there have been numerous debates about the interchangeability of biosimilars and reference products based on concerns of immunogenicity by switching between biological products, which may cause lack of effect and toxicity. Areas covered: The authors provide the reader with an overview of the different positions of regulatory authorities on the interchangeability and automatic substitution of biosimilars and reference products. Presently, the FDA allows automatic substitution without prescriber intervention if the biosimilar is interchangeable with reference products, while the European Medicines Agency delegate to each single EU member state. Expert opinion: Different approaches in defining interchangeability and automatic substitution call for harmonization to increase confidence of healthcare professionals and patients about the clinical impact of switching. Networks of electronic healthcare records and administrative databases, potentially linkable to clinical charts and registries may rapidly assess frequency and benefit-risk profile of different switching patterns in routine care at different levels, thus integrating and strengthening pre-marketing evidence (Trifiro G et. al. 2017)

2.8.1 Definition of Biosimilar Products

As per WHO (2010) a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product

As per USFDA (2012) biosimilar is a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

As per European Medicines Agency (2012) a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

A biosimilar (also known as follow-on biologic or subsequent entry biologic) is a biologic medical product which is a copy of an original product that is manufactured by a different company. Biosimilars are officially approved versions of original "innovator" products, and can be manufactured when the original product's patent expires. Reference to the innovator product is an integral component of the approval (Blanchard, 2010 & Nick, 2012).

2.8.2 Emergence of Biosimilar Products

Developing a new biologic agent costs between $800 million and $1.2 billion. The cost of developing a biosimilar has been estimated to run between $75 million and $300 million; therefore, it is easy to move with biosimilar products those who have limited research scope like developing countries (Jerry, 2103). Biotechnological products are being developed over the past three decades. The expiry of patent protection for many biological medicines has led to the development of biosimilars in UK or follow on biologics in USA. Biosimilars present more challenges than conventional generics and marketing approval is also more complicated. To improve access, US Congress passed the Biologics Price Competition and Innovation act 2009 and US FDA allowed “abbreviated pathway” for their approval (Rajiv & Singh, 2014).

For biosimilars development Asia Pacific, Latin America and Eastern Europe are increasingly important locations as sponsors pursue multinational programs to gain efficient access to appropriate patient populations. Many emerging nations are establishing biosimilars regulatory pathways and sponsors now have opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals (ppd, 2013). India being one of the most preferred manufacturing destinations of biosimilars, there is a need for stringent safety and regulatory guidelines. The New India Guidelines "Draft Guidelines on Similar Biologics were announced in June 2012, by Department of Biotechnology (Rajiv & Singh, 2014).

The first generation of biopharmaceutical products manufactured using recombinant technologies was launched in the 1980s and they are now on the way to patent expiration. Over 50 biopharmaceutical products have been approved for marketing in India in recent years more than half of them being biosimilars. By the time its biosimilars regulatory pathway was issued in 2012, India had already approved more than 25 products designated as similar biologics (Thulasi et al, 2014).

Several Biopharmaceuticals have been marketing in Bangladesh for many years but due to very high prices people have less access to these high valued products. All the active proteins and materials required for the formulation of biopharmaceuticals are importing mainly from India and China. If local companies achieve the ability to develop and produce such biosimilar products in Bangladesh, then people can have easy access to those products at lower cost. A number of biopharmaceuticals have already lost their patent protections recently and many more are at the end stage of patent protections. If Bangladesh can use the opportunity to develop biosimilar products, then it could be an international hub to supply biosimilar products in the world market (CM Hasan, 2013).

2.8.3 Global Status of Biosimilars

2.8.3.1 Biosimilars in Europe

In the European Union (EU), a lawful construction for approving biosimilars was established in 2003. This structure means that biosimilars can only be approved centrally via the European Medicines Agency (EMA) and not nationally. EMA first developed guidelines for the approval of biosimilars via an abbreviated registration process during 2005 to 2006, and since then EMA has developed many general and specific guidelines for biosimilars. (GaBI, 2014)

By January 2016, 19 biosimilars based on eight originator products-including the world's first monoclonal antibody biosimilar had been approved for use in Europe. In 2013, biosimilars were responsible for around a quarter of all sales of biologics for which EU patents had expired. The European experience with biosimilars has revealed substantial cost savings for healthcare providers and patients, with no reports of untoward effects or unexpected adverse events with biosimilars in Europe to date. (Quintiles IMS, 2016). Some studies estimate that by 2020, overall savings in the European Union could range from $16 to $45.2 billion. (Tina Valbh, 2016)

2.8.3.2 Biosimilars in USA

The US FDA was authorized to approve follow-on biologics by the BPCI Act passed by the US Congress on March 23, 2010, and has just issued a draft guidance in early 2012. (Jun Wang and Shein-Chung Chow, 2012)

The market for biosimilars in the U.S. has gained momentum after the launch of Novartis' Zarxio (Filgrastim-sndz) in September 2015. Zarxio, the first biosimilar to be approved in the U.S., was a significant development resulting in promising emerging trends for the growth of global biosimilars market. Sandoz claims that the launch of biosimilar has led to the gradual erosion of

the market share of Amgen's Neupogen; as Amgen's Q1 2016 results Neupogen (filgrastim) sales decreased by 13 % driven by the impact of intense market competition in the U.S. (ppd, 2016)

The major three factors that suggests biosimilars penetration may eventually reach high level in the US market are the price of pharmaceutical (twice compare to average price of the rest of the world), scale of healthcare expenditure (18% of GDP) and new health legislation-2014. (Karsten Dalgaard et al, 2013)

As The U.S. region would contribute single-digit revenue share in overall biosimilar market by 2020. Recently, in March 2016, the U.S. FDA has approved its second biosimilar product Inflectra (infliximab-dyyb) as a reproduction of Janssen Biotech's drug Remicade (infliximab). Though, Inflectra has already got its approval to market in countries such as Canada, Mexico, Australia, and various European regions, it is the first biosimilar monoclonal antibody to be approved in the U.S. Such developments would unlock new opportunities for pharmaceutical companies and drug developers in the global market. (The Pharma Letter, 2016 & ppd, 2016).

However, it is estimated that biosimilars will lead to a $44.2 billion reduction in direct spending on biologic drugs from 2014 to 2024, or about 4 percent of total biologic spending over the same period, with a range of $13 billion to $66 billion. (Andrew W. Mulcahy et al, 2014)

2.8.3.3 Biosimilars in Emerging Countries

China, India, Brazil and Russia, among others, have already kept their footprint in the marketplace, but they are about to dive in and change everything. Each of those markets is massive. Under current conditions, parochial clinical trial requirements and an uneven regulatory playing field would force many external companies to establish separate divisions simply to develop biosimilars

in China and many other countries. The future success of biosimilars is not dependent on the US and Europe alone. The need is greatest in Asia and this market will guide the worldwide situation and be the fastest to adopt biosimilars. Drivers for fast uptake include low clinical development cost, unimpeded product launches due to a different patent landscape, inexpensive workforce, less stringent regulatory framework and therapy primarily chosen by physicians (Rodeina Challand, 2014).

2.8.3.4 Biosimilars in India

India, with its established track record of growth in the generic pharmaceutical industry, can potentially emerge as a strong global player in the biosimilar segment. The Indian biosimilar industry is expected to grow from $4 billion in 2015 to more than $70 billion by 2025. Currently, more than 50 biotherapeutics are approved in the country, and more than half are biosimilars. Although India does not have stringent regulations, it has a big potential for biosimilars. Most innovator biotherapeutics are unaffordable to the average patient in India, even though the price in the local market is usually lower than that in Western countries. (Monica Malik et al, 2016)

2.8.3.5 Biosimilars in China

China was the second largest pharma market by spending in 2017 and the second largest biological market by sales revenue, with the biologicals market representing only 12% of the Chinese market and more than 10% of the global biologics market. When we compare countries regarding global biologics market growth, China is the fastest growing country, with 16% CAGR from 2010 to 2021. (Joseph Pategou, 2019). There are several factors driving the domestic biosimilar market: Firstly, changes in disease pattern; shifting of infectious diseases to non-communicable diseases. Secondly, significant price discounts compared to originator products encourage reimbursements. Thirdly, a window of opportunity has been inadvertently created by today's biosimilar leaders. As

the first wave of biologic originators did not file or adequately protect its IP in China during the 1990s, a number of domestic players took advantage of this window of opportunity. (Phillip Miller, 2012)

2.8.3.6 Biosimilars in Korea

According to the Korea Pharmaceutical Manufacturers Association, the biosimilars market in South Korea will grow to 150 billion won ($130 million) by 2019, nearly doubling in size from its 2013 value. Six biosimilars have been approved in South Korea since 2012, and dozens of other biosimilars are currently in the development pipeline. **(**Big Molecule Watch, 2016)

South Korea is aiming to capture a big share of the $110bn of value that Citigroup expects to flow from innovator companies to biosimilars over the next decade. Biosimilars have higher barriers to entry than traditional generics because of the heavier investment and trickier science involved. Yet Celltrion overcame these hurdles to develop the first copy of Johnson & Johnson's rheumatoid arthritis drug Remicade, the world's third best-selling drug last year with sales of $10bn.This was seen as a landmark not only because of its high value but also because it was the first of a more complex category of biologics called monoclonal antibodies to face biosimilar competition. The Celltrion version, known as Remsima or Inflectra, was launched in Europe in February and is now sold in 40 countries worldwide. But the biggest market by far-the US-so far remains elusive. The US Food and Drug Administration approved its first biosimilar earlier this year in a sign that America is finally opening to the category after years of lobbying against it from some big pharmaceuticals and biotech groups. (Simon Mundy and Andrew Ward, 2016)

2.8.3.7 Biosimilars in South Africa

South African medicine market is very sophisticated; generics make up more than 50% of the market. Biosimilars guidelines were established in 2010. There is a financial pressure on the

system overall and great pressure to utilize generics including biosimilars. There is a cost containment focus from the government and payer side and a quality focus from the physician and patient side. Companies will have to bring in a cost structure that is lower than what currently exists along with the highest quality and safety profiles of their biosimilars (Deloitte, 2015).

Drug firm Cipla will invest around 1.3 billion (over Rs 590 crore) to launch a biosimilars manufacturing facility in South Africa. (The Economic Times, 2016)

2.8.3.8 Biosimilars in Japan

The Japanese pharmaceutical market is the second most important one in the world after the United States, with sales of over US $143 billion in 2014, representing 14% of the global pharmaceutical market. The biopharmaceutical market in Japan is of great significance to the world. However, most of the products sold there are of foreign origin but manufactured locally under license. (Tomas Gabriel Bas and Carolina Oliu Castillo, 2015).

In March 2009, guidelines for biosimilars, based on the European Union's existing processes, were published by the MHLW. These guidelines consider biosimilar drugs to be those products that are equivalent and homogenous to the reference biological product in terms of efficacy, quality and safety. (Tomas Gabriel Bas and Carolina Oliu Castillo, 2016)

The first biosimilar to receive approval in Japan was Sandoz's growth hormone treatment Somatropin BS (somatropin) in June 2009. To date, the PMDA has approved seven biosimilars within the product classes of human growth hormone, granulocyte colony-stimulating factor, erythtropoesis stimulating agent, insulin and tumour necrosis factor (TNF)-inhibitor, for use in Japan. (GaBI, 2014)

2.8.3.9 Biosimilars in Australia

The Australian Government, recognizing the growing role biosimilar medicines will play in providing treatment options to Australians in coming years, has launched an initiative aimed at improving awareness and confidence in biosimilar medicines amongst prescribers, pharmacists and patients in Australia. It has allocated $20 million to this initiative over a three-year period. (TGA, 2016). In accordance with this approach, on 16 December 2015, the Therapeutic Goods Administration **(**TGA**)** released its updated guidelines on biosimilars, specifically referring to a number of European Medicines Agency **(**EMA**)** guidelines providing standards for quality, non-clinical and clinical data requirements for biosimilarity. In particular, the pricing consequences of the listing of a biosimilar medicine on the PBS are now certain a 16% price drop (from the subsidized price the government pays the sponsor) will occur on reference brands following the first listing of a biosimilar medicine on the PBS. The PBS listing of Inflectra brings a total of 21 biosimilar medicines approved for use in Australia (GaBi, 2019)

2.8.3.10 Biosimilars in Canada

In 2010, Health Canada issued the "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)", whose objective was to provide guidance on how to satisfy the data and regulatory requirements under the Food and Drugs Act and Regulations for the authorization of subsequent entry biologics (SEBs) in Canada. (Jun Wang and Shein-Chung Chow, 2012)

The first biosimilar in Canada, Omnitrope, was approved in 2009 and Health Canada approved Celltrion's Remsima/Inflectra in 2014. Health Canada recently issued updated draft SEB guidance, which will likely be finalized in 2016. There are now multiple pending patent cases involving biosimilar products on the Federal Court of Canada's docket, with many novel issues at stake.

Canada's provinces are finally figuring out how to capitalize on biosimilar competition within their formularies. **(**J Bradley White et al, 2012**)**

2.8.3.11 Scope for biosimilars due to patent expiry

Following products are going to be off patented very soon which are giving opportunity for the growth of biosimilars.

Table-6: Scope for biosimilars due to patent expiry

Sl #	Brand	Active	Major Indication	Mkt in $ Bln
1	Humira	Adalimumab	Rheumatoid Arthritis	10.8
2	Lantus	Insulin Glargine	Diabetes	9.2
3	Rituxan	Rituximab	Rheumatoid Arthritis	8.6
4	Enbrel	Etanercept	Rheumatoid Arthritis	8.3
5	Remicade	Infliximab	Crohn's Disease	7.9
6	Avastin	Bevacizumab	Ovarian Cancer	7.0
7	Herceptin	Trastuzumab	Breast Cancer	6.8
8	Avonex	Interferon Beta-1A	Multiple Sclerosis	5.5
9	Copaxone	Glatiramer Acetate	Multiple Sclerosis	4.6
10	Neulasta	Pegfilgrastim	Neutropenia	4.5
11	Lucentis	Ranibizumab	Macular Degeneration	4.5
12	Levemir	Insulin Detemir	Diabetes	2.5
13	NovoMix 30	Insulin Aspart	Diabetes	1.8
14	Xolair	Omalizumab	Allergic Asthma	0.8
15	Erbitux	Cetuximab	Colorectal Cancer	0.25
Total				**83.05**

(Md. Abu Zafor Sadek, 2016)

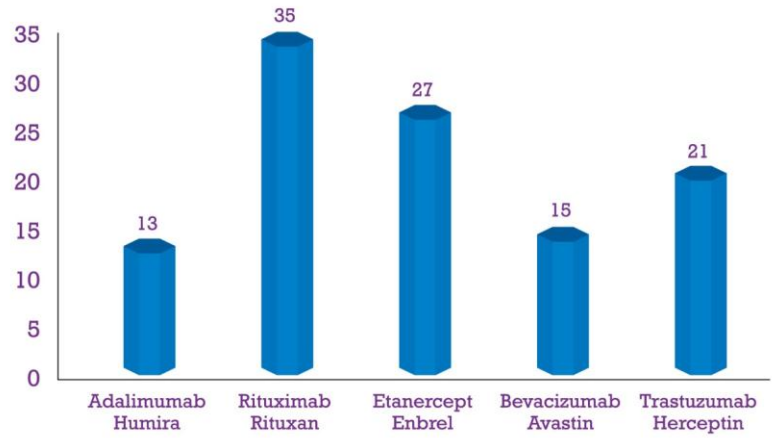
2.8.3.12 Biosimilars under development

According to IMS Health, Americans will spend $220 billion on biologic medicine by 2017, and that amount is likely to climb as more biologics win FDA approval. According to the Pharmaceutical Research and Manufacturers Association of America, there are more than 900 biologic drugs under development.

Because the prices charged for biosimilars are likely to be far north of the prices charged traditionally for generic small molecule drugs, makers of biosimilars should be able to generate significant profitability, even as they undercut the pricing on top-selling drugs like autoimmune disease biologics. (Joanna M Shepherd, 2013 & William W. Fisher and Talha Syed, 2014).

The opportunity created by Humira's patent expiration is exciting, but Humira is far from the only drug that Biogen & other biosimilar manufacturers are going after. Roughly $70 billion in branded biologics will lose patent protection by 2018, and that has industry participants forecasting that the market for biosimilars could reach $20 billion as soon as 2020. (Peter Loftus & D Roland, 2018)

Figure-5: Biosimilars under development against top 5 brands



Source: The Potential for Biosimilars, IMS Health, March 2016

2.8.3.13 Factors Driving Global Biosimilars

Now there are hundreds of biosimilars approved globally. With up to 12 biologics expiring by 2020, it is estimated that the global biosimilars market could reach $25-$35 billion by 2020 representing a CAGR of 62.1 percent. (Jack Cush, 2016). The followings are the driving factors for the growth of the biosimilars.

a. Several blockbuster biologics like Humira, Remicade and Lantus are losing patent guard over the next five to 10 years

The expiration of patents and other intellectual property rights of biological innovators over the next decade unlocks the opportunity for biosimilars to move in the market and increase competition among producers of biologics.

b. Physicians, patients at focus stage as prescription & usage rates are linked to ROI models

Efficacy, safety issues and interchangeability or substitution practices remain key concerns, especially in the U.S. market. These dynamics make it challenging to assess the growth trajectory of the U.S. market, which is expected to take off after 2020.

c. Overheated cost environment drives governments to incentivize biosimilars use

It's not undisclosed that innovator biologics-in particular, the monoclonal antibodies (mAbs)-come with a high price tag. These price tags have led to many governments promoting the use of biosimilars.

d. Clash of global titans brewing in Europe and emerging markets

The growing number of biosimilar approvals in Japan, India, and Latin America, as well as the financial strength of the big pharmaceutical and generic companies, are reasons for the emergence of new market participants.

e. Drug delivery device companies hit the sweet spot

Biosimilar products need to be "only similar as possible" to the innovator product while still offering a unique market differentiation from the innovator product. The norm for biologic

administration used to involve administering the biologic with a simple injectable that did not have volume control.

f. Urbanization of the healthcare industry

The rise of the Gig economy (i.e. Uber) has created a vast pool of healthcare workers in alternative arrangements. As "uberization" continues to catch on, more people are gravitating toward freelance healthcare work. (Nitin Naik, 2016)

2.8.3.14 Strategic locations for biosimilars

Global biosimilars market is dominated by Europe, followed by Asia-Pacific, Rest of the World and North America. However, the Asia-Pacific is likely to witness the highest growth due to increase in health infrastructure, relaxed regulatory requirements, lower labor cost etc. (Markets & Markets, 2016)

2.9.1 Health sector of Bangladesh

It's the 39th largest in the world in nominal terms, and 29th largest by purchasing power parity; it is classified among the next "11" emerging market middle income economies and a frontier market. (Riaz, 2018). Yet, despite improving healthcare indicators such as decline in mortality rates and increase in average life expectancy, the health sector of the country is yet to reach its full potential. In fact, Bangladesh is one of the ten countries with lowest heath expenditure. However, reform policies coupled with innovation and investment by the private sector may translate into rapid rise of this sector.

This segment of the sector report covers the status quo and industry vitals. Later segments will cover individual aspects such as changes occurring in the industry, government initiatives, private sector developments and the overall way forward.

2.9.2 Levels of Medical Care

- **Primary Care:** Basic or general health care traditionally provided by doctors trained in: family practice, pediatrics, internal medicine, and occasionally gynecology.

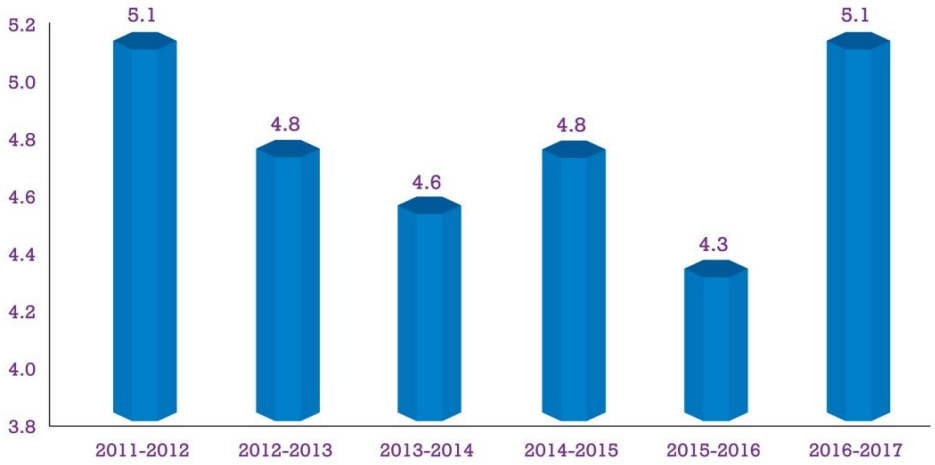
- **Secondary Medical Care:** The medical care provided by a physician who acts as a consultant at the request of the primary physician

- **Tertiary Care:** Specialized consultative care, usually on referral from primary or secondary medical care personnel, by specialists working in a center that has personnel and facilities for special investigation and treatment. (Tasmia Tabassum et al., 2015)

The General government expenditure on healthcare as a percentage of total government expenditure was 7.9% as of 2009 and the citizens pay most of their health care bills as the out-of-pocket expenditure as a percentage of private expenditure on health is 96.5%. (WHO, 2012)

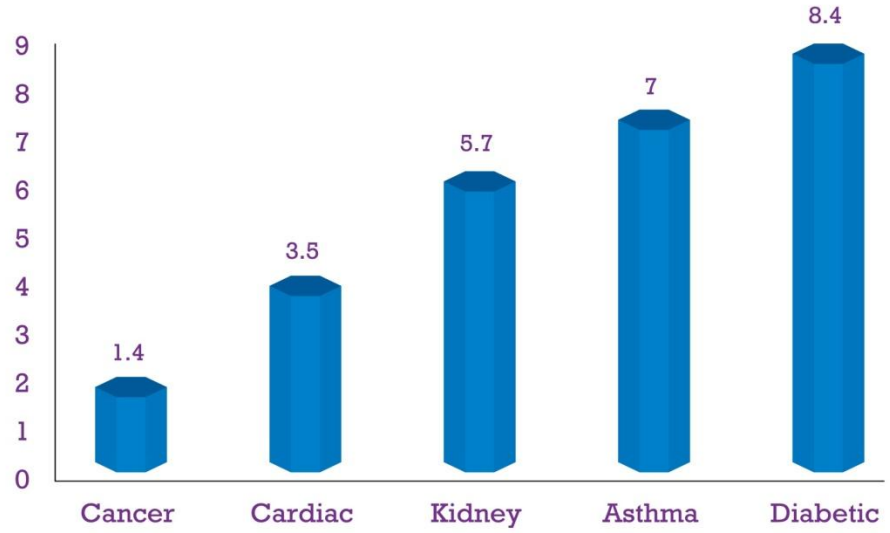
According to the latest Bangladesh National Health Accounts, Bangladesh spends US$ 2.3 billion on health or US$ 16.20 per person per year, of which 64% comes through out-of-pocket payments. (Bangladesh Health System Review, 2015). While, according to WHO estimates, Bangladesh currently spends US$ 26.60 per person on health per year. Public funding for health is the main prepayment mechanism with scope for risk pooling, which constitutes 26% of total health expenditure. The other major funding source is international development partners. Chronic under spending of the Ministry of Health and Family Welfare's budget indicates inefficiency in utilization of resources as observed in the public sector review of the health sector.

Figure-6: Healthcare as a % of GDP



Source: Ministry of Finance (2017), Bangladesh

Figure-7: Disease-wise (major non-communicable) number of patients



Source: Md. Abu Zafor Sadek, 2016

2.9.3 Changes in disease pattern

As per the report of Bangladesh Bureau of Statistics (2012) there was marked an increasing pattern in non-communicable diseases like arthritis 7.5%, diabetes 4.2%, high blood pressure 6.7%, heart disease 1.8%, cancer 0.4% and communicable diseases like tuberculosis 0.6%, acute respiratory infection2.6% and hepatitis-b 1.5% etc. over the years. The prevalence of morbidity per 1000 elderly population among 64+years and older was further dominated by fever 106.4, cardiovascular diseases such as high blood pressure 52.1, arthritis 76.5, diabetes36.4, respiratory diseases asthma 18.9, peptic ulcer 33.2, cataract 31.1 and dysentery 15.4. Prevalence of both high blood pressure 57.9.0 and diabetes 39.0 were higher in male compare to those in female. In the opposite manner prevalence of arthritis was higher in female 91.0 than that of male 63.7. Morbidity prevalence for females is reported higher than males in both rural and urban areas.

Mahmud & Islam (2013) reported that Bangladesh is in the early stages of the demographic transition, which is expected to advance in the future. The proportion of the population (65 years and above) will move from 4.5% in 2000 to 6.6% in 2025 (U.S Census Bureau, 2013). Along with demographic transition, Bangladesh has also been going through a rapid epidemiologic transition in which NCDs now account for two-thirds of all deaths. In 2004, NCDs accounted for 61%, with the remainder from communicable diseases and maternal and child health (MCH) issues. Of the total burden, CVD accounts for 13.4%, mental health 11.2%, cancer 3.9%, respiratory diseases 4.0%, diabetes 1.2%, and injuries 10.7% (U.S Census Bureau, 2013).

2.10.1 Bangladesh Pharmaceutical Industry

There are several sectors on which Bangladesh can be proud of and undoubtedly the pharmaceutical sector is one of these sectors, rather it is the sector, which is the second-largest contributor to the government exchequer. There are about 239 allopathic companies in this sector

and the approximate total market size is about Taka 97,500 million per year of which about 97% of the total requirement of medicines is created by the local companies and the rest 3% is imported. The imported drugs mainly comprise of the cancer drugs, vaccines for viral diseases, hormones etc (Pervez, 2011).

There are about 450 generics registered in Bangladesh. Out of these 450 generics, 117 are in the controlled category i.e. in the essential drug list. The remaining 333 generics are in the decontrolled category, the total number of brands/items that are registered in Bangladesh is currently estimated to be 5,300 while the total number of dosage forms and strengths are 8,300. Bangladesh pharmaceutical industry is mainly dominated by domestic manufacturers. Of the total pharmaceutical market of Bangladesh, the local companies are enjoying a market share reaching around 80%, while the MNCs are having a market share of 20% (Salim, 2011).

The country can continue to produce patented products until 2032 as per trade related intellectual property rights (TRIPS). The industry is legally permitted to reverse engineer, manufacture and sell generic versions of on-patent pharmaceutical products for domestic consumption as well as for export to other LDCs. It created a big opportunity to make Bangladesh a new chemical entity. Bangladesh can share its long years of experience in pharmaceutical formulation and marketing with the Least Developed Countries (LDCs) and developing ones, who need it. Among the 49 LDCs, Bangladesh has the strongest base to manufacture pharmaceutical products.

Bangladesh imports 80 per cent of its pharmaceutical raw materials. A good number of skilled professionals from home and abroad are expected to join the industry to enrich its human resources pool. The pharmaceutical manufacturers in Bangladesh procure raw materials from various countries namely USA, UK, France, Germany, Japan, Holland, Italy, Denmark, China, Switzerland, Austria, Hungary, India, Ireland etc.

Bangladesh has a very strong manufacturing base in pharmaceuticals “toll manufacturing” of current products as a number of companies have already constructed facilities as per USFDA and UKMHRA Standard and are seeking certification in other regulated markets. After gaining the UKMHRA Certification Square Pharmaceutical, one of Bangladesh's leading pharmaceutical industries is now manufacturing cardiovascular drugs and diuretics for overseas clients. A good number of Bangladeshi companies have won accreditation for export from the regulatory authorities in some developed countries. The accreditation will allow them to enter the export market with their competitive prices and standards.

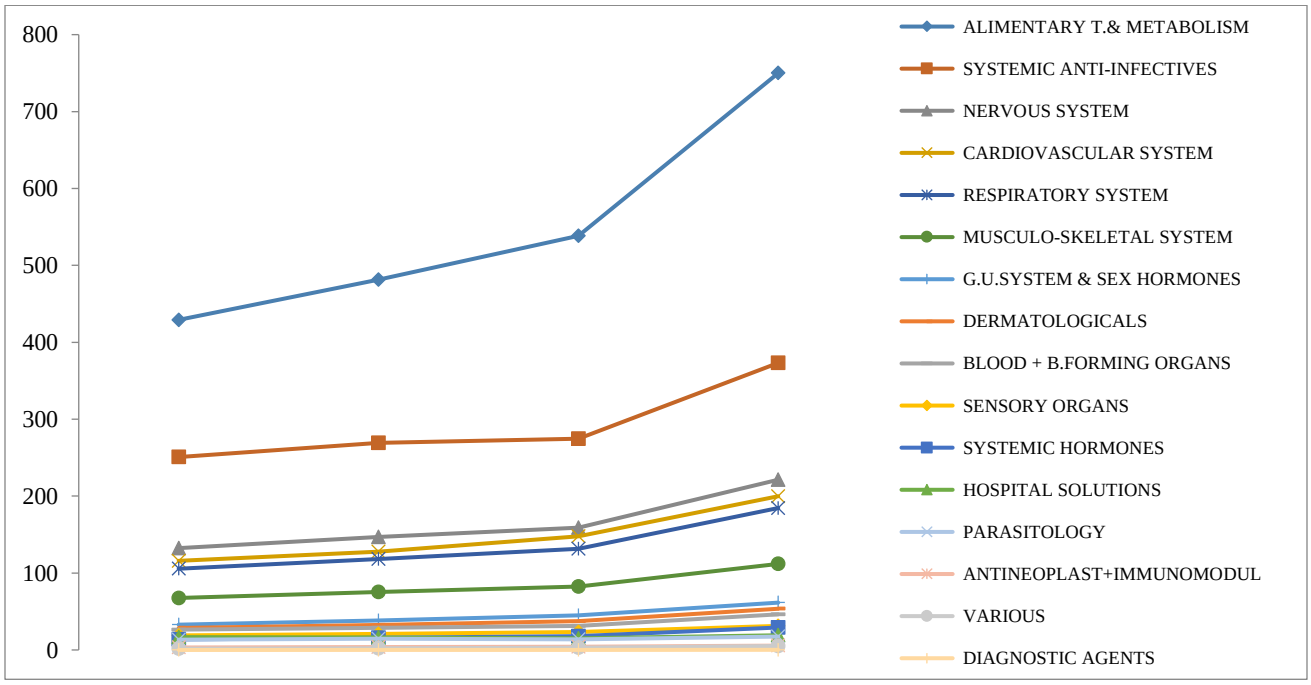
During last couple of years, a good number of investments have taken place in the pharmaceutical sector in the form of facility expansion/upgrading and new entrants. It is estimated that a total investment of US$ 300 million has been made in this sector in last few years. Bangladesh is also a large market for Active Pharmaceutical Ingredients (API) and intermediates. Around 80% of Bangladesh's total need of API is being met through imports. (UK Trade & Investment, 2010)

Table-7: Top 10 Pharmaceutical companies of Bangladesh by value sales in 2018

Sl #	Company	Sales Volume in $ mln
1	Square Pharmaceuticals	417.5
2	Incepta Pharmaceuticals	268.8
3	Beximco Pharmaceuticals	204.5
4	Opsonin Pharmaceuticals	130.3
5	Renata limited	126.4
6	Healthcare Pharmaceuticals	120.9
7	A.C.I. Pharmaceuticals	109.8
8	Eskayef Pharmaceuticals	107.3
9	Aristopharma Limited	102.2
10	The Acme Laboratories	88.5

Source: IMS Health, 2018, 2Q

Figure-8: Therapeutic Class-wise market trend (2015-2018) (mln$)



Source: IMS Health, 2018, 3Q

2.10.2 Export of Pharmaceuticals from Bangladesh

According to the Export Promotion Bureau (EPB) data, Bangladesh earned $89 million from exporting pharmaceutical goods in the last fiscal year, which was $82.11 million in FY2015-16. While in July November of the current fiscal the sector earned $43.14 million posting 23.33% rise.

According to Bangladesh Association of Pharmaceutical Industries (BAPI), approximately 1,200 pharmaceutical products received registration for export over the last two years. According to Bangladesh Export Promotion Bureau, Bangladesh exported pharmaceuticals product to 107 countries in the fiscal year 2016-17. Among 107 exporting countries, top 7 countries (Myanmar, Sri Lanka, Philippines, Vietnam, Afghanistan, Kenya and Slovenia) constitute 60.32% of total pharma export. Rest 39.68% comes from other countries. During this period, Bangladesh has exported pharmaceutical products worth USD 89.17 million as against USD 82.11 million in 2015-16 (EPB, 2017). From July to October 2017-18, Bangladesh exported USD 32.1 million worth of Pharmaceuticals products. From 2011-12 to 2016-17, export revenue CAGR was 13.23%.

However, export sales only contributed 4.59% of pharmaceuticals market in 2015-16 (Considering USD 1 = BDT 80). Hence, the contribution of export sales in pharmaceuticals industry is low.

Pharmaceuticals Company of Bangladesh can only sell different medicine to other country when they get approval of the particular medicine from the drug authority of that particular country. Approval from developed countries signifies that the local medicine has international standard which helps them to build a strong position in local market. In recent time, the Government of Bangladesh has given huge emphasis on the export of Pharmaceutical products from Bangladesh. It is targeted that Pharmaceutical will be the second exporting product after readymade garments.

The Government of Bangladesh has set up an export target of USD 100 million of Pharmaceuticals products for 2017-18 (The Financial Express, 2017).

2.10.3 Opportunities in Global Generic Drugs Market for Bangladesh

Bangladeshi pharmaceutical products have remarkable opportunities to grow in the global generic drugs market. According to Zion Market Research, Global generic drug market is expected to grow at a CAGR of 10.8% from 2016 to 2021 and reach at USD 380.60 billion by 2021 (Global News, 2017). In 2016 alone, patented drugs worth $60 billion are going off patent which opens up opportunities for generic manufacturers around the world (Acme Global, 2017)

Pharma companies of Bangladesh can become a global player utilizing this opportunity. Bangladesh offers significant manufacturing cost advantages due to the lower cost of labor. Major generic Hubs-India and China are losing cost advantages. Cost of labor in Bangladesh is 3 to 4 times lower than that of China and India. Medicine price in Bangladesh is currently among the lowest in the world. (Acme Global, 2017). As a result, Bangladesh has opportunity to export pharmaceuticals products more than India and China. At the same time, major producer of pharmaceuticals raw materials India and China won't be able to produce the patented raw material due to the restrictions from World Trade Organization (WTO). Thus, Bangladesh can export to foreign countries easily. (EBL, 2017)

2.10.4 Backward Linkage of Bangladesh Pharmaceutical Industry

Pharmaceutical industry of Bangladesh is heavily dependent on imported raw materials for manufacturing drugs. 15 companies of Bangladesh including Square Pharma, Beximco Pharma, Active Fine, ACI Limited, Globe Pharma, Gonosastha Pharma, Opsonin Pharma, Drug International and Eskayef produce 40 APIs. Among those, Active Fine is the only company which

is fully involved in producing API i.e. the company does not produce any finished medicine. Ganashastha Pharmaceuticals Limited (GPL) alone accounts for about 60% of the raw materials manufactured in Bangladesh (The Dhaka Tribune, 2017). In 2015, the demand was BDT 60,000 million worth of API & Excipient (Pharmajogot, 2017), where Bangladesh imported BDT 59,720 million worth of API & Excipient. Main suppliers of raw material are India, China, Italy and Germany. According to DGDA, there are 2,805 valid sources of raw material from where Pharmaceuticals manufacturer of Bangladesh can procure raw materials. However, huge amount of money spent for importing raw materials create upward pressure and barrier for the development of Pharma Industry (EBL, 2017).

2.10.5 Active Pharmaceutical Ingredient (API) Park

In order to develop backward linkage, Executive Committee of the National Economic Council (ECNEC), approved the Active Pharmaceutical Ingredient (API) Park at Munshiganj in May 2008 (Bangladesh Economy, 2008). Bangladesh Small and Cottage Industries Corporation (BSCIC) has begun the work of setting up Active Pharmaceutical Ingredients (API) Park on 200 acres of land at Baushia, Gazaria, Munshigonj in the same year. The park is being built under the public-private initiative with the Bangladesh Association of Pharmaceutical Industries (BAPI).

After revising two times, the estimated cost of the project was BDT 3,640 million (The Financial Express, 2015); 13 70.8% up from original estimation of BDT 2,130 million. There will be about 42 number of plots to be set up. The cost of each acre of land is estimated as BDT 31 million. The Companies will get 10 years' time to pay for the plot. There are 30 plots in "A" category (3.27 acre each), 5 plots in "B" category (2.35 acre each), and 7 plots in "S" category (different size). 32 member companies of BAPI had applied for 57 plots. All infrastructural facilities including

Common Effluent Treatment Plant (CETP) and Waste Dumping Yard will be available in this project. The cost of the Common Effluent Treatment Plant (CETP) is estimated as BDT 800 million, to be established by the companies. This API Park is expected to create employment of 25,000 individuals. The API Park was expected to be operational by late of 2011. But the construction work was delayed. The construction work of infrastructure at API Park is set to begin by February, 2018 (The Financial Express, 2015). API Par It is expected that some part of API Park will be operational by 2019. However, the project is expected to be fully completed by June, 2020 (EBL, 2017)

The Government has handed over 42 plots in the industrial area to 28 drug manufacturers in 20th September, 2017. Square pharma, Beximco Pharma, Globe, Opsonin, Eskayef, JMI got several plots in the park. The companies are required to submit their building layout by February 2018. The construction work of factory building is expected to begin by March 2018. With the completion of API Park, Bangladesh will be able to decrease the cost of locally manufactured drugs and it will add to the cost advantage for exports. It is expected that the country can save at least 70% of import cost of raw material by producing raw material at the API Park. This will dramatically reduce the cost of production and help Bangladesh to achieve price competitiveness in Global Market.

API can also be exported to other countries. Currently, Global API market stands at USD 238 billion (Prenews, 2017). At the same time, the Government of Bangladesh has declared Pharmaceuticals sector as thrust sector. The Government has announced Pharmaceuticals "The product of the year 2018." (The Dhaka Tribune, 2018). This gives immense opportunity for Bangladesh to export APIs to foreign countries (EBL, 2017).

2.10.6 Potential of Bangladesh

Bangladesh is poised to follow China and India's recent growth pattern of rising per capita income as the recent distribution of economic growth has shifted in favor of low and middle income countries. Bangladesh's estimate of economic growth is predicated upon its impressive growth performance of per capita income averaging 5-7.5 percent over the last decade, and expectation of continued positive economic performance. Moreover, it was able to reduce its population growth rate from 2.7 percent in 1970 to 1.58 percent in 2012, which will contribute to its population control and a steady rise of per capita income.

In addition, Bangladesh has a good prognosis to achieve the United Nation's Millennium Development Goals as they have reduced poverty below 40 percent, gained gender equality, enhanced education levels, maintained relative political stability over the last 20 years, and shifted their economy from agriculture in favor of industrial technology and communication including capturing employment in the "international outsourcing labor market." (Nake M. Kamrany et al. 2012).

Bangladesh has experienced a consistent GDP growth trajectory-more than six percent over the last 10 years. Cheap labor cost (one-fifth of China and half of India), and a young consumer base of 160 million with progressively higher purchasing power, have led to its development. Add to that several key fundamental drivers and we have the most valuable gem in Asia.

The macro-economy has been driven by exports and remittance, leveraging workforce both of which have been growing at a Compound Annual Growth Rate (CAGR) of over 15 percent in last 10 years and have accounted for over one-third of GDP. The central bank has actively managed

the growth of the financial system while ensuring stability across key economic variables like exchange rate volatility and inflation. (Reaz Islam, 2014).

2.10.7 The Adoption of Pharmaceutical Biotechnology in the Pharma Industry of Bangladesh

With the patent expiration of most first-generation biologicals internationally in 2004, and new biologics having a patent period of just twenty years (Azevedo et al., 2014), prospects for developing biosimilars are brighter than ever. Taking advantage of the biosimilar movement would see Bangladesh keep up with other growing Southeast Asian pharmaceutical industries (such as those of India, Vietnam and Thailand) seeking the clinical and economic benefits of biosimilars (Farhat, 2017). However, there is currently a large gap in documented literature of the country's biosimilar need, usage, regulatory policy and post marketing surveillance strategies which we aim to fill through this study. Although in its initial stages, the pharmaceutical industry of Bangladesh has steadily begun to employ biotechnology in the field of medicine. The industry aims to meet global pharma trends and reduce the local demand for biotechnology developed products. As a result, pharmaceutical companies are investing huge capital behind the development of anti-cancer, anti-HIV/AIDS, vaccines, insulin and several other bio-drugs to meet local demand.

2.10.8 Biological Products' Market in Bangladesh

Pharmaceutical industry is one of the technology oriented high-flying manufacturing sectors of Bangladesh with the market value of $1,897,000 per annum. Despite of limited number of new products in the domestic market the average growth was around 15% in last 5years. Among different therapeutic segments antidiabetic, anticancer, cardiovascular and some others grew at a higher speed where biological products' contribution was remarkable. In 2012 biological products contributed almost 1% of the entire market whereas in 2016 this part becomes more than doubled

(3%). Also, biological products grew 6% higher than the regular chemical drug market in last year. However, the drug regulatory guidelines of Bangladesh restrict the pharmaceutical marketer only to prefer individual selling out of the available communication mix. Study found that price is the most considerable element for choosing biological products in Bangladesh. (Zafor & Ferhat, 2017)

2.10.9 Biosimilars potential in Bangladesh

Countries like Bangladesh have limited health budget, strong drug policies and a lower income earning population. The above scenario strongly seeks to get benefits from the rapid growth of biologics within the local industry (Jois, R, 2017).

Furthermore, an increase in demand for highly valued biologicals such as cardiovascular, antiasthmatic, anticancer and anti-diabetic medication has pushed pharmaceutical giants within South Asia to undertake a more holistic approach towards biosimilar development (Raj Kumar et al., 2018).

Internationally recognized regulatory bodies such as the USA (United States Food and Drug Administration), WHO (World Health Organization), EMA (European Medicines Agency) and IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) offer an abbreviated and streamlined approval process for biosimilars, which facilitates their commercialization if they can be shown to be highly similar to already approved reference products. This creates a potential opening for developing countries like Bangladesh into several international pharma markets such as that of the U.S and EU (Farhat, 2017).

2.10.10 Cost benefit of biosimilars in Bangladesh

Kabir et. al. (2018) reported that one of the advantages of biosimilars is its promise of potentially lowering healthcare costs (voiced by 83% of Industry Experts, 80% of Academicians, and 67% of Clinicians). It also assures to treat the same indications as those remedied by the reference biologic (voiced by 44% of Industry Experts, 44% of Clinicians and 35% of Academicians). The possible advantages of a lower therapeutic dose or utilization of an administration route varying from the original biologic were less favored by the candidates surveyed.

2.10.11 Regulatory status of biosimilars in Bangladesh

The biosimilars guidelines of Bangladesh released by DGDA on 2018. The definition of biosimilars was set based on WHO biosimilar guidelines (WHO, 2017) as "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product". The approval process for bioproducts such as vaccines are currently handled by three expert committees. These three committees are the CMC (Chemistry, Manufacturing and Controls) committee, the clinical trial document evaluation body and the legal system utilized for all drugs within the policy. Approval is also directed by the Drug Control Committee and technical sub committees. However, under current guidelines, the Directorate General of Drug Administration (DGDA) promotes the operation and development of a pharmacovigilance system on biologics and other drug products. There are currently no regulatory boundaries set with regard to interchangeability issues of biologics and biosimilar drugs in the clinical setting. This means that the Clinician has to make an independent an informed decision on which drugs should be prescribed for treatment. A guideline on the evaluation of biosimilar products was released by the DGDA at the start of the year 2018. This guideline is prepared in harmony with that of several globally accepted guidelines, such as the EMEA guideline on similar

biological medicine, the WHO guideline on similar biotherapeutic products (SBPs) and the Korean guideline on Biosimilar products. This signals a large step forward for the country's biosimilar industry in terms of attaining high standards with regard to global reputation. In order to obtain a better understanding of the presiding regulatory guidelines governing biosimilars within the country, data was collected from the reigning drug regulatory authority (Sarker et. al., 2017).

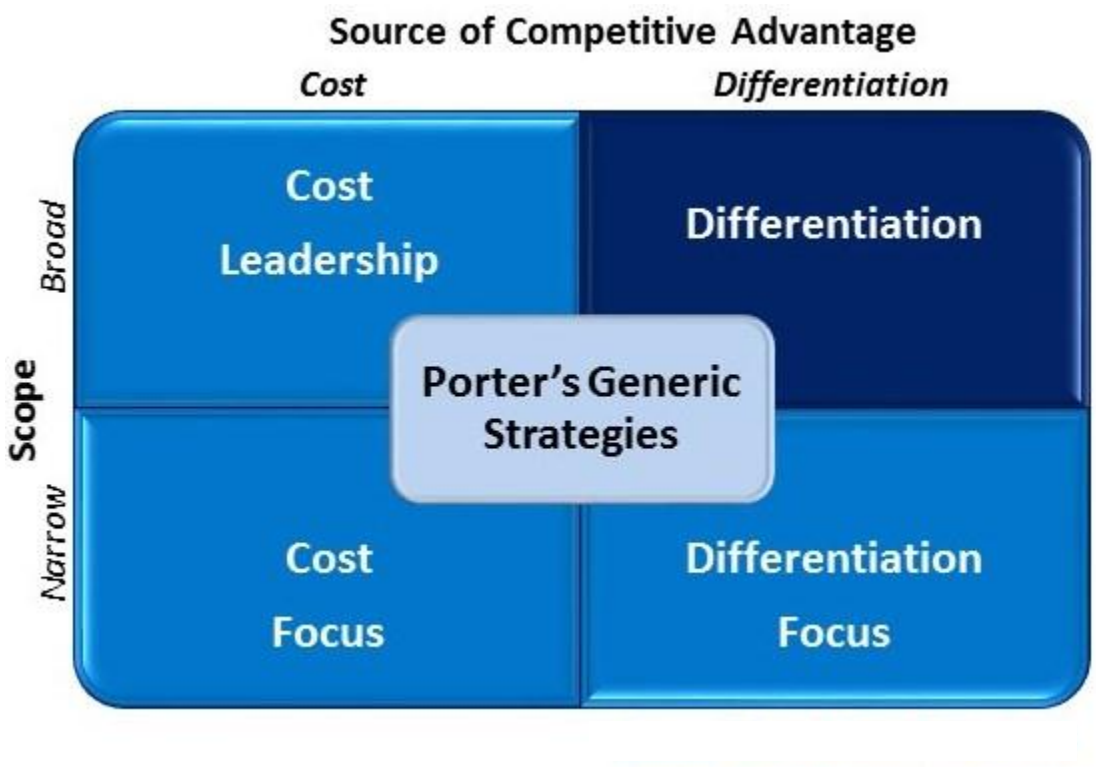
2.10.12 Concept of Biosimilars and Non Comparable Biologics in Bangladesh

Biosimilars are often become confused with non-comparable biologic products (also termed as biomimics) in Bangladesh. The said non-comparable biologics (NCBs) are copies of the innovator product which have not experienced the strict assessments and regulatory necessities to encounter biosimilarity. (Kabir et. al. 2018). The endorsement of these products is equivocal as they lack data from clinical studies. These products have very limited critical evidence and clinical trial data which is making it tough to satisfactorily compare their safety and efficacy profile with the innovator biologic. There are some come countries with less stringent drug regulatory pathways and these NCBs are frequently marketed without clinical trials or sufficient evidence to prove biosimilar (Castaned et. al., 2015 & Kabir et. al. 2018). A clear insight on Non-Comparable Biologics is utmost priority to distinguish them from biosimilars in terms of their safety and efficacy profile. Educating the understanding of the differences between the two would bound the figure of poor quality drugs attaining the Bangladesh drug market. Consequently, this would also benefit patients who are undergoing treatment inside the country. (Kabir et. al. 2018).

2.10.13 Theories related to biosimilars marketing

2.10.13.1 Porter's Generic Theory

Figure-9: Porter's Generic Theory



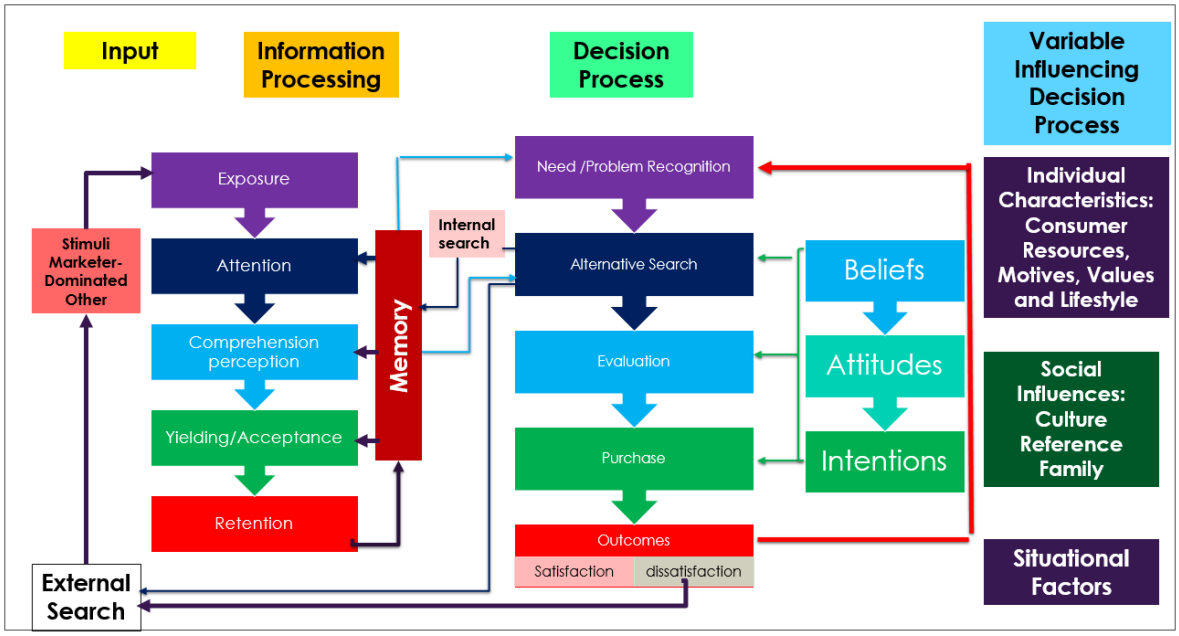
Porter's generic strategies describe how a company pursues competitive advantage across its chosen market scope. There are three/four generic strategies, either lower cost, differentiated, or focus. A company chooses to pursue one of two types of competitive advantage, either via lower costs than its competition or by differentiating itself along dimensions valued by customers to command a higher price. A company also chooses one of two types of scope, either focus (offering its products to selected segments of the market) or industry-wide, offering its product across many market segments. The generic strategy reflects the choices made regarding both the type of competitive advantage and the scope. The concept was described by Michael Porter in 1980.

Porter's theory emphasizes on competitive advantages either by focus or by cost. Biosimilar products will be price competitive due to relatively less R&D cost; so, price benefit will be an important tool for biosimilar products

2.10.13.2 Engel Kollat Blackwell Model

The Engel Kollat Blackwell Model of Consumer Behavior was created to describe the increasing, fast-growing body of knowledge concerning consumer behavior. This model, like in other models, has gone through many revisions to improve its descriptive ability of the basic relationships between components and sub-components.

Figure-10: Engel Kollat Blackwell Model

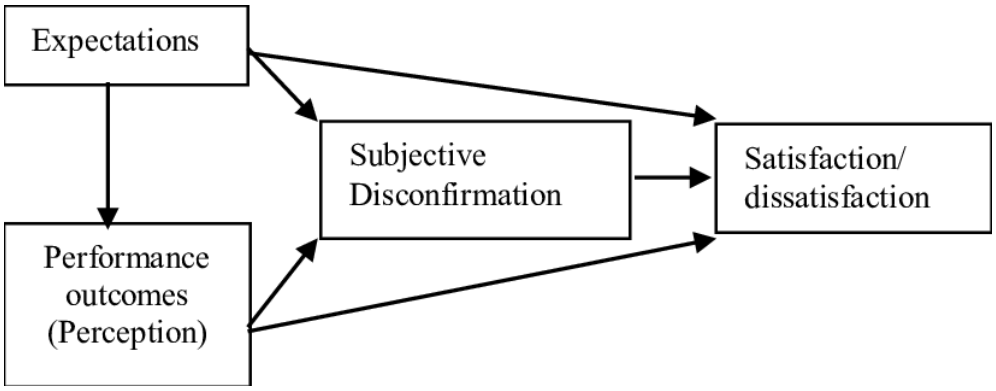


Increased number of aging population is driving the higher demand of biological products as cardiovascular, metabolic disorders, cancer are more common to them ; therefore, biosimilars will be the alternative as Bangladesh market is price sensitive. (Heraldkeeper, 2018 & Md. Abu Zafor Sadek, 2016)

2.10.13.3 Oliver's theory

Expectation confirmation theory (alternatively ECT or expectation disconfirmation theory) is a cognitive theory which seeks to explain post-purchase or post-adoption satisfaction as a function of expectations, perceived performance, and disconfirmation of beliefs. The structure of the theory was developed in a series of two papers written by Richard L. Oliver in 1977 and 1980. Although the theory originally appeared in the psychology and marketing literatures, it has since been adopted in several other scientific fields, notably including consumer research and information systems, among others.

Figure-11: Oliver's theory

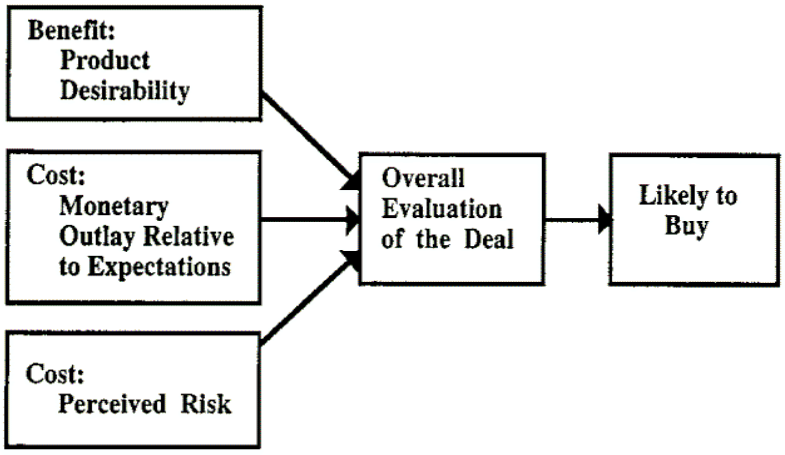


In view of the nature of the products pharmaceuticals are very sensitive to quality & performance. It is worth mentioning that considering quality & performance biotech & biosimilar are almost same. Nevertheless, in view of price biosimilars are ahead of biotech. (Lilian Rumi Tsuruta et. al. 2015)

2.10.13.4 Charles M. Wood and Lisa K. Scheer's Theory

This theory describes how buyers' budget constraints influence buyers' perceptions of discounts presented in a dollars-off versus percentage-off format.

Figure-12: Charles M. Wood and Lisa K. Scheer's Theory

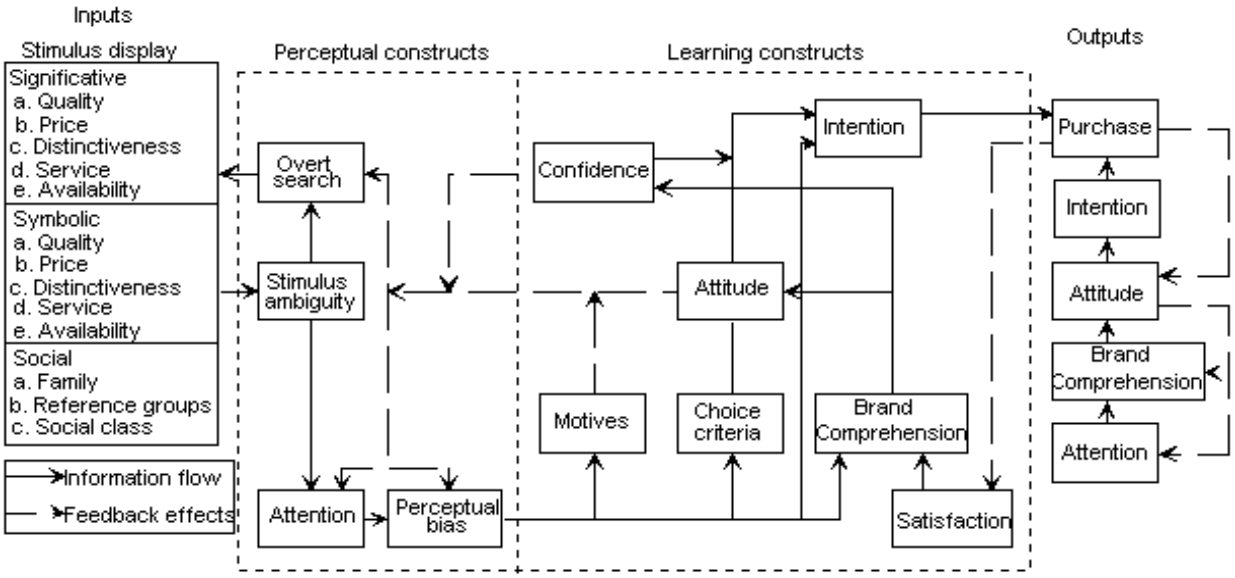


This model reveals that monetary outlay & risk factors are related to evaluation process. Biosimilars are risk free and matches with monetary expectations.

2.10.13.5 Howard-Sheth model:

This is one of models that represent consumer behavior on the market. It attempts to explain the rationality of choice of the product by the consumer under conditions of incomplete information and reduced processing capability. It analyses the external symptoms of behavior, reactions and thought processes that cannot be subject to direct observation. Howard-Sheth model is based on the assumption that the consumer behaves rationally during purchase, process is repeatable and is result of incentives which have their source in the environment (input variables). It consists of four main groups of variables.

Figure-13: Howard-Sheth model



This model emphasizes on quality, price, impact of reference group (prescription habit of renowned practitioners), availability, feedback etc. which are related with upcoming biosimilars.

2.10.14.1 Recent landscape of biobetter

In the evolving world of biologic therapies, a class of follow-on biologics so-called “biobetters” is emerging as a new category of products that could compete with biosimilars for market share.

The term “biobetter” was coined, according to the Generics and Biosimilars Initiative, by G.V. Prasad, CEO of Dr Reddy’s Laboratories, while speaking at an industry conference in Mumbai, India, in 2007. While the term “biosimilar” is applied to a drug that has been demonstrated to be highly similar to its reference, with no clinically meaningful differences from the originator product, the term “biobetter” refers to a therapy that has resulted from intentionally altering a biologic product in order to improve its clinical effects, require less frequent administration, or enhance tolerability.

In a recent review, published in Biotechnology and Applied Biochemistry, Malgorzata Kesik-Brodacka, PhD, explains that biobetters of monoclonal antibodies may be created through pegylation (which may increase half-life of a therapy) or combination with a cytoxic agent (which may enhance efficacy).

Examples of biobetters include Roche’s ado-trastuzumab emtansine (Kadcyla). The therapy, an antibody–drug conjugate, is a biobetter of trastuzumab (Herceptin, also developed by Roche), that has been demonstrated to slow disease progression in patients with HER2-positive advanced cancer. Another such product is obinutuzumab (Gazyva), a biobetter of rituximab, which has a different method of action, has been demonstrated to be less immunogenic, and triggers greater cytotoxicity than rituximab.

While these 2 drugs have been demonstrated to have advantages over the innovator biologics on which they were modeled, the term “biobetter,” when applied to such therapies is largely a matter

of marketing. While guidelines exist for demonstrating biosimilarity of molecules, no regulatory pathway exists to demonstrate that an altered biologic is “biobetter” than the innovator biologic.

The lack of a specific approval pathway for altered biologics presents an opportunity for product developers; altering an originator biologic will result in a therapy that must be addressed as a new product under existing regulatory pathways. Approval of a new drug may lead to patent protection and market exclusivity, and could be used to help defend a company’s market share against biosimilar competition for originator products that have lost or are about to lose patent protection. “Both biosimilars and biobetters are natural alternatives for the reference biopharmaceuticals and therefore compete for the same market,” writes Kesik-Brodacka.

However, according to Nicola Davies, MD, writing in The Pharma Letter, the increased costs associated with biobetters, especially relative to the savings offered by biosimilars, could have an effect on uptake: “Many payers are searching for the most affordable treatment option available, which raises the concern of whether they will allow access for biobetters that may cost much more than biosimilars.” Biobetters, says Davies, would have to demonstrate a significant clinical advantage over biosimilar therapies in order to “flourish and even co-exist with biosimilars.” (Kelly Davio, 2017)

Biobetters are new and improved versions of already approved biological drugs. They are being developed to overcome some of the challenges associated with original drugs, which could range from a known in vitro or in vivo chemical or structural instability, product heterogeneity, immunogenicity, through to poor bioavailability, lack of targeting to disease site, and a short half-life leading to a requirement for either high dosing frequency or large volume dosing, which can result in suboptimal safety, efficacy, tolerability, and dosing regimens.

Although working against the same target as an original biological drug and potential biosimilars of that product, biobetters are modified to offer increased effect on the target, fewer side effects, or higher treatment convenience. Modifications may include structural changes by chemical modification, amino acid alteration or protein fusion as well as improved formulations over the original biological drug. With the development of more effective and/or longer-acting therapeutics, biobetters have the potential to reduce healthcare costs through greater efficacy and/or less frequent dosing.

The advantage for pharmaceutical companies is also evident in terms of commercial potential. Due to a lack of formal recognition of the term biobetter from regulatory bodies, "biobetters, for all practical purposes, are considered as new products as per current regulatory guidelines," says Durgaprasad Annavajjula, director of scientific affairs at India's Stelis Biopharma.

This means that biobetter developers can apply for patent protection. Compared to originator products, biobetters constitute lower costs and developmental risks since the development process depends on pre-existing scientific data from the reference biologic.

Biobetters can be a comparatively easier way for innovator companies to build on what they have, extending a franchise, rather than letting it fade away to biosimilars and other competitors. (The Pharma Letter, 2017).

Ideally, biobetter makers have the capacity to command a price premium, but with payers seeking to lower costs and increasingly preferring the most affordable treatment options available, is there really room for biobetters in the healthcare market.

2.10.14.2 Biobetters versus biosimilars

The terminology biobetter states to a recombinant macro molecule drug that is in the same class as a prevailing biopharmaceutical but is not identical; it is upgraded over the original. Biobetters build on the victory of existing, approved biologics but are measured less of a commercial risk than developing a brand new class of biologic. (Biotech Industry, 2018)

Biobetters are not completely novel drugs and they aren't generic forms of drugs, either. While some experts consider biosimilars to be generic versions of biotech drugs; however, it is not possible to create a generic biologic drug. That's because biopharmaceuticals are produced in living organisms such as animals or bacteria and cannot be copied exactly. (Kathly Stone, 2018).

Biosimilars are designed to be as effective as the originator as possible, while also offering a lower price. Notably, the market uptake of many biosimilars has been a struggle, such that biosimilar developers have been required to rely on discount schemes to get their products in formularies and special contracts.

Many payers are searching for the most affordable treatment option available, which raises the concern of whether they will allow access for biobetters that may cost much more than biosimilars. Research suggests that biosimilars are appealing to payers precisely because of the significant cost savings they offer, but they do not provide clinical advantages, whereas biobetters do. (Dr. Nicola, 2017 & Darrell Sleep, 2017).

Biopharmaceutical companies have concentrated on several strategies to develop biobetters. They are only working with molecules that have mechanisms of action (MOA) that are clinically proven or have a proof-of-efficacy that has been well-known and where addition values can be gained.

They are focusing on areas where there are unmet medical requirements within a known class of mediators, where existing drugs or their biosimilars do not already serve well.

They aim to create biobetters where current agents are inadequate to treat refractory patients, relapsed patients, or those that have inconvenient dosing systems or safety concerns. To do this, they are focusing on application of best science and antibody technologies to create highly differentiated and potent biologics within the same general MOA as already established agents. (R&D Magazine, 2018)

2.10.14.3 Advantages of Biobetters

Biobetters have the potential to offer tremendous commercial advantages over originator or biosimilar drugs as well as to receive patent protection and market exclusivity.

a) Commercial Value

By providing a more effective or longer-acting medicine, biobetters create the potential to take over and control the market prior to entry of biosimilars of the originator drug. For example, in Europe, where biosimilars of Neupogen are marketed at a 20 percent to 30 percent discount over Neupogen, Amgen has retained significant market share by having Neulasta to offer patients. Neulasta, as a long-acting biobetter of Neupogen, provides advantages to patients that Neupogen or its biosimilars do not have. Similarly, although Granix, Teva's version of Amgen's Neupogen, has been on the U.S. market since 2013, Neulasta continues to be a blockbuster product in the U.S. due to the benefits it provides to patients.

Biobetters also have the potential to reduce healthcare costs due to greater therapeutic efficacy or by having to be administered less frequently, as in the case of Neulasta. Also, unlike biosimilars,

biobetters are not faced with the burden of having to be similar to the originator biologic. This frees companies to use more modern and potentially less costly manufacturing methods. In addition, as a better or more convenient medicine, biobetters offer a marketing advantage over the originator biologic or its biosimilars.

b) Patents

Biobetters also are likely eligible for patent protection. Patents can potentially be obtained for the biobetter itself, a pharmaceutical composition of the biobetter, a method of treatment or manufacture. Biobetters may be eligible for all of the same types of patent protection available for originator biologics. Amgen, for example, obtained patent protection for its Neulasta biobetter. Similarly, Roche obtained patent protection for Mircera (a biobetter of Amgen's Epogen), Gazyva (a biobetter of Roche and Biogen's Rituxan antibody) and Kadcyla (a biobetter of Roche's Herceptin antibody).

c) Regulatory Advantages and Non-Patent Exclusivity

Biobetters, just as any new biologics, allow manufacturers to avoid the complex litigation provisions, a 12- year bar to final FDA approval and regulatory uncertainty associated with the BPCIA. Because biobetters are approved through submission of a full BLA rather than an abbreviated BLA (aBLA), they are not subject to the litigation provisions of the BPCIA and are not blocked by the originator biologic's 12 years of non-patent exclusivity provided in the BPCIA. Under the BPCIA, a biosimilar cannot receive final regulatory approval from the FDA and cannot be marketed until the reference biologic has enjoyed 12 years of marketing exclusivity from the time it was first licensed. By contrast, the FDA can approve biobetters at any point in time, and therefore biobetters can enter the market prior to the marketing of any biosimilars.

Further, while approval of a biologic through a traditional BLA with a full complement of pre-clinical and clinical data is much more costly than approval through submission of an aBLA, the BPCIA is still a largely untested regulatory pathway. To date, only Sandoz's biosimilar of Neupogen, known as Zarxio, has been approved through the BPCIA regulatory pathway. While Zarxio's approval earlier this year was a milestone event, it is unlikely to offer significant insight into the regulatory requirements for obtaining approval of complex biologics due to its simplicity. Zarxio is a small protein made in bacteria with no glycosylation (attached sugars). Biobetters, by being approved through submission of a traditional BLA, benefit from a more certain and established regulatory approval pathway.

As with other new biologics, the BPCIA provides a significant advantage to biobetters. Biobetters have the potential to receive their own 12 years of market exclusivity from biosimilar competition. The BPCIA automatically provides biobetters with that advantage if the regulatory application is filed by a company that is not related to or a licensee of the company that applied for or manufactured the originator biologic. When the company that applied for approval of the originator biologic seeks FDA approval of a biobetter of its own product, the biobetter will likely receive 12 years of market exclusivity as long as it is a true biobetter, *i.e.*, it is (1) structurally different from the originator biologic and (2) provides a change in safety, purity or potency as compared to the originator product.

Guidance from the FDA confirms that biobetters likely will be entitled to their own 12-year exclusivity. The FDA considers any of the following differences to be a structural modification of the originator biologic for purposes of the 12-year exclusivity provision of the BPCIA: "any differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational

events (including any chemical modifications of the molecular structure such as pegylation), and infidelity of translation or transcription, among others." The typical biobetters strategies, discussed above, all meet this requirement.

In assessing whether such structural differences result in a change in safety, purity or potency as compared to the originator product, the FDA intends to make a case-by-case determination based on information provided by the biobetter applicant about a "measurable effect (typically demonstrated in preclinical or clinical studies and shown by relevant methods such as bioassays)." The FDA recommends that the biobetter applicant present "evidence that the change will result in a meaningful benefit to public health, such as a therapeutic advantage or other substantial benefit when compared to the previously licensed biological product." Since the goal of biobetter development is to provide a superior medicine that is meaningfully different in terms of safety, purity or potency, this further requirement should be readily met, providing the biobetter with 12 years of non-patent exclusivity against biosimilar entrants.

2.10.14.4 Challenges of Biobetters

Biobetters also pose formidable challenges. As with originator biologics, biobetter development is fraught with risk and requires significant research and development. Biobetters are bound to have a higher success rate than originator biologics due to a validated target for the biologic, but an improved biologic is far from certain and may require significant experimentation. In addition, biobetters may have new and unexpected side effects that are different from that of the originator biologic. Approval of a biobetter also requires a traditional BLA with a full complement of pre-clinical and clinical data. As a result, research and development costs for biobetters will be significantly greater than that for a biosimilar of an originator biologic and approach that of an

originator biologic. But the development of the biobetter benefits from the established efficacy of the originator biologic and validated target. (Irena Royzman and Andrew D. Cohen, 2015)

3.1 Objectives

Global Biosimilar Market report offers a comprehensive valuation of the market. It does so via in-depth comprehensions, appreciative market growth by following historical developments and analyzing the present situation and future forecasts next seven years based on progressive and likely states of Biosimilar industry. Biosimilar research report assists as a depository of analysis and data for every side of the industry, including but unlimited regional output, types, applications, emerging technology developments and the competitive landscape.

Biosimilar Market is highly fragmented and is based on new product launches and clinical results of products. Hence the major players have used various strategies such as new product launches, clinical trials, market initiatives, high expense on research and development, agreements, joint ventures, partnerships, acquisitions, and others to increase their footprints in this market.

The broad study on the biosimilars market encompasses the market size, market share analysis, market dynamics, value chain analysis, market forecast, market classification, and company profiles.

Nevertheless, biosimilars industry is vastly dependent on the advanced technologies used in various procedures of development and manufacturing. These technologies are acting as a mandate for every single operation in biopharmaceutical and healthcare research industry.

Manufacturers are the most important stakeholders for the biosimilars; pharmaceutical companies are largely focusing on the development of novel pharmaceuticals, especially for the blockbuster drugs (Allied Market Research, 2018)

3.1.1 Broad Objective

To identify the growth potential of biosimilar products of Bangladeshi Companies.

From literature review and expert survey the researcher found that the followings are the drivers for the growth of biosimilars in Bangladesh. Therefore, specific objectives have been identified accordingly.

Table-8: Drivers for biosimilars

Sl #	Drivers for Biosimilars	Support
1	Present Market Trend	Industry Experts
2	Perception about biosimilars	Erwin A. Blackstone and P. Fuhr Joseph (2013)
3	Perception about biologics	Industry Experts
4	Price Concern	T. Sayandhan et. al (2010)
5	Competitiveness of the local manufacturer	Industry Experts & KOL Specialist Doctors
6	Total health cost reduction	Key Opinion Leaders (Doctors)
7	Export Possibilities	Industry Experts

3.1.2 Specific Objective

a. To identify the present market trend of biological products in Bangladesh
b. To identify the perception of specialists doctors in Bangladesh regarding biologic products
c. To identify the perception of specialists doctors in Bangladesh regarding biosimilar product
d. To identify the price related views of specialists doctors in Bangladesh
e. To identify the perception of specialists doctors in Bangladesh regarding competitiveness of the local manufacturers
f. To identify the reduction of total health cost due to biosimilars
g. To identify the export possibilities of biosimilar products from Bangladesh

3.2 Methodology

This research aims to identify the growth potential of biosimilar products in Bangladesh. Initially growth potential will be defined and then research methodology will be stated step by step.

3.2.1 Growth Potential: As per Business Dictionary (2017) growth potential is the probability that a business will become larger in the upcoming days. The growth potential also refers to amount of sales or revenues the organization generates. Merriam-Webster (2017) defined growth potential as the chance of an industry to become larger. Margaret Rouse (2017) defined growth potential as an organization's future ability to generate larger profits, expand its workforce and increase production. In the business sense, an organization's growth potential depends heavily upon its leadership's expectations for success and the quantitative and qualitative measures used to determine expansion readiness. Therefore, growth potential of biosimilar products in Bangladesh ultimately reveals the future prospects of biosimilar products in Bangladesh pharmaceutical market.

As per Euromonitor (2018) there are eight ways to identify market opportunities for business growth. The ways are:

1. Consumer segmentation
2. Purchase situation analysis
3. Direct competition analysis
4. Indirect competition analysis
5. Analysis of complementary products and services
6. Analysis of other industries
7. Foreign markets analysis

3.2.2 Growth Potential of Biosimilars: Erwin A. Blackstone and P. Fuhr Joseph (2013) reported that physician acceptance is the one of the key driving factors for the growth of biosimilar products. T. Sayandhan et. al (2010) reported that doctors perceive price as the most important element of the marketing mix when pharmaceutical products are being prescribed. Therefore, acceptance by the physicians and price competitiveness are the two major drivers for the growth of the biosimilars.

From our in-depth interviews with the academic and industry experts (13 Managing Directors/CEOs/COOs/Head of Marketing of top pharmaceutical companies who already launched or planning to launch biologics and 12 Professors/Faculty Members of Pharmacy/Biotechnology & Genetic Engineering Department of different public and private universities it was found that biosimilars is involved with high technology; so, competitiveness and perception about the manufacturer are also utmost priority. From the above said interviews we also found that health cost reduction, export possibilities and other drivers of biosimilars in

Bangladesh. Therefore, the researcher has considered the growth potential of biosimilars in Bangladesh by the following ways:

a) Perception of specialists doctors regarding biologics
b) Present market trend of biologics
c) Perception of specialists doctors regarding biosimilars
d) Price concern of the specialist doctors
e) Perception about the competitiveness of local manufacturers
f) Total health cost reduction due to biosimilars
g) Export possibilities

3.2.3 Defining Perception: Perception is a biological and cognitive function (Esperanza, 2001). However, this definition is vague. A clearer definition could be that perception is concerned with the process by which our five senses are organized and interpreted (Solomon & Rabolt, 2004). This definition is supported by other authors. Perception can be defined as the process by which an individual select, organizes and interprets stimuli into a meaningful and coherent picture of the world (Schiffman and Kanuk, 2000) People can form different perceptions of the same stimulus because of 3 perceptual processes: selective attention, selective distortion, and selective retention (Kotler, 2004). Perception is concerned with how individual see and make sense of their environment. Perception also leads to decision making and the decisions to act or not to act depends on how you develop motivation (Kotler, 2003). Perception usually depends on the following factors:

a) Individual factors
b) Country of origin (COO)
c) Sales person Behavior
d) Emotion
e) Price promotion

3.2.4 Research issue-wise data source

Table-9: Research issue-wise data source

Sl	Objective	Data Source
1	To identify the present market trend of biological products in Bangladesh	IMS Health (Bangladesh)
2	To identify the perception of specialists doctors in Bangladesh regarding biologic products	Survey questionnaire for the specialist doctors
3	To identify the perception of specialists doctors in Bangladesh regarding biosimilar product	Survey questionnaire for the specialist doctors
4	To identify the price related views of specialists doctors in Bangladesh	Survey questionnaire for the specialist doctors
5	To identify the perception of specialists doctors in Bangladesh regarding competitiveness of the local manufacturers	Survey questionnaire for the specialist doctors
6	To identify the reduction of total health cost due to biosimilars	Literature review & IMS
7	To identify the export possibility of biosimilar products in Bangladesh	In-depth interview with CEO/Export Manager & Literature review

IMS Health: IMS Health is an American company that provides information, services and technology for the healthcare industry.

3.2.5 Philosophy of the research

A research philosophy is a belief about the way in which data about a phenomenon should be gathered, analyzed and used. The term epistemology (what is known to be true) as opposed to doxology (what is believed to be true) encompasses the various philosophies of research approach. The purpose of science, then, is the process of transforming things believed into things known: doxa to episteme. Two major research philosophies have been identified in the Western tradition of science, namely positivist (sometimes called scientific) and interpretivist (also known as antipositivist) (Galliers, 1991).

Our research philosophy is pragmatism. The following literature study guide us to choose this strategy.

Table-10: Philosophy of different research approach

Philosophy	Research approach	Ontology	Axiology	Research strategy
Positivism	Deductive	Objective	Value-free	Quantitative
Interpretivism	Inductive	Subjective	Biased	Qualitative
Pragmatism	Deductive/Inductive	Objective or subjective	Value free/biased	Qualitative and/or quantitative

Saunders, M., Lewis, P. & Thornhill, A. (2012)

	Pragmatism	Positivism	Realism	Interpretivism
Data Collection	Mixed or multiple, method designs, quantitative and qualitative	Highly structured, large samples, measurement, quantitative, but can use qualitative	Methods chosen must fit the subject matter, quantitative or qualitative	Small samples, in-depth, investigations, qualitative

Collis, J. & Hussey, R. (2014)

3.2.6 Type of Research

This is an applied research because potential of biosimilars will solve the practical problems of accessibility towards high cost biotech products. From the literature it is known that applied research is designed to solve practical problems of the modern world, rather than to acquire knowledge for knowledge's sake. The goal of applied research is to improve the human condition. It focuses on analysis and solving social and real life problems. This research is generally conducted on a large scale basis and is expensive. According to Hunt, "applied research is an investigation for ways of using scientific knowledge to solve practical problems" (Bajpai N, 2011)

This is a descriptive research because it will investigate the market potential of biosimilars in Bangladesh. From the available literature it is found that the objective of descriptive research is to describe the characteristics of various aspects, such as the market potential for a product or the demographics and attitudes of consumers who buy the product. (Kotler & Gary Armstrong, 2011)

This involves the collection of data that will provide an account or description of individuals, groups or situations. This research will use the following instruments to obtain data from the respondents.

- Questionnaires
- Interviews (Denise F. Polit, Cheryl Tatano Beck, 2004)

Both qualitative and quantitative approach has been used in this research because biosimilars are comparatively new issue in Bangladesh with lot of undefined areas.

From the literature it is known that quantitative research is inquiry into an identified problem, based on testing a theory, measured with numbers and analyzed using statistical techniques. The goal of quantitative methods is to determine whether the predictive generalizations of a theory hold true. The researcher will explore some of the issues and challenges associated with quantitative

research in this section. Literature also revealed that a study based upon a qualitative process of inquiry has the goal of understanding a social or human problem from multiple perspectives. Qualitative research is conducted in a natural setting and involves a process of building a complex and holistic picture of the phenomenon of interest. The researcher will explore some of the issues and challenges associated with qualitative research in this section. Look for colleagues who engage in qualitative research to serve as a sounding board for procedures and processes you may use as a new faculty member (CDIP, 2008)

3.2.7 Development of questionnaire

Primary data for the study was obtained via the design and implementation of a questionnaire-based survey. Three sets of self-response questionnaires were made each individually designed with questions targeting Physicians, Industry Experts and Academicians respectively. A brief summary of the above is given below:

Table-11: Source of qualitative data collection

Sl	Target Group	Issues	Type of Questionnaire	Selection Criteria
01	Physicians	Overall perception about biosimilars	07 Points Likert Scale	At least one post-graduation degree in relevant field and have scope to prescribes biologics randomly
02	Academic Experts	Development of Human Resources and Research Facilities	In-depth Interview	Who works on pharmaceutical biotechnology/clinical pharmacology
03	Industry Experts	Future Plan, Market Opportunity and Experience	In-depth Interview	CEO/Head of Marketing of top 20 Companies

* Top 20 companies represents more than 80% of the total market

3.2.8 Type of Sampling:

During the presenting process, it was found that pure probabilistic sampling methods alone could not be employed for this study as it would result in high non-response rates. Therefore, the selection for subjects within the targeted stakeholder groups were carried out utilizing Judgement and Snowball Non-Probability sampling methods. The selection criteria were dependent on the rational judgment of the experts within the sample study who stood as representatives of the targeted stakeholders group. The Snowball Sampling method used is a non-probability selection technique where the selection of additional respondents is based on referrals from the initial respondents. The sub-type of sampling was Stratified Sampling for Doctors (Cardiologists, Diabetologists, Nephrologists, Hepatologists and Oncologists).

From the available literature it is known that Non-probability sampling is a sampling technique in which the researcher selects samples based on the subjective judgment of the researcher rather than random selection. In non-probability sampling, not all members of the population have a chance of participating in the study unlike probability sampling, where each member of the population has a known chance of being selected. Non-probability sampling is used in studies where it is not possible to draw random probability sampling due to time or cost considerations. Non-probability sampling is a less stringent method, this sampling method depends heavily on the expertise of the researchers. Non-probability sampling is carried out by methods of observation and is widely used in qualitative research. (Lund Research, 2012)

The researchers studied that in judgmental sampling, the samples are selected based purely on researcher's knowledge and credibility. In other words, researchers choose only those who he feels are a right fit (with respect to attributes and representation of a population) to participate in research study. This is not a scientific method of sampling and the downside to this sampling technique is

that the results can be influenced by the preconceived notions of a researcher. Thus, there is a high amount of ambiguity involved in this research technique.

Snowball sampling helps researchers find sample when they are difficult to locate. Researchers use this technique when the sample size is small and not easily available. This sampling system works like the referral program. Once the researchers find suitable subjects, they are asked for assistance to seek similar subjects to form a considerably good size sample. (Explorable, 2018)

Qualitative part of this research used judgmental sampling based on eminence on academic or industrial arena of the participants. From the text it is know that the Judgment Sampling is the non-random sampling technique wherein the choice of sample items depends exclusively on the investigator's knowledge and professional judgment. In other words, the investigator chooses only those sample items which he feels to be the best representative of the population with regard to the attributes or characteristics under investigation. The judgment sampling is not a scientific method as the sample items are selected on a judgment basis and hence the results could be affected by the personal prejudice or bias of the investigator. (Business Jargon, 2018)

3.2.9 Sampling Frame:

Table-12: Sampling Frame

Sl #	Specialists	Target Biosimilar
1	Orthopedists	Adalimumab, Rituximab, Etanercept
2	Diabetologists	Insulin
3	Oncologists	MABs (Monoclonal antibodies), Filgrastim
4	Cardiologist	Streptokinase
5	Nephrologists	Erythropoietin
6	Hepatologists	Interferon

3.2.10 Survey Period: The researcher conducted the qualitative survey between January and March'2018 and the quantitative survey was carried out during June to October 2018.

3.2.11 Survey Place: The survey was conducted in big cities like Dhaka, Chattogram, Khulna, Sylhet, Barishal, Rajshahi, Rangpur, Mymensingh as old and big government medical colleges are located in the above places. All the diseases treated with biologics are very critical and the specialist doctors of government medical colleges play the key role in this type of treatment.

3.2.12 Sample Size: The sample size for quantitative portion of the research has been calculated based on population size, confidence interval and margin of error by using Daniel's Equation.

$$n = \frac{Z^2 P (1-P)}{d^2}$$

Where n = sample size

Z = Z statistic for a level of confidence

P = Expected prevalence or proportion

d = precision

The detail sample size is given below:

Table-13: Sample & Population Size

Sl	Specialists	Population Size*	Sample Size
1	Cardiologist	600	145
2	Diabetologists	300	45
3	Nephrologists	300	45
4	Oncologists	100	25
5	Hepatologists	100	25
6	Orthopedists	300	45
Total		**1700**	**330**

* As per the information of respective society. Confidence Interval: 95% & Margin of Error: 5%

For qualitative portion of our research sample has been selected based on the academic and professional expertise of the respondent and it was judgmental sampling. The researcher has interviewed 13 Managing Directors/CEOs/COOs/Head of Marketing of top pharmaceutical

companies who already launched or planning to launch biologics and 12 Professors/Faculty Members of Pharmacy/Biotechnology & Genetic Engineering Department of different public and private universities with an open ended questionnaire (In-depth interview).

3.2.13 Industry Experts

Table-14: List of industry experts

Sl	Name	Designation	Organization
1	Mr. Abdul Muktadir	Managing Director	Incepta Pharmaceuticals Ltd.
2	Mr. Mosaddek Hossain	Managing Director	UniMed UniHealth Pharma
3	Dr. Abdul Momen	Managing Director	General Pharmaceuticals Ltd.
4	Mr. M Halimuzzaman	CEO & Board Member	Healthcare Pharmaceuticals Ltd.
5	Dr. Md. Mustafizur Rahman	Director General	Directorate General of Drug Administration
6	Mr. Iftekhar Ahmed	Ex. Managing Director	Sanofi Bangladesh
7	Mr. Anand Shetty	Managing Director	Novo Nordisk, Bangladesh
8	Dr. Riad Mamun Prodhani	Managing Director	Novartis Bangladesh Ltd.
9	Mr. Muhibuz Zaman	Chief Operating Officer	ACI Pharma Limited
10	Mr. Arshadul Alam	Ex. Executive Director, Marketing	The Acme Laboratories Ltd.
11	Mr. Ahmed Kamrul Alam	General Manager, Marketing	Square Pharmaceuticals Ltd.
12	Mr. Anwarul Hoque	Ex. Director Marketing	Beacon Pharmaceuticals Ltd.
13	Mr. Istiak Ahmed*	Technical Advisor	Aristopharma Limited

(*participated in the discussion and shared his views while interviewing CEO, Healthcare Pharmaceuticals Ltd. since he was present at that moment)

3.2.14 Academic Experts

Table-15: List of academic experts

Sl	Name	Designation	Department & University
1	Dr. Munir Uddin Ahmed	Professor	Pharmacy Department, University of Dhaka
2	Dr. Sharif Akhteruzzaman	Professor	Genetic Engineering & Biotechnology Department, University of Dhaka
3	Dr. Zeba Islam Seraj	Professor	Department of Biochemistry & Molecular Biology, University of Dhaka
4	Dr. Selim Reza	Professor	Pharmacy Department, University of Dhaka
5	Dr. Sukalyan Kumar Kundu	Professor	Pharmacy Department, Jahangirnagar University
6	Dr. Md. Abu Reza	Professor	Genetic Engineering and Biotechnology, Rajshahi University
7	Dr. Mustafizur Rahman	Professor	Pharmacy Department, Khulna University
8	Dr. S. M. Abu Sayem	Professor	Genetic Engineering and Biotechnology, Shahjalal University of Science & Technology
9	Dr. Eva Rahman Kabir	Professor & Head	Pharmacy Department, BRAC University
10	Dr. Hasan Mahmud Reza	Professor & Ex. Chairman	Pharmaceutical Sciences Department, North South University
11	Dr. Sohidul Islam	Associate Professor & Chairman	Biochemistry & Microbiology Department, North South University
12	Mr. Mahbub Hossain	Faculty Member	Biotechnology & Genetic Engineering Department, University of Chittagong

From literature it is known that sample is the part of the population that helps us to draw inferences about the population. Collecting research of the complete information about the population is not possible and it is time consuming and expensive. Thus, an appropriate sample size is needed so that the researcher can make inferences about the population based on that sample. (Thasaurus, 2018)

3.2.15 Data Collection:

Data collection is the process of gathering and measuring information on variables of interest, in an established systematic fashion that enables one to answer stated research questions, test hypotheses, and evaluate outcomes. The data collection component of research is common to all fields of study including physical and social sciences, humanities, business, etc. While methods vary by discipline, the emphasis on ensuring accurate and honest collection remains the same. (Knatterud, 2008)

The researcher used both primary and secondary data for our research. For primary data the researcher has used two questionnaires. One questionnaire was prepared for getting responses from the doctors and another one from the industry or academic experts. The questionnaire for doctors was quantitative and used Likert Scale method whereas questionnaire for industry and academic experts was qualitative and used in-depth interview method.

From the literature it is known that in social science research, the terms primary data and secondary data are common parlance. Primary data is collected by a researcher or team of researchers for the specific purpose or analysis under consideration. Here, a research team conceives of and develops a research project, collects data designed to address specific questions, and performs their own analyses of the data they collected. In this case, the people involved in the data analysis are familiar with the research design and data collection process.

Secondary data analysis, on the other hand, is the use of data that was collected by someone else for some other purpose. In this case, the researcher poses questions that are addressed through the analysis of a data set that they were not involved in collecting. The data was not collected to answer the researcher's specific research questions and was instead collected for another purpose. So, the same data set can actually be a primary data set to one researcher and a secondary data set to a different one. (Ashley Crossman, 2018)

Questionnaire refers to a research instrument, in which a series of question, is typed or printed along with the choice of answers, expected to be marked by the respondents, used for survey or statistical study. It consists of formalized set of questions, in a definite order on a form, which are mailed to the respondents or manually delivered to them for answers. The respondents are supposed to read, comprehend and give their responses, in the space provided. (Surbhi S, 2016)

Secondary source

Secondary data refers to data that was collected by someone other than the user. Common sources of secondary data for social science include censuses, information collected by government departments, organizational records and data that was originally collected for other research purposes. Primary data, by contrast, are collected by the investigator conducting the research. (Schutt, 2006)

For primary data a questioner was developed with proper customization. The questionnaire was distributed among selected samples to get necessary answers. The feedback of the questionnaire was used as primary data. Apart from the above interviews with concerns & IMS data will be used. For qualitative part type of data collection method was In-depth interview.

3.2.16 Pre-Testing: In order to assess the clarity of the questionnaire, suitability to the participants, assess the needed time and possible obstacle the researcher conducted a pretesting with 20 samples. Some terminology was modified based on the suggestions of the respondents. The researcher also analyzed the comments of outliers. As per outliers Bangladesh have scarcity of manpower to handle biologics. In order to verify that the researcher again talked to university graduates and some renowned professors. As per their observation Bangladesh have trainable graduates and well recognized researchers who are working home and abroad; therefore, if any company comp up with any proposal then they can handle it.

3.2.17 Method of Analysis: This research used one sample t-test for comparing the means. The one sample t-test is a statistical procedure used to determine whether a sample of observations could have been generated by a process with a specific mean.

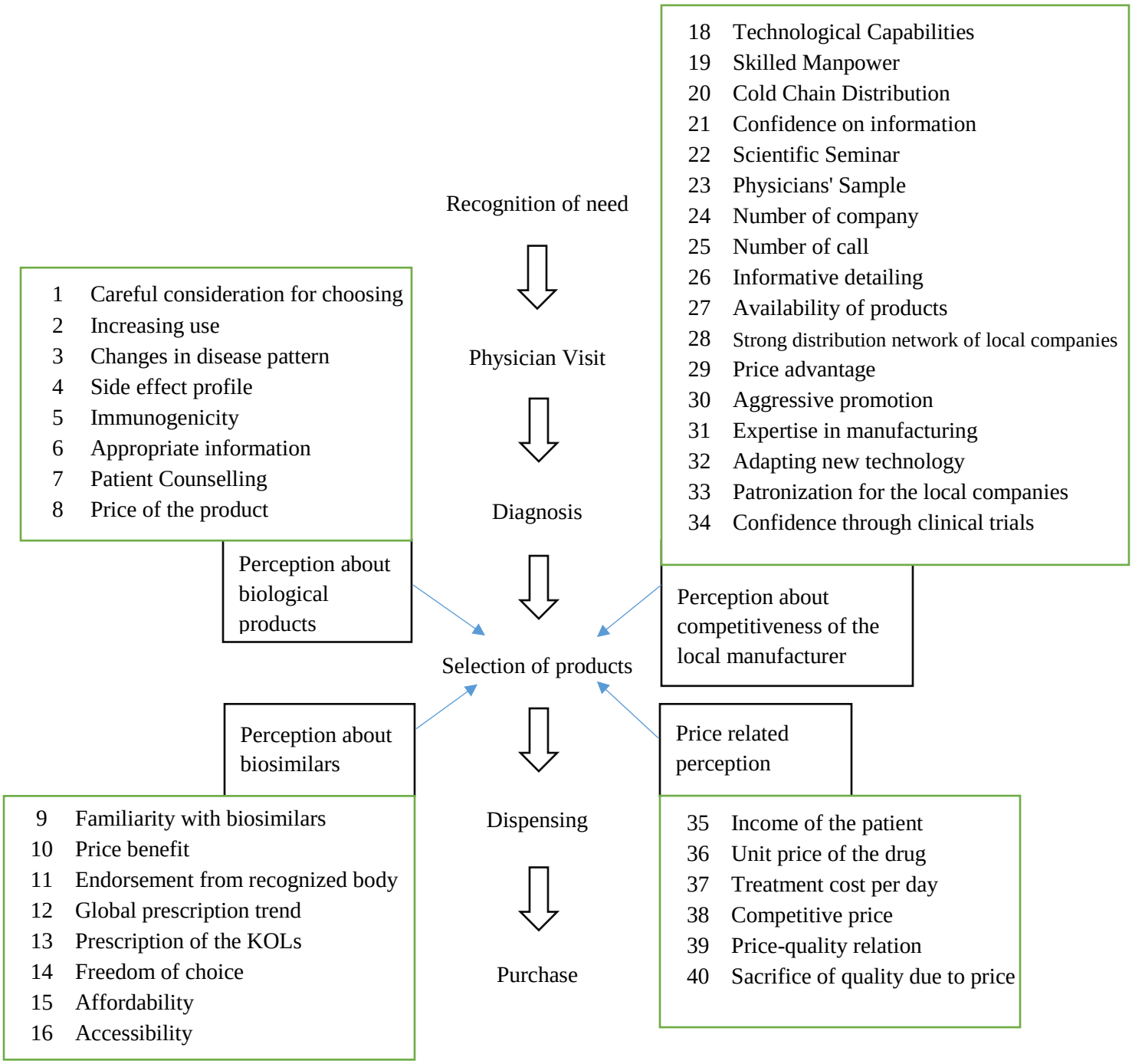
Factor analysis were applied to determine the most contributing components. Factor analysis is a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. For example, it is possible that variations in six observed variables mainly reflect the variations in two unobserved (underlying) variables.

In case of other calculation and analysis the researcher has used Xcel software.

3.2.18 Ethical Issues

The privacy and confidentiality of the participants was strictly maintained during data collection, and participants were not forced to respond any questions.

4.1 Conceptual Framework



4.2 Hypotheses

Ho: More careful consideration is not required to choose biological products than that of chemical products

H1: More careful consideration is required to choose biological products than that of chemical products

Ho: Use of biological products is not increasing day by day
H1: Use of biological products is increasing day by day

Ho: Changes in disease pattern is not leading to increase use of biological products
H1: Changes in disease pattern is leading to increase use of biological products

Ho: Biological products does not offer less side effect compared to chemical products
H1: Biological products offer less side effect compared to chemical products

Ho: Unwanted immunogenicity is not being considered while choosing biological products for the patients
H1: Unwanted immunogenicity is being considered while choosing biological products for the patients

Ho: Appropriate information is not crucial for prescribing biological products
H1: Appropriate information is crucial for prescribing biological products

Ho: In case of biological products less patient counseling is required compared to chemical drugs
Ho: In case of biological products more patient counseling is required compared to chemical drugs

Ho: Biological products are not avoided by some doctors due to high price
H1: Biological products are avoided by some doctors considering high price

Ho: Biosimilar products are known by many Bangladeshi doctors
H1: Biosimilar products are not known by many Bangladeshi doctors

Ho: Doctors will not prescribe price competitive biosimilar products
H1: Doctors will prescribe price competitive biosimilar products

Ho: Endorsement from recognized bodies like WHO, USFDA etc. does not give confidence to choose certain products

H1: Endorsement from recognized bodies like WHO, USFDA etc. give confidence to choose certain products

Ho: Doctors do not follow global prescription trend while choosing products for patients

H1: Doctors follow global prescription trend while choosing products for patients

Ho: Doctors do not follow the prescription trend of local Key Opinion Leaders (KOLs) while choosing products for patients

H1: Doctors does follow the prescription trend of local Key Opinion Leaders (KOLs) while choosing products for patients

Ho: Doctors do not look for freedom of choice while choosing products for my patients

H1: Doctors look for freedom of choice while choosing products for my patients

Ho: Many patients are getting access to high cost branded biologics

H1: Many patients are not getting access to high cost branded biologics

Ho: Due to unavailability of biosimilars many patients are getting access to biological drugs

H1: Due to unavailability of biosimilars many patients are not getting access to biological drugs

Ho: Considering positive increment in socioeconomic condition biosimilars have no scope to grow in Bangladesh

H1: Considering positive increment in socioeconomic condition biosimilars have scope to grow in Bangladesh

Ho: I don’t believe that local companies are capable enough to manufacture biological products

H1: I believe that local companies are capable enough to manufacture biological products

Ho: I don’t believe that local manpower is capable enough to handle the manufacturing of biological products

Ho: I believe that local manpower is capable enough to handle the manufacturing of biological products

Ho: Top local pharma companies don't have the capabilities to maintain cold chain for distributing their products

H1: Top local pharma companies have the capabilities to maintain cold chain for distributing their products

Ho: I don't have confidence on the information provided by top local pharma companies
H1: I have confidence on the information provided by top local pharma companies

Ho: Scientific Seminar doesn't influence me to choose certain products
H1: Scientific Seminar influence me to choose certain products

Ho: I prefer Physicians' sample as a promotional tool for biological products
H1: I don't prefer Physicians' sample as a promotional tool for biological products

Ho: There is no positive relation between numbers of companies offer any product and escalation possibilities
H1: There is positive relation between numbers of companies offer any product and escalation possibilities

Ho: More number of sales call does not remind me to prescribe certain product
H1: More number of sales call remind me to prescribe certain product

Ho: I don't like informative detailing by the Medical Representative
H1: I like informative detailing by the Medical Representative

Ho: I don't consider availability of biological product while choosing it for my patients
H1: I consider availability of biological product while choosing it for my patients

Ho: I think local companies' products are not more available than multinationals operate in Bangladesh

H1: I think local companies' products are not more available than multinationals operate in Bangladesh

Ho: I think local manufacturer do not offer price advantage over multinationals operates in Bangladesh

H1: I think local manufacturer offer price advantage over multinationals operates in Bangladesh

Ho: I think local manufacturers are not more aggressive in product promotion compared to multinationals operates in Bangladesh

H1: I think local manufacturers are more aggressive in product promotion compared to multinationals operates in Bangladesh

Ho: I think our pharmaceutical companies don't have experts to manufacture biosimilar products
H1: I think our pharmaceutical companies have experts to manufacture biosimilar products

Ho: I think our companies are not accommodating new technology as per my need
H1: I think our companies are accommodating new technology as per my need

Ho: I don't patronize local manufacturer to grow by choosing their products
H1: I patronize local manufacturer to grow by choosing their products

Ho: Clinical trials on certain products do not give me confidence to choose for my patients
H1: Clinical trials on certain products give me confidence to choose for my patients

Ho: I don't consider income of the patient while choosing biological products
H1: I consider income of the patient while choosing biological products

Ho: I don't consider unit price while choosing biological products for my patients
H1: I consider unit price while choosing biological products for my patients

Ho: I don't consider cost per day while choosing biological products
H1: I consider cost per day while choosing biological products

Ho: I don't look for price competitive products for my patients
H1: I look for price competitive products for my patients

Ho: Low price indicates substandard products
H1: Low price does not indicate substandard products

Ho: I shall not sacrifice the quality up to a tolerable limit considering the affordability of the patient
H1: I shall sacrifice the quality up to a tolerable limit considering the affordability of the patient

5.1.1 Location-Wise Distribution of Respondent

Although a sample size of 330 was determined; however, it was possible to collect feedback from 217 respondents. Highest 103 respondents were from Dhaka followed by 25 from Chattogram and Rangpur each. The following table shows the location-wise distribution of respondents.

Table-16: Geographical distribution of the survey respondents

Sl #	Division	Number of Respondent	In %
1	Dhaka	103	47.5
2	Chattogram	25	11.5
3	Rangpur	25	11.5
4	Khulna	15	6.9
5	Sylhet	14	6.5
6	Rajshahi	13	6.0
7	Barishal	12	5.5
8	Mymensingh	10	4.6
Total		**217**	**100**

5.1.2 Specialty-Wise Distribution of Respondents

Among 217 respondents highest 27.5% was Cardiologists followed by 23% Diabetologists. Orthopedists and Nephrologists are almost similar in number with a figure of 40 each group. The other figures represent who have limited scope to prescribe biologics but due to present duty station they prescribe biologics like Gynecologists prescribe insulin for gestational diabetes.

Table-17: Specialty-wise distribution of the survey respondents

Sl #	Area of Specialty	Number of Respondent	In %
1	Cardiology	60	27.6
2	Diabetology	50	23.0
3	Orthopedic	40	18.4
4	Nephrology	40	18.4
5	Oncology	15	6.9
6	Hepatology	10	4.6
7	Others	2	0.9
Total		**217**	**100**

5.1.3 Demographic Distribution of the Respondents:

59.6% of the respondents were male and 40.6% were female. The following table shows the quantity and % of male and female respondents.

Table-18: Number of Male and Female respondent

Sl #	Sex	Number of Respondent	In %
1	Male	129	59.4
2	Female	88	40.6
Total		**217**	**100**

5.2.1 Market trend of biological products in Bangladesh

The biological product market of Bangladesh is mostly dominated by insulin with 90% of the total market (biologic) of $ 125 mln. The average annual growth of this market is 25%-30% whereas the regular pharmaceutical products (other than biologics) are growing at the rate of 10%-15% annually. Among all biologics insulins, erythropoietin/darbepoetin, monoclonal antibodies (trastuzumab, rituximab, tocilizumab, bevacizumab, adalimumab), pegfilgastim are growing fast. Although interferons and streptokinase are available from long-time; however, their growth is almost flat. Among MABs trastuzumab, rituximab and adalimumab are highly potential. Still now adalimumab is not healthy enough in size due to high price but growth is significant. The following graph shows individual biologic-wise market and growth in different years.

Table-19: Biologic-wise market size and total growth % in different years in Bangladesh

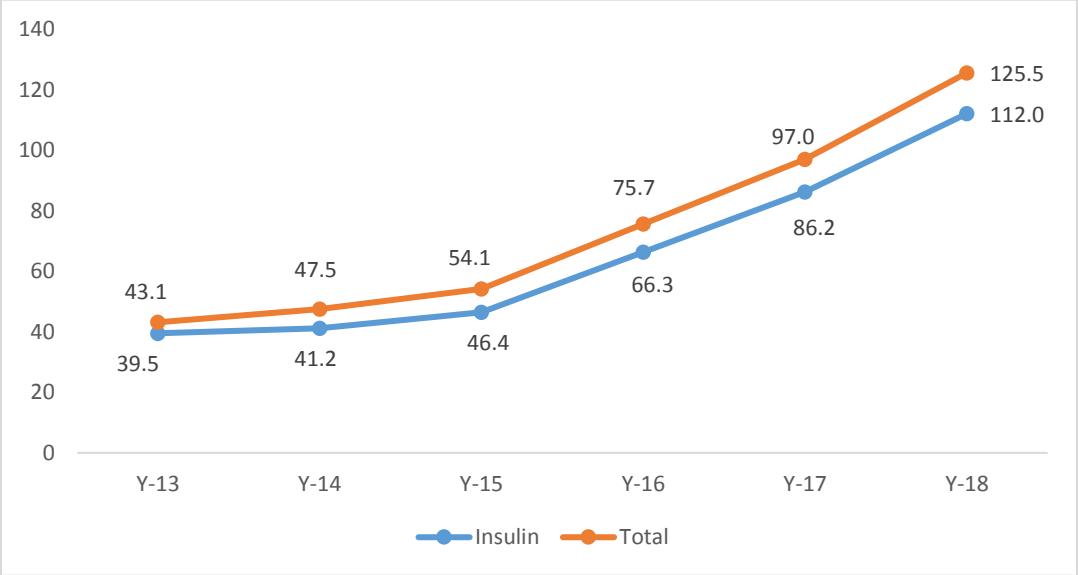
Sl	Biologic	Y-13	Y-14	Y-15	Y-16	Y-17	Y-18
1	Insulin	39.5	41.2	46.4	66.3	86.2	112
2	Interferon	1.83	2.81	3.33	3.85	4	4.3
3	MABs*	1.62	2.82	3.33	3.95	4.8	5.9
4	Erythropoietin/Darbepoetin	0.02	0.37	0.86	1.17	1.5	2.3
5	Filgrastim/Pegfilgastim	0.08	0.09	0.1	0.17	0.2	0.2
6	Streptokinase	0.07	0.14	0.08	0.15	0.2	0.3
7	Others	0.01	0.04	0.04	0.08	0.1	0.3
Total		**43.1**	**47.5**	**54.1**	**75.7**	**97**	**125.4**
Growth %			**10.1**	**14.1**	**39.8**	**28.2**	**29.3**

Figures are in mln $, MABs: Monoclonal Antibodies (Trastuzumab, Rituximab, Denosumab, Tocilizumab, Bevacizumab, Adalimumab)

Source: IMS, 2Q, 2013-2018 & Internal Source

Considering the changes in disease pattern found in the literature review Monoclonal Antibodies (Trastuzumab, Rituximab, Tocilizumab, Bevacizumab, Adalimumab) have huge potentiality to grow; however, due to high price limited number of patients are getting access to these treatments. Due to dysentery lifestyle diabetes is almost common in every family and this prevalence is increasing day by day. Earlier only one company was offering insulin at a high price and there were limited access but after 2014, five local companies offered insulin to the market at a competitive price which give a boost to the biological product market. It is worth mentioning that except Novo Nordisk and Eli Lily insulin all others are NCBs (Non Comparable Biologics). The following graph shows that market of biologics is largely depends on insulin.

Figure-14: Total Biologic market and Insulin market in different years (figures are in mln $)



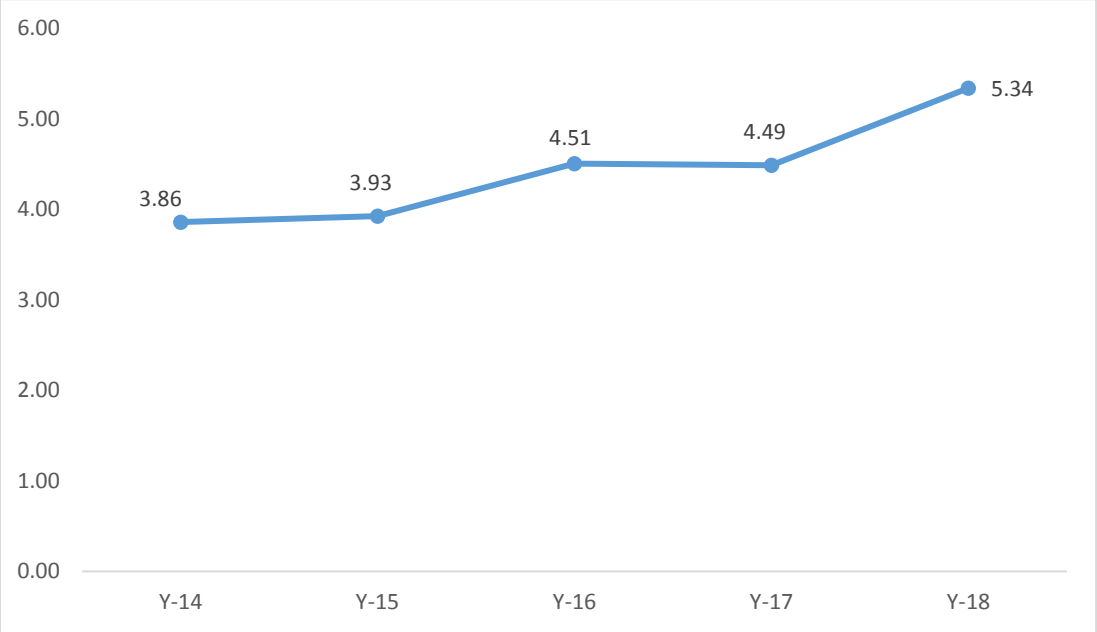
Source: IMS, 2Q, 2013-2018 & Internal Source

In Bangladesh only eight local companies are offering biologics to the market and all of the biologics are Non Comparable Biologics (NCBs). Two companies claimed their Erythropoietin as biosimilars based on import source declaration; however, they have no local clinical study so far. Incepta Pharmaceuticals Ltd. offers highest number of biologics and their revenue is also highest among the rivalry. Beacon Pharmaceuticals Ltd. have created a good company image with interferons and MABs. Healthcare is trying to create a market for darbepoetin. Novo Nordisk is enjoying the lion share of insulin market with more than 60% of the total Insulin market. Insulin offered by Eli Lily is the true biosimilar. Some companies like General Pharmaceuticals Ltd., Orion Pharmaceuticals Limited, Ziska Pharmaceuticals Limited, Opsonin Pharmaceuticals Ltd. are planning to offer biologic products in the market. Globe Pharmaceuticals Ltd. is the only local company who are going to offer biosimilars dedicatedly for the first time in Bangladesh.

In 2012 biological products contributed almost 1% of the entire market whereas in 2016 this part becomes more than doubled (4.5%). Also, biological products grew 10% higher than the regular chemical drug market in last year (2017).

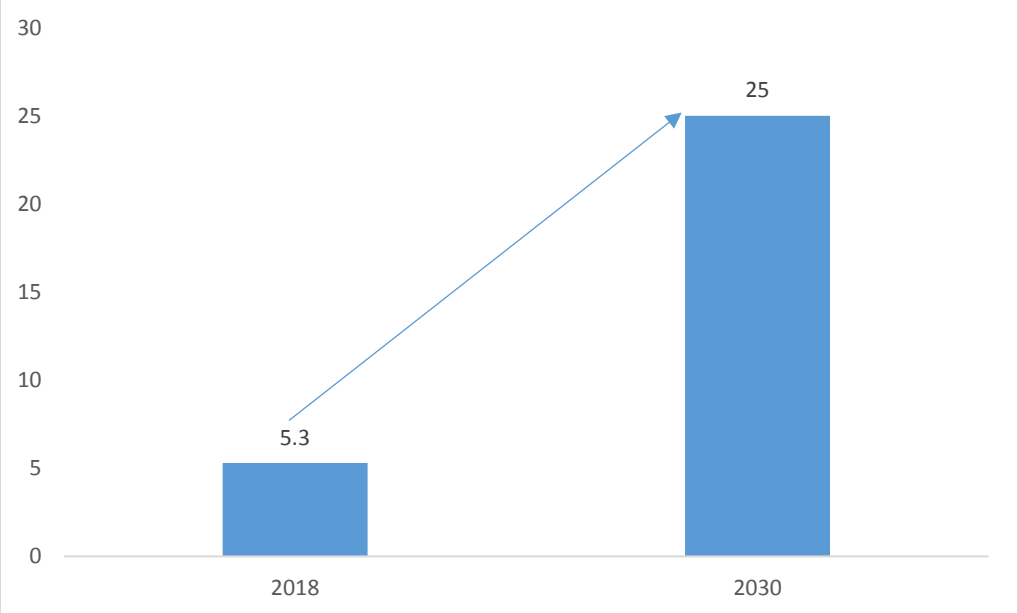
The following graph shows the increasing share of biologics among total pharmaceutical market. In last 05 years the share has grown by more than 2% with a current figure of 5.3%. If this trend continues then in 2030 this share % will be around 20% to 25% which match with the current global status.

Figure-15: Share % of biologics among total market in different years



Source: IMS, 2Q, 2014-2018 and Internal Source

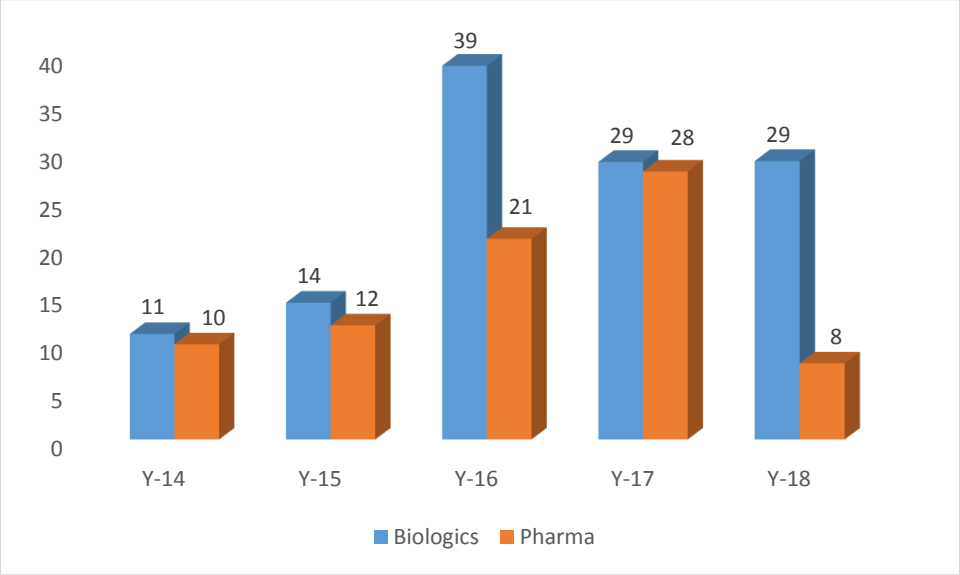
Figure-16: Change in share % of Biologics among total pharma market (2018 vs 2030)



Source: IMS, 2Q, 2018 and Internal Source

In the recent past the growth % of biological products was higher than that of conventional pharma products. In 2018 the conventional pharmaceuticals market grew at 8% whereas the growth of biologics was a 29%. The following graph shows the growth % biologics and pharma products in different years.

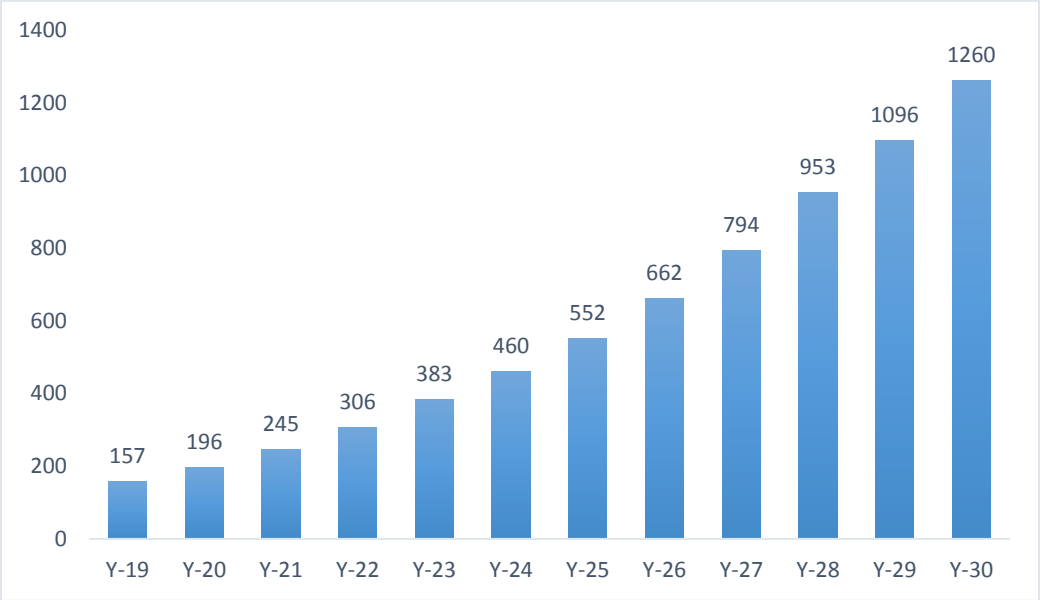
Figure-17: Growth % of conventional pharmaceutical market and biologics market



Source: IMS, 2Q, 2014-2018

Considering the present global and local growth trend in 2030 the biological products market in Bangladesh will be around $1260 mln (1st five years: 25%, 2nd five years: 20% and 3rd five years: 15%).

Figure-18: 12 years' sales projection of biological products (mln $)



Source: Analysis of the researcher based on previous growth trend

Among the different specialist categories Diabetologists prescribe highest numbers of biologic products followed by Cardiologists. Nephrologists are now prescribing biological products considering the patients' economic status. Interferons are prescribed by very few Hepatologists chiefly located at Dhaka and Chittagong. Oncologists are also prescribing different MABs as targeted therapies. Nevertheless, Orthopedists rarely prescribes biological products as their preferable options like (Adalimumab) are involved with high cost.

The above figures and statement clearly demonstrates that biologic products have huge potentiality to grow in the upcoming days and if biosimilars are offered in this market then it will certainly get a boost.

5.2.2 Perception about biologics by the specialist doctors in Bangladesh

A biologic is manufactured in a living arrangement such as a microorganism or plant or animal cells. Most biologics are very large, complex molecules. Many biologics are produced by using recombinant DNA technology.

A chemical drug is characteristically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process.

Drugs generally have well-defined chemical structures and a finished drug can usually be analyzed to determine all its various components.

By contrast it is difficult and sometimes impossible, to characterize a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown.

Therefore, while selecting any biologic for the patient doctor become more aware about its appropriate information, side effect, unwanted immunogenicity etc.

Research finding suggests that doctors are more concern about appropriate information for choosing biological products. They perceive biologicals as lifesaving precarious care option; so, a holistic information approach is important for them. Doctors are also endorsing that use of biological products are increasing day by day. Increased promotional approach due to local manufacturer is one of the important drivers of this growth. Also they supported that patient counselling is an important part of treatment protocol and compared to chemical drugs more patient counselling is required for biological products. Therefore, prescribing biological products involved with more time. Specialist doctors also recommends that changes in disease pattern is leading to increased use of biological products. Increased prevalence of Diabetes, Cancer,

Rheumatoid Arthritis, Cardiovascular Diseases, Hepatitis, Chronic Kidney Diseases (CKD) is triggering the potential of biosimilars in Bangladesh.

Nevertheless, in most cases treatment with biologics is lifelong option which involved with huge cost and till to date biological are costly; so, many patients are not getting access to costly biologics. Doctors also believe that many patients are not in a socio-economic condition to accept treatment with biologics.

Doctors are also concern about the unwanted immunogenicity (ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human and other animal. In other words, immunogenicity is the ability to induce a humoral and/or cell-mediated immune responses) and side effects of the biological treatment options.

In comparison with small molecule drugs, protein pharmaceuticals are complex entities; and since they are usually expressed in cellular systems, they are exposed to factors which could influence PTMs (Posttranslational modifications). The PTM profile is dependent on several factors including the type and differentiation status of the host cell, upstream and downstream manufacturing process, formulation, and storage conditions and micro heterogeneities formed during fermentation and downstream processing.

Table-20: Measurement of the perception about biologics by the specialist doctors in Bangladesh

Sl #	Variables	N	Mean	Std. Deviation	Std. Err. Mean
1	Appropriate information	217	6.06	1.17	0.08
2	Increasing use of biologics	217	6.01	1.13	0.08
3	More patient counselling	217	5.8	1.33	0.09
4	More careful consideration	217	5.79	1.2	0.08
5	Changes in disease pattern	217	5.69	1.4	0.1
6	Price barrier	217	5.61	1.41	0.1
7	Unwanted immunogenicity	217	5.49	1.53	0.1
8	Less side effect	217	5.46	1.44	0.1

The above findings suggest that disease patterns are changing day by day and use of biologics are increasing sharply. Due to less side effects many doctors are showing interest on biologics; however, price is a concern here. Therefore, if biosimilars are offered at a competitive price in this rising market then escalation possibilities will go up.

5.2.3 Perception of specialists doctors in Bangladesh regarding biosimilar product

The concept of biosimilars is still in early stage in Bangladesh. Except Globe Pharmaceuticals (to be operated soon) none of the companies are claiming themselves as Biosimilar Company.

In many cases the Specialist Doctors of Bangladesh are not clearly known about the difference between biosimilars and Non-Comparable Biologics (NCBs). In most cases they treated the local company's biologics as generic version of the original biotech products. However, Non-Comparable Biologics (NCBs) are not proven clinically in local subjects. Some of them have small scale local trial organized by individual or institutional level which is not worthy enough to claim the appropriate safety and purity.

In regulated market Non-Comparable Biologics (NCBs) are not approved by the respective drug regulatory authorities. So, the entire market is captured by either innovators brands or biosimilars.

However, after necessary reading many doctors become impressed about biosimilars and showed their very positive attitude.

As per research findings biosimilars have ampoule scope to grow in Bangladesh. If biosimilar companies promote the quality concerns, then Non-Comparable Biologics (NCBs) may face crisis in building quality perception.

Right at this moment many doctors believe that they have some patients who are taking innovator's brand considering quality perception although they have financial troubles, these patient will easily accept biosimilars if proper counselling is done.

If more number of companies offers biosimilars then price will be very competitive and hopefully near to NCBs which will add extra value to the customers. Also, freedom of choice for prescription will give additional scope to prescribe certain products.

Globally biosimilars are hot cake and global Key Opinion Leaders (KOLs) are choosing biosimilars for their patients. They are using biosimilars in lieu of innovator brand considering 60% price reduction. Many Bangladeshi specialist doctors especially big practitioners are frequently visiting the above scholars in different seminars, symposium and conferences. This meeting influences the Bangladeshi specialist to prescribe available biosimilars. It is one sort of confidence they are getting from the global leaders. There are lot of specialists who have limited scope to visit global KOLs and they follow the prescription pattern of the local KOLs. Since local leaders are keeping confidence; so, their fellow colleagues are also feeling confident to prescribe biosimilars.

The above finding express that confidence towards biosimilars is growing fast and KOLs are motivating the followers. If price is competitive, then accessibility will go up which will give lead in the market growth. Also, freedom of choice due to more number of brands will facilitate the entire market in a holistic manner.

Table-21: Measurement of the perception of specialists doctors in Bangladesh regarding biosimilar product

Sl #	Variables	N	Mean	Std. Deviation	Std. Error Mean
1	Scope for biosimilars to grow	217	6.16	0.97	0.07
2	Inaccessibility to costly biologics	217	6.07	1.14	0.08
3	Confidence towards biosimilars	217	5.94	1.16	0.08
4	Price competitiveness of biosimilars	217	5.93	1.09	0.07
5	Freedom of choice	217	5.87	1.21	0.08
6	Accessibility towards biosimilars	217	5.84	1.2	0.08
7	Global trend	217	5.79	1.24	0.08
8	Influence of KOLs	217	5.28	1.61	0.11
9	Familiarity with biosimilars	217	3.2	1.24	0.08

5.2.4 Perception about competitiveness (technical and marketing) of the local companies

Clinical trial is one of the main weapons to give confidence towards certain products specially biologics. This research finding suggest that for biosimilar marketing clinical trial is number one component. Every biosimilar must have clinical trial but Non-Comparable Biologics (NCBs) have very limited or no clinical study. So, if any local company introduces biosimilars in a competitive price then it will easily challenge the NCBs.

Availability of products is another important concern. Biologics products need to maintain cold-chain from production to dispensing. Therefore, unlike other products making availability of biosimilars in every chemist shop is not possible. Usually they are available in big chemist shops with refrigerator facility. Research findings includes that local company's' products are more available than that of multinational companies operate in Bangladesh as local companies are operated with larger number of field force. If any local company offer biosimilar then it will be an added benefit that the products will be available readily.

From the available literature it is known that considering cheap labor and utility cost local company can offer price benefits. Our research findings also demonstrate that doctors perceived in the same way. They believe that if local company offer biosimilars then it will be cost effective for the patients.

In product promotion local companies are more aggressive than that of MNCs. Their doctor as well as chemist coverage is far higher than MNCs. Due to more number of field force their share of voice is high.

Scientific seminar is another very important marketing tool for biologics. From earlier case it is found that appropriate information is highly expected for biosimilar prescription. Scientific seminar is a both way communication approach to share that information.

This research also finds that physicians like informative detailing by the Medical Representative. Again the point holistic information requirement becomes affiliated with this finding. Therefore, for biosimilar product marketing highly qualified and trained personnel is utmost priority.

Specialist doctors would like to patronize the local manufacturer due to patriotism, also one thing is mentionable that the local companies already proved them through their high quality chemical products in both domestic and global market.

Physicians also believe that local pharmaceutical companies are adapting new technology very quickly. They are using so many current technologies in different dosage forms.

Cold-chain is highly important issue for the distribution of biologics and some local companies like Incepta and Renata are maintaining it. The practicing physicians supports that local companies are capable enough to maintain cold-chain system from manufacturing to dispensing.

Our doctors also endorse that local manufacturer have enough capable manpower and facility to handle biosimilars manufacturing and they have confidence on the information shared by them.

If more number of local companies offer biosimilars then more number of people will promote that same many times and our doctors slightly believe that more number of sales call remind and influence them to choose certain products.

Physicians' sample is one of the oldest tool for promoting pharmaceuticals; however, research finding suggests that doctors don't prefer Physician sample as the tool of promotion.

Table-22: Measurement of the perception about competitiveness (technical and marketing) of the local companies

Sl	Variables	N	Mean	Std. Deviation	Std. Error Mean
1	Confidence due to clinical trials	217	6.01	1.01	0.07
2	Availability of biologics	217	5.94	1.11	0.08
3	Local company products are more available	217	5.9	1.17	0.08
4	Price advantage of local companies	217	5.88	1.15	0.08
5	Aggressiveness of the local companies	217	5.86	1.27	0.09
6	Influence of scientific seminar	217	5.79	1.05	0.07
7	Preference for informative detailing by the doctor	217	5.76	1.32	0.09
8	Patronization for the local companies	217	5.74	1.19	0.08
9	Adaptation of new technology	217	5.66	1.2	0.08
10	Capabilities of maintaining cold chain	217	5.66	1.09	0.07
11	Availability of expert manpower	217	5.59	1.25	0.08
12	Confidence on information offered by local companies	217	5.55	1.15	0.08
13	Capabilities of manufacturing	217	5.39	1.41	0.1
14	Capabilities of operational handling	217	5.31	1.37	0.09
15	More number of companies	217	5.18	1.55	0.1
16	Influence of more number of sales call	217	4.68	1.78	0.12
17	Preference of physicians' samples	217	3.78	1.71	0.12

From the findings it is clear that our doctors believe that top local companies are capable enough to handle biosimilars manufacturing and marketing. Therefore, they have confidence on local manufacturers which is very positive for the growth of local company's' biosimilars.

5.3.5 Price related perception on biosimilars

The research finding demonstrate that income of the patient is the number one component for price related perception regarding biosimilars. Due to high price and lifelong treatment requirement doctors are very aware about the income.

Just after income of the patient doctor think treatment cost per day while choosing medication for his/her patients. Unit price per day also influence in the decision making process of the doctors.

Nevertheless, doctors look for price competitive products for their patient if quality is out of question.

Our doctors do not believe that low price products are substandard products. They also don't agree to sacrifice the quality considering price.

The above findings support that while launching biosimilars price should be considered very carefully. Both high and low price will be great challenge as patient income and perception of the doctors both are equally important.

Table-23: Measurement of the price related perception on biosimilars

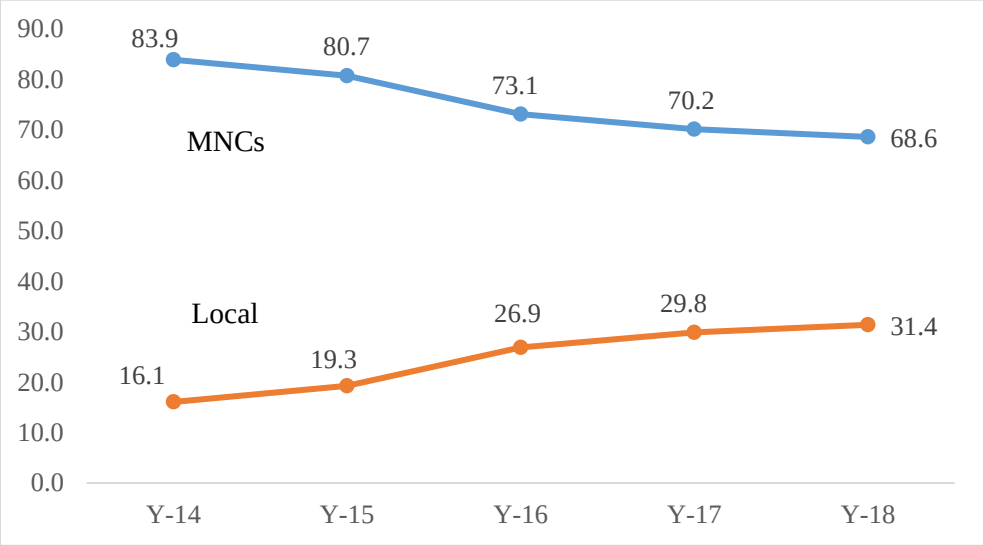
Sl	Variables	N	Mean	Std. Deviation	Std. Error Mean
1	Income of the patients	217	6.11	1.16	0.08
2	Treatment cost/day	217	6.04	1.1	0.07
3	Unit Price/day	217	6.01	1.11	0.08
4	Looking for price competitiveness	217	5.91	1.14	0.08
5	Low price indicates substandard products	217	3.56	1.59	0.11
6	Price commensurate quality	217	3.23	1.85	0.13

5.3.6 Reduction of total health cost due to biosimilars

Eva Kabir et al. (2018) reports that one of the advantages of biosimilars is its ability of potentially lowering healthcare costs (voiced by 83% of Industry Experts, 80% of Academicians and 67% of Clinicians). It also comforts to treat the same indications as those remedied by the reference biologic (voiced by 44% of Industry Experts, 44% of Clinicians and 35% of Academicians).

As per IMS (2014-2018) analysis it was identified that introduction of insulins by the local companies gradually decreasing the market share of MNCs (Multinational Companies) who were dominating the global insulin market earlier. In 2014 MNCs were enjoying the almost 84% and local companies were enjoying 16%. However, in 2018 the above figures have been changed and the local companies are enjoying almost double share % than that of 2014. This figures demonstrate that health cost has been reduced sharply due to local introduction. It is worth mentioning that local companies usually offer at least 25% to 40% less price compared to innovator brands.

Figure-19: Share % of Local and MNC insulins (approximate)



Source: IMS, 2Q, 2014-2018 and Internal Source

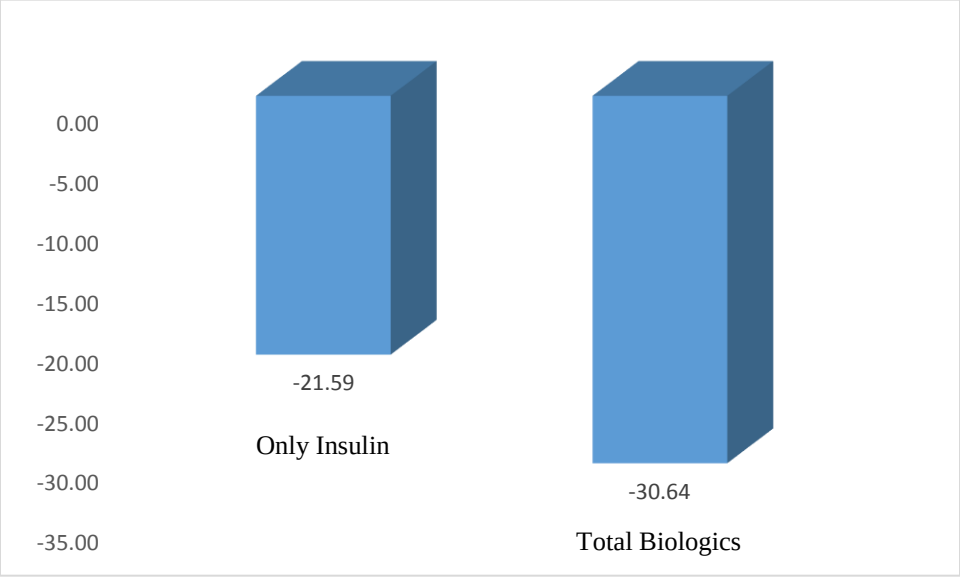
In case of other products like Erythropoietin, Interferon alpha, Trastuzumab and some other biologics the scenario is almost same.

Table-24: Approximate Health-cost reduction (mln $) due to the introduction of insulin by local manufacturers

Year	2018	2017	2016	2015	2014
Total	82.9	68.7	52.2	42.1	35.9
MNCs	59.4	48.2	38.2	34.0	30.1
Local	23.5	20.5	14	8.1	5.8
130 % of Local	30.6	26.7	18.2	10.5	7.5
Total (considering no local products)	90.0	74.9	56.4	44.5	37.6
Health-cost reduction	7.1	6.2	4.2	2.4	1.7
Total (5 years)	21.58				

Source: IMS, 2Q, 2013-2018 & Analysis of the researcher

Figure-20: Health-cost reduction ($ mln) in last 5 years (2014-18) due to the introduction of biologics by local manufacturers (Insulin & Total Biologics)



Source: IMS, 2Q, 2013-2018 & Analysis of the researcher

5.3.7 Export possibility of biosimilar products from Bangladesh

In view of regulatory guidelines, it is difficult to export biologics from Bangladesh even in the under developed or developing countries where regulation is comparatively relaxed. However, if any biologic becomes qualified by head to head trial only then it is possible to export in some markets with easy regulatory barriers. For that case possibilities are enormous. Some African and Asian countries can be targeted primarily for exporting biosimilars. Nevertheless, it will take time to export of biosimilars from Bangladesh. Since Bangladesh have some facilities endorsed by USFDA, UKMHRA, TGA and other regulatory bodies; so, researcher may think that in near future Bangladeshi manufacturers will be able to export biosimilars in the first world countries.

Global market research and consulting organization Infoholic Research has concluded that the global biosimilar drugs market will experience a compound annual growth rate (CAGR) of 57.03% to reach an aggregate of $99.28bn by 2024 in its study titled Global Biosimilars Market-Drivers, Restraints, Opportunities, Trends, and Forecasts: 2018–2024.

Infoholic Research has analyzed the biosimilar market based on three segments: products, applications and regions. The sub-segments of products include recombinant glycosylated protein, recombinant non-glycosylated protein and therapeutic peptides and others. Recombinant glycosylated proteins had the largest market share in 2017. It was also expected to have high CAGR because they cost less than biological drugs, wide therapeutic applications and many blockbuster products going off-patent in the next few years.

Applications of biosimilar drugs include cancer, blood disorders, infectious disorders and chronic and immune diseases. Cancer had the largest market share; blood diseases and chronic and immune diseases are expected to grow the fastest between 2018 and 2024.

The regions studied were North America, Europe, Asia Pacific and the Rest of the World. Europe had the largest market share in 2017, followed by Asia Pacific, which was also predicted to have the largest CAGR in the next 6 years.

Country image may be a setback in exporting biologics as they are very sensitive treatment option where saving life is the key concern. Our major competitors will be India, China and Korea; so, it is important to handle this issue very smartly. Bangladesh need to promote the success history of our pharmaceutical industry across the world. Apart from the above factory visit by the concern delegates, endorsement by the recognized bodies, assurance by the government, liaison with the local embassy/high omission of the importing countries, promotion of individual strength and inclusive relation with the stakeholders by the foreign missions of Bangladesh may be the great help in this case.

5.3.8 Factor Analysis

From factor analysis it is observed that 63% of the total variance is explained by 09 major components. Component one includes several factors including price, confidence, patronization of the local companies etc. The most important driver for biosimilars is price; especially unit price per day followed by confidence of the physicians. Income of the patients is also utmost priority as it is directly related with price factor. For building trust among the physicians' clinical trials and prescription endorsement from the Key Opinion Leaders (KOLs) are two important parameters. Some doctors are keen for the patronizing the local manufacturers which also noticeable.

Component two mostly comprised of careful selection, elaborate information for prescription, increasing use of biologics, adaptation with new technology by local manufacturers and influence through scientific seminar.

Component three is describing the technical aspects of biosimilars that include availability of expert manpower, technical soundness, maintaining cold-chain.

Component four is related with unwanted immunogenicity, escaping of biologics due to high cost, requirement of more patient counselling, familiarity with biosimilars, availability in chemist shops etc.

Component five composed of endorsement from the recognized body for biosimilars like USFDA, TGA, EMA etc, inaccessibility towards biologics due to high price, global prescription trend, freedom of choice (if more companies offer a particular biologic then physician get freedom of choice) and confidence on the information of the local companies.

The other components are also important; however, their contribution is comparatively lower.

Rotated Component Matrix									
	Component								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Cost per day	.762								
Income of the patients	.737								
Unit price	.647								
Price competitiveness	.590								
Clinical trials	.557								
Patronization to the local company	.500								
Following the Rx of KOLs	.496								
Acceptance of cost effective biosimilars	.395								
More careful consideration for biologics		.640							
Increasing use of biologics		.576							
Changes in disease pattern		.575							
Availability of expert manpower		.556							
More accessibility due to price competitive biosimilars		.504							
Adaptation with new technology		.498							
Influence by scientific seminar		.465							
Scope of biosimilars to grow		.459							
Capabilities of local manpower to handle biologics			.782						
Technological soundness of local companies			.768						
Maintaining of Cold Chain			.558						
Consideration of unwanted immunogenicity				.790					
Escaping of prescribing biologics due to high price				.682					
More patient counselling for biologics				.641					
Familiarity with biosimilars				.578					
Availability of biologics				.415					

Rotated Component Matrix									
	Component								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Importance of appropriate information					.624				
Endorsement from recognized bodies					.593				
Inaccessibility to biologics due to high cost					.546				
Following global Rx trend					.484				
Freedom of choice					.467				
Confidence on local company's' information					.434				
Informative detailing by MR						.655			
Less side effects of biosimilars						.652			
Local companies products are more available							.712		
Price advantage offered by local companies							.647		
Aggressive marketing by local companies							.539		
Branding by more number of sales call								.813	
Preference towards physicians' sample								.753	
More number of sales call for market growth								.667	
Price commensurate quality									-.789
Low price indicates substandard products									-.670

Total Variance Explained							
Component		Initial Eigenvalues			Extraction Sums of Squared Loadings		
		Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
	1	12.016	30.041	30.041	12.016	30.041	30.041
	2	2.865	7.164	37.204	2.865	7.164	37.204
	3	1.891	4.728	41.932	1.891	4.728	41.932
	4	1.783	4.457	46.389	1.783	4.457	46.389
	5	1.600	4.001	50.390	1.600	4.001	50.390
	6	1.558	3.896	54.286	1.558	3.896	54.286
	7	1.276	3.189	57.476	1.276	3.189	57.476
	8	1.219	3.047	60.523	1.219	3.047	60.523
	9	1.065	2.662	63.185	1.065	2.662	63.185
	10	.991	2.476	65.661			
	11	.970	2.425	68.086			
	12	.891	2.227	70.314			
	13	.878	2.196	72.509			
	14	.804	2.009	74.519			
	15	.749	1.872	76.391			
	16	.667	1.667	78.057			
	17	.646	1.614	79.672			
	18	.635	1.587	81.258			
	19	.594	1.485	82.743			
	20	.564	1.410	84.153			
	21	.528	1.321	85.474			
	22	.501	1.254	86.728			
	23	.465	1.161	87.889			
	24	.445	1.113	89.001			
	25	.427	1.068	90.069			
	26	.395	.988	91.057			
	27	.387	.967	92.024			
	28	.376	.939	92.963			
	29	.335	.837	93.800			
	30	.312	.779	94.580			
	31	.296	.739	95.318			
	32	.275	.688	96.007			
	33	.269	.673	96.680			
	34	.239	.598	97.278			
	35	.234	.586	97.864			

Total Variance Explained							
Component		Initial Eigenvalues			Extraction Sums of Squared Loadings		
		Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
	36	.209	.522	98.386			
	37	.200	.501	98.887			
	38	.171	.427	99.315			
	39	.152	.380	99.695			
	40	.122	.305	100.000			

5.4 Qualitative Findings

5.4.1 Prospects of biological products in Bangladesh

Considering the rising number of patients, changes in the disease pattern, better side effect profile, exposure to chemical environment, path of origin of diseases, changes in income level of the middle/lower group patients, cost effective option to choose certain medication, government patronization, changes in perception of the local physicians, increasing global demand, sound competitiveness of the local companies, awareness to diseases, accessibility to diagnostic facilities and other dynamics it is assumed that the above biologics have huge scope to grow in Bangladesh. Although the present amount is not so high but the trend supports that there are huge potentialities of the above treatment options. It is worth mentioning that biologicals accounts for almost 20% of total global pharmaceutical market and in our country this therapeutic segments comprises 4-5% of the total market. Already 111 biological products have been registered at DGDA by different local companies, some companies are coming with biologics dedicatedly (eg. Globe Biosimilars); so, there are huge potentialities for the above products.

5.4.2 Concept of Non-Comparable Biologics (NCBs) and Biosimilars

Non-Comparable Biologics are those biologics who have not head to head study with the originator's brand yet. They may be as effective and safe as originator's brand or may not be that standard. Since NCBs are new in Bangladesh market, so, it will take time to go for head to head clinical trials. Some companies are planning to setup the clinical trial practices. They also think that government, regulatory bodies, academic/research institutions can play a significant role here. On the other hand, feedback from the physicians is the primary benchmark for NCBs. Although local NCB manufacturers are confident about the purity, efficacy and safety of their products but

definitely there are so many physicians and patients who are in dilemma about the quality perception of the NCBs offered by the local companies. Some experts are little worried about the future outcomes of the NCBs; they emphasize on clinical trials on immediate basis which will be helpful for all the stake holders.

5.4.3 Perception of local physicians regarding biotech products and biosimilars

Still now many physicians are not well informed about biotech, biosimilars and NCBs. They differentiate the biologics into two broader categories; one from MNCs and other from local manufacturers. There are very few practitioners who are biased to the originator's brand considering their quality perception but nowadays they are in pressure since some of their patients are price concern. However, most of the practitioners have confident on the local manufacturers since they have a long history of success. Due to aggressive promotional campaign of Insulin towards all categories of doctors by local manufacturers, the market dynamics is becoming positive towards biosimilars or NCBs.

5.4.4 Prospects of biosimilars in Bangladesh

Bangladesh pharmaceutical market is price sensitive, some local companies are very aggressive with biologics, capabilities of the local companies are increasing day by day, perception of the physicians is changing positively towards local products, there are some good outcomes in small scale informal trials and clinical practices, huge number of biologics are in new product pipelines, API park is going to be functioning, Contract Research Organization (CRO) is going to be introduced by some renowned local companies ; so it can be assumed that Bangladeshi companies will take over the major market share of biologics. Recently it has been observed that growth percentage of local companies' insulin is higher than that of originator's one, it is one of the

indications that biosimilars will take over the major market share. It is worth mentioning that Insulin and Vaccines are the key role playing biologics in Bangladesh pharmaceutical market. Some experts believe that after 05 years' major biologics market will be controlled by local companies. They also believe that there are some patients and physicians who are brand sensitive, these groups will be the key factor for the survival of the originator brands.

5.4.5 Campaign required for the promotion of biosimilars

Since many biologics are lifesaving high cost treatment options, so, doctors are very concern about the entire value chain of biologics production. Therefore, promotions of company image, technology, knowledge based detailing (medico-marketing), overall quality perception, cool chain system and cost advantages may be the special feature for the marketing of biosimilars. As per experts vigorous Continuous Medical Education (CME) in different institutions/community may be the very important tactics for the promotion of biologics. It is better if they speakers of the above said CMEs are Key Opinion Leaders (KOLs) and do advocacy for biosimilars.

5.4.6 Competencies of the local manufacturers to manufacture biosimilars

Some local companies are already manufacturing biologics and many others are in pipelines. It gives an impression that Bangladesh have capable as well as trainable manpower for manufacturing biologics. Bangladeshi universities are producing trainable graduates who are working for local and MNCs both in home and abroad. However, we are not involved with basic materials production where we need capable human capital. Our universities are involved with the above research activities in a very limited scale which needs to be expended. For marketing biosimilars we have enough competent manpower.

5.4.7 Dilemma of the local companies for launching biosimilars

The concept of biosimilars is not old. Very few countries are aggressive with biosimilars like India, China, and Korea etc. However, developing a new biologic agent costs between $800 million and $1.2 billion. The cost of developing a biosimilar has been estimated to run between $75 million and $300 million. Therefore, considering the present local market size many companies are not interested to go for such huge investment. Some companies are investing in biosimilars considering future prospects and export market.

5.4.8 Price competitiveness of the local companies for biosimilars

Biotech products involved with very high technology; so, offering cost advantage based on production equipment is difficult but we have comparative advantages in support services and infrastructure development which will be helpful in offering competitiveness. Apart from the above our human capital cost and economy of scale may be some additional positive elements to be price competitive.

5.4.9 Biosimilars will facilitate the access towards biologic treatment option

31% of Bangladeshi lives below the national poverty line of $2 per day and one of positive signs is that extreme poverty rate dropped to 12.9% in 2016. However, biologics treatment option involved with high cost which is affordable only by rich people. In this connection a large number of patients from lower and middle income group do not get access to this biologic treatment option. Cost effective biosimilars/NCBs may be a good option for the above patients to get access to the treatment. Inclusion of such huge number of patients to biosimilars/NCBs treatment option will give a boost to the market.

5.4.10 New technology adaptation in Bangladesh pharma industry

Pharmaceutical industry is the second most regulated industry after civil aviation industry, adaptation to new technologies has to go parallel with the regulation. Bangladesh is adopting new technology very swiftly in pharmaceutical sector. As per several experts we are even in better situation compared to India and China in adapting new technology. We have trainable graduates who are facilitating the adaption with new technology. We have so many companies with fully automated state of the art facilities. Some of them have approval from regulatory bodies like USFDA, TGA, UKMHRA etc.

5.4.11 Impact of TRIPS on Bangladesh

On 6 November 2015 the World Trade Organization (WTO) TRIPS Council agreed to extend a waiver already in place in favor of Least Developed Countries (LDCs) which exempts them from having to implement provisions of the TRIPS Agreement on the protection of pharmaceutical patents and clinical trial data.

With the previously agreed upon deadline of 1 January 2016 fast approaching, the extension gives LDCs a further 17 years before they need to fully comply with provisions in TRIPS dealing with pharmaceutical patents. This extends the deadline to 2033, but the agreement also leaves room for further extensions to be made in the future.

It is expected that Bangladesh will be a middle income country by 2021 and will come out automatically from the waiver list of under LDCs. So, Bangladesh needs not to be worried about 2033. However, considering the challenge of launching new molecule we need to invest in R&D sector especially in API production.

5.4.12 Industry-academia relationship for the development of pharma sector of Bangladesh

Till to date our industry-academia relationship is insignificant to directly contribute in the growth of our pharmaceutical industry. But the good point is that they are producing trainable graduates. Very few academics are personally involved with some companies as consultant. However, collaboration for basic research is still rare. Several experts suggest that a consortium may be developed by Department of Pharmacy/Biotechnology & Genetic Engineering of different renowned universities, ICDDR, B, BSMMU, BCSIR for basic research where pharmaceutical companies will be the patrons.

5.4.13 Major limitations for launching biosimilars by local companies

Huge capital investment, lack of basic research, undefined regulatory guidelines. We can go for collaboration with global giants to address technical and investment issues. Dealing with API Park will hopefully help us to go for basic research where academicians and experts may be the key stakeholders. To solve the regulatory uncertainty government may take initiatives to finalize the proper guidelines for biosimilars.

5.4.14 Controversy about biosimilars

Very few industry experts believe that still now the future of biosimilars is uncertain as regulatory and safety issues are not clearly settled. They think that the investment required for biosimilars development may not match with the Bangladesh market. It is worth mentioning that the manufacturing processes for RHI (Regular Human Insulin) and insulin analogues are similar. API (Active Pharmaceutical Ingredient) prices were US$24 750/kg for RHI (Regular Human Insulin), US$68 757/kg for insulin glargine and an estimated US$100 000/kg for other analogues. Estimated biosimilar prices were US$48–71 per patient per year for RHI, US$49–72 for neutral protamine

Hagedorn (NPH) insulin and US$78–133 for analogues (except detemir: US$283–365). They also think that it is difficult to wait 10 years by a local company for marketing a biosimilars with such huge investment (Dzintars et al., 2018). Also, it is mentionable that development of different biosimilars involve with different cost and the amount is around $ 80-100 mln. For set up a new line for biosimilars the assumed cost is $ 3mln.

Essentially, $100/gram appears to be the current lowest cost attainable with GMP biosimilar mAb manufacture. This is attainable by some products at some of the largest facilities, whether old or new. Samsung and some legacy Big Pharma facilities were cited as having these very low costs, while some other legacy facilities likely have costs 20-30 percent more, generally viewed as a trivial increase. Costs at the new Korean facilities were expected by interviewees to continue to decrease further, below $100/gram, in coming years as efficiencies are attained and 100s of expensive onsite staff and consultants required for start-up, leave. Although there are few good examples, many presume that new commercial scale single-use biosimilar mAb facilities optimized for a company's products can reduce costs to be very competitive with even the lowest costs facilities (keeping in mind that costs below $500/g are considered by the industry as still rather competitive).

5.4.15 Regulatory consideration of biosimilars: Presently there is substantial interest in the legislative debate around generic biological drugs or "biosimilars" in the EU and US due to the large, lucrative market that it offers to the industry. While some countries have issued a few regulatory guidelines as well as product specific necessities, there is no universal harmony as to a single, simple mechanism similar to the bioequivalence determination that leads to approval of generic small molecules all over the world. The intrinsic complex nature of the molecules, along with convoluted manufacturing and analytical techniques to characterize them make it difficult to

rely on a single human pharmacokinetic study for declaration of safety and efficacy. In general, the concept of comparability has been used for evaluation of the currently approved "similar" biological where a step by step assessment on the quality, preclinical and clinical aspects is made. In India, the focus is primarily on the availability and affordability of life-saving drugs. In this context every product needs to be evaluated on its own merit irrespective of the innovator brand. The formation of the National Biotechnology Regulatory Authority may provide a step in the right direction for regulation of these complex molecules. However, in order to have an efficient machinery for initial approval and ongoing oversight with a country-specific focus, cooperation with international authorities for granting approvals and continuous risk-benefit review is essential. Several steps are still needed for India to be perceived as a country that leads the world in providing quality biological products.

5.4.16 Consideration for biobetter: Whether biobetters reveal improved value over originators, for patients, such new and innovative products provide value through developments in convenience and by offering further treatment options should a disease progress.

For manufacturers, having an objective in mind and optimizing the clinical trial program can support earlier market access. In this respect, biobetters currently appear to be one way of maintaining market share and defending against biosimilar entry-if superiority can be achieved.

For payers, the issue becomes one of immensity of improvement-how much more efficacious is a biobetter over its originator. Willingness to pay for a biobetter will be directly proportionate to this, so, if an originator takes patients 80 percent of the way to being cured, can the biobetter offer 90 percent? And, if so, what is a 90-percent cure worth.

Attaching a high price tag to a biobetter will hinder commercial success in a price competitive market, unless it can be justified on many levels, not just primary efficacy outcomes. Innovation typically affords new products with leverage to command higher prices but, in the biologics market, differentiation will be key, not simply innovation. Furthermore, pricing expectations will need to be realistic in a world where your comparators are fast going generic and biosimilar products are entering the market with around 30 percent lower prices. (James, 2017).

5.5 Testing the theoretical model and hypotheses

Type of Hypothesis	Statement	Result	Interpretation
Null Hypothesis	More careful consideration is not required to choose biological products than that of chemical products	Null Hypothesis Rejected	In comparison to chemical drugs biologics required more careful consideration while selecting it for the patients; therefore, more information and patient counselling are utmost priority for biologic products marketing practices
Alternative Hypothesis	More careful consideration is required to choose biological products than that of chemical products		
Null Hypothesis	Use of biological products is not increasing day by day	Null Hypothesis Rejected	Use of biological products is increasing day by day; therefore, biosimilars have scope to grow in the upcoming days
Alternative Hypothesis	Use of biological products is increasing day by day		
Null Hypothesis	Changes in disease pattern is not leading to increase use of biological products	Null Hypothesis Rejected	Changes in disease pattern leading to increase use of biologics, ultimately scope biosimilars will be increased
Alternative Hypothesis	Changes in disease pattern is leading to increase use of biological products		
Null Hypothesis	Biological products does not offer less side effect compared to chemical products	Null Hypothesis Rejected	Specialist Doctors experienced that Biological products offer less side-effects
Alternative Hypothesis	Biological products offer less side effect compared to chemical products		
Null Hypothesis	Unwanted immunogenicity is not being considered while choosing biological products for the patients	Null Hypothesis Rejected	While choosing biologics doctors become concerned about immunogenicity; therefore, unlike chemical drugs biologics need more attention to select properly
Alternative Hypothesis	Unwanted immunogenicity is being considered while choosing biological products for the patients		
Null Hypothesis	Appropriate information is not crucial for prescribing biological products	Null Hypothesis Rejected	Biologics involved future actions which have risk of changing basic human structure; therefore, a detail information is utmost priority
Alternative Hypothesis	Appropriate information is crucial for prescribing biological products		
Null Hypothesis	In case of biological products less patient counseling is required compared to chemical drugs	Null Hypothesis Rejected	Biologics involved with more patient counselling so

Alternative Hypothesis	In case of biological products more patient counseling is required compared to chemical drugs		more time required to consult a single patient
Null Hypothesis	Biological products are not avoided by some doctors due to high price	Null Hypothesis is not Rejected	Biotech products are high cost products which is not accessible by many patients; so, in many cases doctors avoid to prescribe it although it is important
Alternative Hypothesis	Biological products are avoided by some doctors due to high price		
Null Hypothesis	Biosimilar products are known by many Bangladeshi doctors	Null Hypothesis is not Rejected	Still now biosimilars concept is not familiar in Bangladesh. Non-Comparable Biologics (NCBs) are replacing the high cost branded biotech products
Alternative Hypothesis	Biosimilar products are not known by many Bangladeshi doctors		
Null Hypothesis	Doctors will not prescribe price competitive biosimilar products	Null Hypothesis Rejected	If biosimilars are offered at a very competitive price then it will be accepted by the doctors
Alternative Hypothesis	Doctors will prescribe price competitive biosimilar products		
Null Hypothesis	Endorsement from recognized bodies like WHO, USFDA etc. does not give confidence to choose certain products	Null Hypothesis Rejected	Biosimilars are approve by recognized body like USFDA, WHO, EMA etc so it will get a preference over NCBs as they are not recognized
Alternative Hypothesis	Endorsement from recognized bodies like WHO, USFDA etc. give confidence to choose certain products		
Null Hypothesis	Doctors do not follow global prescription trend while choosing products for patients	Null Hypothesis Rejected	Globally biosimilars are growing fast. Local doctors very often follow the global prescription trend means it will facilitate the potential of biosimilars in Bangladesh
Alternative Hypothesis	Doctors follow global prescription trend while choosing products for patients		
Null Hypothesis	Doctors do not follow the prescription trend of local Key Opinion Leaders (KOLs) while choosing products for patients	Null Hypothesis Rejected	Usually every KOL has some followers and some KOLs are prescribing imported biosimilars that is a hope to grow biosimilar market in Bangladesh
Alternative Hypothesis	Doctors does follow the prescription trend of local Key Opinion Leaders (KOLs) while choosing products for patients		
Null Hypothesis	Doctors do not look for freedom of choice while choosing products for my patients	Null Hypothesis Rejected	Biosimilars offer freedom of choice compared to originator's brand and doctors always prefer freedom of choice
Alternative Hypothesis	Doctors look for freedom of choice while choosing products for my patients		
Null Hypothesis	Many patients are getting access to high cost branded biologics		Due to socio-economic condition many patients are

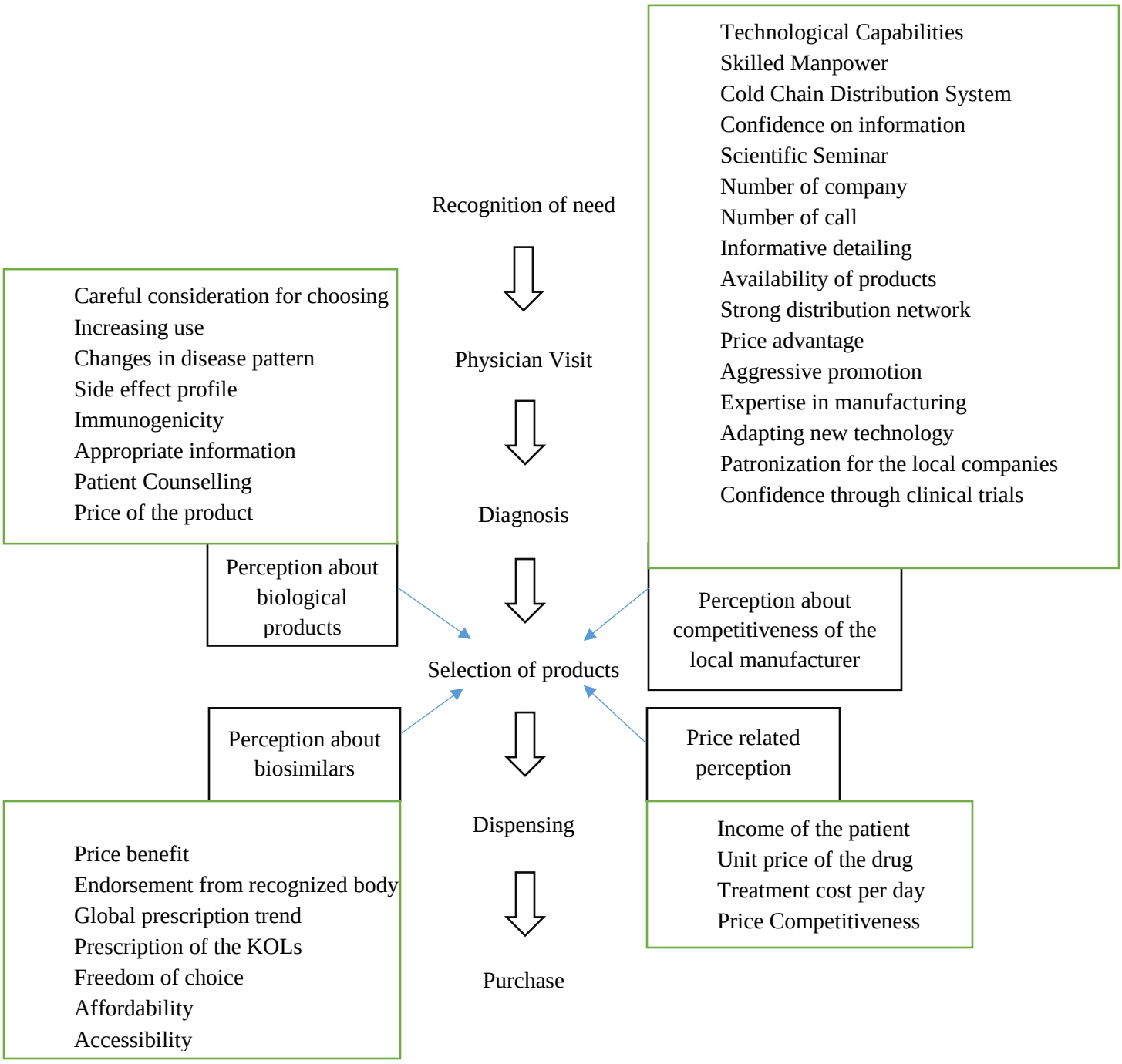
Alternative Hypothesis	Many patients are not getting access to high cost branded biologics	Null Hypothesis Rejected	not getting access to costly biotech products
Null Hypothesis	Due to unavailability of biosimilars many patients are getting access to biological drugs	Null Hypothesis Rejected	Biosimilars are offered at 30-40% reduced price compared to innovator's product; so, due to unavailability of biosimilars many patients are not getting access to biosimilars
Alternative Hypothesis	Due to unavailability of biosimilars many patients are not getting access to biological drugs		
Null Hypothesis	Considering positive increment in socioeconomic condition biosimilars have no scope to grow in Bangladesh	Null Hypothesis Rejected	Purchasing power of Bangladeshi patients are increasing that is giving hope to more access towards biologics specially biosimilars
Alternative Hypothesis	Considering positive increment in socioeconomic condition biosimilars have scope to grow in Bangladesh		
Null Hypothesis	I don't believe that local companies are capable enough to manufacture biological products	Null Hypothesis Rejected	Doctors have confidence that local companies are capable enough to handle hi-tech biologic products
Alternative Hypothesis	I believe that local companies are capable enough to manufacture biological products		
Null Hypothesis	Doctors think that Bangladesh don't have capable manpower to produce biosimilars	Null Hypothesis Rejected	Bangladesh have expert manpower to produce biosimilars
Alternative Hypothesis	Doctors think that Bangladesh have capable manpower to produce biosimilars		
Null Hypothesis	Top local pharma companies don't have the capabilities to maintain cold chain for distributing their products	Null Hypothesis Rejected	Doctors have confidence that local companies are capable to maintain distribution channel required for hi-tech products
Alternative Hypothesis	Top local pharma companies have the capabilities to maintain cold chain for distributing their products		
Null Hypothesis	I don't have confidence on the information provided by top local pharma companies	Null Hypothesis Rejected	Doctors have confidence that local companies are capable to share all the necessary information related to biosimilars
Alternative Hypothesis	I have confidence on the information provided by top local pharma companies		
Null Hypothesis	Scientific Seminar doesn't influence me to choose certain products	Null Hypothesis Rejected	Since multidimensional information is the key issue in biologics; therefore, scientific seminar may be the key marketing tools for biosimilars
Alternative Hypothesis	Scientific Seminar influence me to choose certain products		

Null Hypothesis	I prefer Physicians' sample as a promotional tool for biological products	Null Hypothesis is not Rejected	Although physician sample is the common tool in conventional pharmaceutical marketing; however, in case of biologics doctors don't prefer physician sample
Alternative Hypothesis	I don't prefer Physicians' sample as a promotional tool for biological products		
Null Hypothesis	There is no positive relation between numbers of companies offer any product and escalation possibilities	Null Hypothesis Rejected	If more number of companies offer any generics/biologics then escalation possibilities go up as promotional issues give boosts. In case of biosimilars more number of companies will offer particular item so escalation opportunity will go up
Alternative Hypothesis	There is positive relation between numbers of companies offer any product and escalation possibilities		
Null Hypothesis	More number of sales call does not remind me to prescribe certain product	Null Hypothesis Rejected	If more number of MR promote any particular biologic then it influence the doctors to choose that particular as share of voice goes up. In case of biosimilars it will be an advantage as it will be offered by many companies and will be promoted by many MR
Alternative Hypothesis	More number of sales call remind me to prescribe certain product		
Null Hypothesis	I don't like informative detailing by the Medical Representative (MR)	Null Hypothesis Rejected	Since medico-marketing is information dependent; so, doctors like informative detailing from the MR
Alternative Hypothesis	I like informative detailing by the Medical Representative (MR)		
Null Hypothesis	I don't consider availability of biological product while choosing it for my patients	Null Hypothesis Rejected	Doctors consider the availability of products while prescribing it. In case of biosimilar more number of company will offer particular biologic and it will be more readily available then originator's brand
Alternative Hypothesis	I consider availability of biological product while choosing it for my patients		
Null Hypothesis	I think local companies' products are not more available than multinationals operate in Bangladesh	Null Hypothesis Rejected	Availability is an important issue for biologics. If local companies offer biosimilars it will be more available then that of MNCs
Alternative Hypothesis	I think local companies' products are not more available than multinationals operate in Bangladesh		
Null Hypothesis	I think local manufacturer do not offer price advantage over multinationals operates in Bangladesh	Null Hypothesis Rejected	Local companies are offering price benefits over MNCs; so, it can be

Alternative Hypothesis	I think local manufacturer offer price advantage over multinationals operates in Bangladesh		assumed that if local companies offer biosimilars then it will be cost efficient
Null Hypothesis Alternative Hypothesis	I think local manufacturers are not more aggressive in product promotion compared to multinationals operates in Bangladesh I think local manufacturers are more aggressive in product promotion compared to multinationals operates in Bangladesh	Null Hypothesis Rejected	Doctors perceived that local companies are aggressive in capturing market share
Null Hypothesis	I think our pharmaceutical companies don't have experts to manufacture biosimilar products	Null Hypothesis Rejected	Doctors perceived that local manpower have expertise to handle biosimilars production
Alternative Hypothesis	I think our pharmaceutical companies have experts to manufacture biosimilar products		
Null Hypothesis	I think our companies are not accommodating new technology as per my need	Null Hypothesis Rejected	Doctors perceived that local companies are accommodating new technology as required
Alternative Hypothesis	I think our companies are accommodating new technology as per my need		
Null Hypothesis	I don't patronize local manufacturer to grow by choosing their products	Null Hypothesis Rejected	Doctors try to patronize local companies as already they built good reputation
Alternative Hypothesis	I patronize local manufacturer to grow by choosing their products		
Null Hypothesis	Clinical trials on certain products do not give me confidence to choose for my patients	Null Hypothesis Rejected	Clinical trials give confidence for prescribing certain products
Alternative Hypothesis	Clinical trials on certain products give me confidence to choose for my patients		
Null Hypothesis	I don't consider income of the patient while choosing biological products	Null Hypothesis Rejected	Doctors consider income of the patients while choosing product for his/her patient
Alternative Hypothesis	I consider income of the patient while choosing biological products		
Null Hypothesis	I don't consider unit price while choosing biological products for my patients	Null Hypothesis Rejected	Doctors consider unit price while choosing product for his/her patient
Alternative Hypothesis	I consider unit price while choosing biological products for my patients		
Null Hypothesis	I don't consider cost per day while choosing biological products	Null Hypothesis Rejected	Doctors consider treatment cost per day while choosing product for his/her patient
Alternative Hypothesis	I consider cost per day while choosing biological products		
Null Hypothesis	I don't look for price competitive products for my patients	Null Hypothesis Rejected	Doctors look for price competitive products for his/her patient
Alternative Hypothesis	I look for price competitive products for my patients		

Null Hypothesis Alternative Hypothesis	Low price indicates substandard products Low price does not indicate substandard products	Null Hypothesis Rejected	Low price does not indicate substandard products
Null Hypothesis	I shall not sacrifice the quality up to a tolerable limit considering the affordability of the patient	Null Hypothesis is not Rejected	Doctors are not interested to sacrifice product quality considering the price
Alternative Hypothesis	I shall sacrifice the quality up to a tolerable limit considering the affordability of the patient		

5.6 Empirically Tested Model



6. Recommendations & Conclusions

6.1 Recommendations

6.1.1 Emphasizing on biosimilars by the local companies: In view of the changes in disease pattern, increasing life expectancy, changes in healthcare expenditure and other pertinent factors necessity of biologics is increasing day by day. At present roughly 20% of the global pharmaceutical sales come from biologics which will be more than 30% within next five years. However, biologic segment in Bangladesh pharmaceuticals industry is less than 5% of the total sales. If we exclude insulin then the figure will be very insignificant. Due to high investment requirement, lack of skilled human capital, inadequate disease awareness campaigns, healthy growth in conventional business model local companies were little late with biologics. Now the scenario is changing, some companies are coming with biologics but still the number is very poor, only 09 local companies among more than 200 companies are partially playing with biologics. Considering the recent upward trend of certain chronic diseases like diabetes, asthma, arthritis, stroke and huge number of patients Bangladesh will be a potential destination for biologics. Also, taking into account that Bangladeshi universities are producing trainable graduates, there are so many companies that have capacity to go for huge investment, lot of global giants are ready to come in Bangladesh with technical assistances, an industry friendly guidelines by Directorate General of Drug Administration (DGDA), enormous export possibilities, it is high time for Bangladesh to go for massive investment with biologics.

6.1.2 Special attention towards emerging countries for exporting biosimilars: An emerging market is a country that has some characteristics of a developed market, but does not meet standards to be a developed market. Pharmaceutical sales in BRICS (Brazil, Russia, India, China

and South Africa) & MIT (Mexico, Indonesia and Turkey) countries have been doubled in last five years and many of them are highly import dependent. Between 2015-2020 pharmaceutical sales growth estimates scored higher in emerging countries than developed countries. Therefore, considering the upward trend in pharmaceutical spending, present status of requirements and regulatory frameworks Brazil, Russia, Chile, Colombia, Hungary, Malaysia, Mexico, Peru, Philippines, Poland, Russia, South Africa, Thailand and Turkey may be an exceptionally impressive destination for the pharmaceuticals export from Bangladesh. Although few of the Bangladeshi companies are exporting medicine to some of the above countries in a limited scale but more attention is required by all top companies. However, due to rapid urbanization, sedentary lifestyle, changes in income level antidiabetic, cardiovascular and anticancer therapeutic segments may the target for emerging countries.

6.1.3 Technical collaboration with global giants: Pharmaceutical is highly technology oriented and research based industry but still now Bangladesh is far behind with the above issues. The country is highly dependent on other countries for technology and research. High investment requirement and lack of skilled human capital are the two basic hindrances for necessary researches. Therefore, considering the above requirement technical collaboration with global giants is highly important. Technical collaboration will give an immediate boost also a longtime opportunity to develop local human capital.

6.1.4 Strengthening industry academia relationship: In Bangladesh industry-academia relationship is diminutive to directly contribute in the growth of the pharmaceutical industry. But the good point is that they are producing trainable graduates. Very few academics are personally involved with some companies as consultant. However, collaboration for basic research is still

rare. University of Dhaka and North South University have very good research facilities that can be used for basic research. Also, a consortium may be developed by Department of Pharmacy/Biotechnology & Genetic Engineering of different renowned universities, ICDDR, B, BSMMU and BCSIR for basic research where pharmaceutical companies will be the patrons.

6.1.5 Inclusion of biosimilars in medical education: Till to date the concept of biosimilars and Non-Comparable Biologics is not clear to many physicians as very few companies are promoting biosimilars; therefore, for clear understanding advantages of biosimilars may be included in the medical education system.

6.1.6 Introduction of patient centric approach: In generic marketing it is very difficult to differentiate one from others but it is utmost priority. Patient centric approach may be an important tool for distinguish one from others. A patient-centric approach is a system that establishes a partnership among practitioners, patients and their families to align decisions with patients' wants, needs and preferences. Here patient records, health information, procedure costs and practitioner data are made more easily available over the Internet. It is a personalized care that values the whole person in mind, body and spirit ultimately brand loyalty develops.

6.1.7 Launching more number of Contract Research Organizations (CROs): CROs provide clinical trial and other research support services for the pharmaceutical, biotechnology, medical device industries and also serve government institutions. For exporting as well as to maintain high local standard there is no alternative of various clinical trials. Local pharmaceutical companies are increasingly looking to outsource for the above research which involved with high cost. Recently few companies like Khwaza Yunus Ali Medical College & Hospital, Clinical Research Organization Ltd., International Centre for Diarrheal Disease Research, Bangladesh, Filaria and

General Hospital., Beximco Bioequivalence Center going to establish CRO which is a positive sign. However, to increase product standard and to meet the global requirement almost all the top ranked companies need to have research based unit.

6.1.8 Developing more patient awareness campaigns: Disease awareness campaign is the connection between patients and manufacturers. It generates a positive perception about the company/brand. From literature we knew that specific awareness campaigns have driven more people to see their doctors' means possibility of getting more consumers. Many awareness campaigns are already lead generators. It's an effective way to build email databases of potential patients which can be used for multiple purposes.

6.1.9 Drawing attention for toll manufacturing: Bangladesh have ampoule opportunity for toll manufacturing. The country has so many world class manufacturing facilities which can be used for toll manufacturing. This will help for proper capacity utilization. Considering worker wage, salary of managerial staffs, price of industrial land, office rent, income tax, geographical location, water, electricity and gas bill etc. Bangladesh is ahead than Shanghai, New Delhi, Seoul and other competitors. Therefore, Bangladesh may be an impressive hub for the toll manufacturing of pharmaceuticals.

6.1.10 Outsourcing of biosimilars development as an alternative: Since the controversy continues over the high cost biosimilars development; so, outsourcing may be an alternative in many cases. Biosimilar companies are working at an intense pace to develop the next generation of follow-on products. Outsourcing to a growing group of contract development and

manufacturing organizations (CDMOs) is a key strategy for perception developers to accelerate their products' launch.

6.1.11 Central laboratory for testing purposes: In order to minimizing the cost of testing biosimilars a central testing laboratories can be set up by the government where every company will get the opportunity to test their products. As a consequence no individual quality control facilities need to be developed immediately.

6.2 Conclusions

There are six chapters in this study. Chapter one comprises background of the study, research gap, problems statements, justification of the study, definition of related terminology, scope of the study and limitations. Chapter two describe the literature review, chapter three encompassed conceptual framework for biosimilars marketing, chapter four described methodology, chapter five reveals findings & analysis and chapter six includes conclusions that give an outline of the entire works.

Chapter one refers that pharmaceutical sector of Bangladesh is comparatively doing better among hi-tech sectors; however, recent growth trajectory is not that much promising. As per expert opinions limited number of new products, increasing awareness against infectious diseases, diminutive impact on season change are the main causes of this stumpy growth. Nevertheless, Bangladesh pharmaceutical industry has very few or no basic research to invent any new molecule; so, they mostly depend on research companies for copying their products. Recently number of new molecules in the global arena also decreased compare to the previous years. On the other hand, number of biologics are increasing globally compared to the previous years. Very few Bangladeshi companies are serious about biologics. Considering the above this research aims to find out the growth potential of biosimilars in Bangladesh. Since biologics are still in early phase here so perception about biologics, competitiveness of the local companies, familiarity with biosimilars, export potential, availability of expert manpower, price competitiveness compared to multinational companies (MNCs) were considered for the growth potential measurement of the biosimilars.

As mentioned chapter two of this study encompasses literature review. The review was started from the early history of modern pharmaceutical industry and gradually proceeded to the recent biosimilars. Changes in disease pattern, overview on global pharmaceutical industries, trends and growth pattern in different regions, introduction of biotechnology in pharmaceuticals, different

marketing concepts, new product launching status, regulatory landscapes, global issues related to healthcare cost, changes in regional healthcare spending, R&D activities, global product pipelines, present status of biosimilars in different parts of the world, scope of biosimilars due to patent expiry of innovators' products, emerging pharmaceutical markets, healthcare system of Bangladesh, overview on Bangladesh pharmaceutical market, potential of Bangladesh, competitiveness of Bangladesh pharmaceutical industries, biotechnology in pharmaceutical industry of Bangladesh and other relevant topics were reviewed carefully. After literature review it was obtained that in global arena biologics are growing very fast and their share is increasing sharply. Among biologics biosimilars are gaining huge attention and their growth potential is very high.

Chapter three describes a framework for biosimilars potential for Bangladesh market based on the above literature survey. To describe the framework some models like Porter's Generic Theory, Engel Kollat Blackwell Model, Oliver's theory, Charles M. Wood and Lisa K. Scheer's Theory, Howard-Sheth model were studied and explained why they are relevant with biosimilars marketing.

Chapter four consists of methodology of the research. To identify the measuring criteria of the growth potential, literature review and in-depth interview with industry & academic experts were carried out. After that scale items were selected for individual complex variables based on available literature and opinion of the experts. Philosophy, type, approach, sampling, data collection and method of analysis were selected based on justification. The philosophy of this research is interpretivism. This descriptive research applied both quantitative and qualitative approach to find the fact. The sampling technique was non-probability, snowball and judgmental.

Chapter five comprise analysis and findings. This part of the research used both primary and secondary data. For primary data survey feedback was the main source and for secondary data IMS and literature review were the bases.

The research findings suggest that biologic products market is growing at higher rate compared to conventional pharmaceutical products and by 2030 the value of biological products will be 1260 mln $ (approx.) which will be 25% among total pharmaceutical market, it is worth mentioning that the present market share of biologics is about 5% of the total market.

The research found that concept of biosimilars and NCBs are not still clear to many physicians. They perceived local products as generic of innovators' products although the real story is different. Comprehensive information, unwanted immunogenicity, patient counselling, income of the patients, treatment cost per day, prescription trend of KOLs, available clinical trials, price competitiveness, perception about the local manufacturer, informative detailing by the MR (Medical Representatives) are very considerable factors for choosing biologics for the patients.

Almost all the respondents recognized that biosimilars have growth potential in Bangladesh and many of them had a tendency to patronize local manufacturers if quality is maintained properly.

This research also reveals that treatment cost due to biologics will be reduced sharply if more number of local manufactures offers biosimilars. It is assumed that around 30 mln $ has been saved in last five years in Bangladesh due the introduction of biologics by the local companies.

The research found that Globe Biotech and Ziska Pharmaceuticals are coming shortly with biologics which will give a sudden boost in the growth of biologics in Bangladesh.

The global product pipeline of biosimilar is very rich; so, it is very promising for Bangladesh to move forward with biosimilars.

The six chapter of the research is conclusion that summarizes all the chapters.

References

Armantier., Olivier., & Soiliou Daw Namoro. (2008). Prescription Drug Advertisement and Patient Compliance: A Physician Agency Approach. Advances in Economic Analysis & Policy 6(1). Article 5.

Azevedo VF., Mysler E., Alvarez A., Hughes J., Flores-Murrieta FJ.,& Castilla EM. (2014). Recommendations for the regulation of biosimilars and their implementation in Latin America. Generics Biosimilars Initiat. J. 3, 143-148.

Andrew W. Mulcahy., Zachary Predmore., & Soeren Mattke. (2014, November). The Cost Savings Potential of Biosimilar Drugs in the United States. Rand Corporation, US.

Ashley Crossman. (2018). Pros and Cons of Secondary Data Analysis. Retrieved from https://www.thoughtco.com/secondary-data-analysis-3026536

Arshad Ahad. (2018). The growth in the global biosimilars market. BIO Science today.

Big Molecule Watch. (2016, June): South Korea's Biosimilars Industry Poised to Grow Domestically and Abroad. Big Molecule Watch, GoodwinProcter LLP, US. Retrieved from http://www.bigmoleculewatch.com/2016/06/16/south-koreas-biosimilars-industry-poised-to-grow/)

Blanchard, A., Helene D Iorio., & Robert Ford. (2010). "What you need to know to succeed: Key trends in Canada's biotech industry ". Insights, Spring

Blackett, T. (2001). Brand Medicine: Use and Future Potential of Branding in Pharmaceutical Markets. International Journal of Medical Marketing: 45-61., N. (2011)

Bangladesh Health System Review. (2015). Asia Pacific Observatory on Public Health Systems and Policies. Health Systems in Transition Vol. 5 No. 3 2015

Cheryl Swanson. (2015). "5 Largest markets for pharmaceutical", Flickr: Creative Commons. Sansome Street, 6F, San Francisco, California 94111, USA.

Collis, J. & Hussey, R. (2014) "Business Research: A Practical Guide for Undergraduate and Postgraduate Students" 4th edition, Palgrave Macmillan, p.54

Crossman. (2018, May). Pros and Cons of Secondary Data Analysis. Retrieved from https://www.thoughtco.com/secondary-data-analysis-3026536

Cassels, A. (2017, January). Why biosimilars should be interchangeable with biologics. The Pharmaceutical Journal (A Royal Pharmaceutical Society Publication). Retrieved from https://www.pharmaceutical-journal.com/opinion/insight/why-biosimilars-should-be-interchangeable-with-biologics/20202121.article?firstPass=false

Castaneda-Hernandez, G., Gonzalez-Ramirez, R., Kay, J., Scheinberg, M.A. (2015, February). Biosimilars in rheumatology: What the clinician should know. BMJ Journal. Vol 1, Issue

CDIP (2008): Chancellor's Doctor Incentive Program, California State University. Retrieved from http://teachingcommons.cdl.edu/cdip/facultyresearch/Typesofresearch.html

Catherine Saez. (2015, August). WIPO Patent Committee Agrees On Future Work, After Uncertainty. Intellectual Property Watch.

Daniel Workman. (2017). "Drugs and Medicine Exports by Country", The World Factbook, Washington, D.C. USA.

DGDA (Directorate General of Drug Administration of Bangladesh). (2018). (www.dgda.gov.bd). Retrieved from www.dgda.gov.bd/ index.php/ export/export-reports

Dzintars Gotham, Melissa J Barber & Andrew Hill. (2018). Production costs and potential prices for biosimilars of human insulin and insulin analogues, BMJ Global Health, Volume 3, Issue 5

Darrell Sleep Ph.D. (2017, March).Biobetter: Full filling Potential. Genetic Engineering & Biotechnology News.

Dr Nicola Devis. (2017, March). Is there a future for biobetters? Thepharmletter

Dr. Md. Moklesur Rahman Sarker. (2014, March). Recent Trend and Future Prospective of Biotechnology in Pharmaceuticals-Bangladesh Perspective" The Pharma World. Dhaka, Bangladesh.

Dr. Md. Moklesur Rahman Sarker. (2015, January). Global trends, future prospects and challenges of Biotechnology in Pharmaceuticals: Bangladesh perspective. The Pharma World. Dhaka, Bangladesh

Dr. Choudhury M Hasan. (2013, July 25-26). Bangladesh Pharmaceutical Sector: R&D Status. Regional Consultation for developing a Strategic work plan as a follow-up of Consultative Expert Working Group on Research and Development: Financing and Coordination Bangkok, Thailand.

Deloitte. (2014). Global life sciences outlook Resilience and reinvention in a changing marketplace, PP.8-10. Retrieved from https://studyres.com/doc/15533716/2014-global-health-care-outlook.

Delottie. (2015). Global life sciences outlook: Adapting in an era of transformation. Deloitte Touche Tohmatsu Limited, UK. Retrieved from https://www2.deloitte.com /content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-life-sciences-report.pdf)

Denise F. Polit, & Cheryl Tatano Beck. (2004). Nursing Research: Principles and Methods. Lippincott Williams & Wilkins, 2004-Medical-758 pages

DGDA (Directorate General of Drug Administration of Bangladesh). (2018). (www.dgda.gov.bd). Retrieved from http://www.dgda.gov.bd/ index.php/ export/export-reports

Eva Rahman Kabir., Shannon Sherwin Moreino and Mohammad Kawsar Sharif Siam. (2018). An Empirical Analysis of the Perceived Challenges and Benefits of Introducing Biosimilars in Bangladesh: A Paradigm Shift. Biomolecules, MDPI, Basel, Switzerland.

Erwin A. Blackstone and Joseph P. Fuhr, Jr. (2012). Innovation and Competition: Will Biosimilars Succeed? Biotechnology Healthcare, USA. Spring; 9(1): 24-27. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC3351893/)

Erwin A. Blackstone, Joseph P. Fuhr, Jr, PhD, and Steve Pociask, MA. (2014). The Health and Economic Effects of Counterfeit Drugs, Am Health Drug Benefits. 2014 Jun; 7(4): 216–224.

EBL Securities Ltd. (2017): Pharmaceuticals Industry of Bangladesh. Retrieved from http://www.eblsecurities.com/AM_Resources/AM_ResearchReports/SectorReport/Pharmaceuticals%20Industry%20of%20Bangladesh.pdf

Evaluate Pharma. (2015). World Preview 2015, Outlook to 2020. Retrieved from http://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf

European Medicines Agency. (2012). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). European Medicines Agency-Europa, May 24, 2012. (Cited: August23, 2012.) Retrieved from www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127960.pdf)

Esperanza Lopez Vazquez, (2001). "Risk perception interactions in stress and coping facing extreme risks", Environmental Management and Health, Vol. 12 Issue: 2, pp.122-133. Retrieved from https://doi.org/10.1108/09566160110389889

Farhat, F., Torres, A., Park, W., Lopes, G.D., Mudad, R., Ikpeazu, C., Aad, S.A. (2017). The Concept of Biosimilars: From Characterization to Evolution-A Narrative Review. Oncologist, 23, 346–352.

Gary Walsh. (2007). Pharmaceuticals, biologics and biopharmaceuticals. Pharmaceutical biotechnology; Concepts and Applications. Ireland: John Wiley and Sons, ISBN: 978-0-470-01244-4

GaBi. (2014, July). EU guidelines for Generics and Biosimilars Initiative (GaBi), Belgium. biosimilars. Mol, Belgium: Pro Pharma Communications International. Retrieved from: www. gabionline.net/Guidelines/EU-guidelines-for-biosimilars.

Gonul, F. F., Franklin, C., Petrova, E., Kannan, S. (2001). Promotion of Prescription Drugs and Its Impact on Doctors' Choice Behavior. Journal of Marketing, July: 79-90

Grewal, S., Ramsey, S., Balu, S., Carlson, J.J. (2018). Cost-savings for biosimilars in the United States: A theoretical framework and budget impact case study application using filgrastim. Expert Rev. Pharmacoecon. Outcomes Res, 18, 447–454.

Hugo Almeida., Maria Helena Amaral., & Paulo Lobao. (2011, June). Drugs obtained by biotechnology processing. Brazilian Journal of Pharmaceutical Sciences, Vol-47, N. 2.

Henriette Jacobsen. (2013). EU countries singled out for misguided healthcare budget cuts, euractiv

Industry Overview. (2012, December). Pharmaceuticals and Biotech, WETFEET. Retrieved from https://carey.jhu.edu/uploads/files/IRG_Biotech_corrected.pdf

IFPMA. (2017, April). Considerations for Physicians on Switching Decisions Regarding Biosimilars. Retrieved from https://www.ebe-biopharma.eu/publication/ebe-efpia-and-ifpma-position-biosimilars paperconsiderations-for-physicians-on-switching-decisions-regarding

Irena Royzman and Andrew D. Cohen.(2015, July). Biobetters: The Advantages and Challenges of Being Better. Patterson Belknap Webb & Tyler LLP

Jun Wang and Shein-Chung Chow (2012, April): On the Regulatory Approval Pathway of Biosimilar Products, Pharmaceuticals (Basel), USA. 5(4): 353–368. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles /PMC3763644/

Jerry Bugel. (2013, November). Weighing the Prospects of Biosimilars. Practical Dermatology. Retrieved from http://practicaldermatology.com/pdfs/pd1113_clinicalFocus.pdf http://practicaldermatology.com/pdfs/pd1113_clinicalFocus.pdf

Jan Ascher., Boris Bogdan., Julio Dreszer., & Gaobo Zhou. (2015, July). Pharma's next challenge. Insights & Publication. Retrieved from https://www.mckinsey.com /industries/pharmaceuticals-and-medical-products/our-insights/pharmas-next-challenge

Jane Owen and Rebecca Currey. (2016, March). Australian Government embarks on push for growth of Biosimilars, Bird & Bird, London, UK. March. Retrieved from http://www.twobirds.com/en/news/articles/2016/australia/australian-government-embarks-on-push-for-growth-of-biosimilars

J Bradley White, Nathaniel Lipkus, Osler, Hoskin and Harcourt. (2012). Biosimilars in Canada: at a tipping point, Intellectual Asset Management (IAM), London, UK. Retrieved from http://www.iam-media.com/Intelligence/IAM-Life-Sciences/2016/Articles/Biosimilars-in-Canada-at-a-tipping-point

Jack Cush. (2016, October). Biosimilar Reports. Rheumnow, Texsas, USA. Retrieved from http://rheumnow.com/content/biosimilar-reports-%E2%80%93-october-2016

Jois, R. (2017). The brave new world of biosimilars ('similar biologics') in India. Postgrad. Med. J, 93, 577–579.

James Wright. 2017. Are Biobetters Better. Eyeforpharma. 7-9 Fashion Street, London, UK.

Joan-O-Callaghan, Margaret Bermingham, Maurice Leonard, Frank Hallinan, J. Michael, Morris UnaMoore, Brendan T.Griffin. (2017). Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland. Regulatory Toxicology and Pharmacology. Volume 88, August, Pages 252-261

Joanna M Shepherd. (2014). Biologic Drugs, Biosimilars and Barriers to Entry. Emory University School of Law

Knatterud., G.L., Rockhold, F.W., George, S.L., Barton, F.B., Davis, C.E., Fairweather, W.R., Honohan, T., Mowery, R, O'Neill, R. (1998). Guidelines for quality assurance in multicenter trials: a position paper. Controlled Clinical Trials, 19:477-493. Key Differences. Retrieved from https://keydifferences.com/difference-between-questionnaire-and-interview.html

Kabir Humayan. (2012, October). New Challenges for Pharma Industry; Business Outlook.

Karsten Dalgaard, Matthias Evers Jorge Santos De Silva. (2013, February). Biosimilars Seven years on: where are we and what's next. McKinsey & Company, USA.

Kotler, P. and Armstrong, G. (2004). Principles of Marketing. 10th Edition, Pearson-Prentice Hall, New Jersey, USA.

Knatterud., G.L., Rockhold, F.W., George, S.L., Barton, F.B., Davis, C.E., Fairweather, W.R., Honohan, T., Mowery, R, O'Neill, R. (1998). Guidelines for quality assurance in multicenter trials: a position paper. Controlled Clinical Trials, 19:477-493.

Kotler, P. (2003). Marketing Management. 11th Edition, Prentice-Hall, Upper Saddle River.

Kelly. (2017, November). Will Biobetters and Biosimilars Compete for Market Share? Health economics experts. November

Lalit Kumar Sharma. (2012, January). A Study of Physicians Behavior toward Marketing of Pharmaceutical Products: A Case Study of Indian Market. Zenith International Journal of Business Economics & Management ResearchVol.5, Issue 6.

L. Naing , T. Winn, B. N. Rusli. (2006). Practical Issues in Calculating the Sample Size for Prevalence Studies. Department of Community Dentistry, School of Dental Sciences, Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia

Lilian Rumi Tsuruta, Mariana Lopes dos Santos, Ana Maria Moro. (2014). Biosimilars Advancements: Moving on to the future. AIChE, The Global Home of Chemical Engineers

Michael R. Solomon & Nancy Rabolt (2004). Consumer Behavior: In Fashion, Saint Joseph's University & San Francisco State University, ISBN 9780130811226

Monica Malik, Sergei Tjulandin and Gilberto de Lima Lopes, Jr. (2016, May). Biosimilars in Low-and Middle-Income Markets: A Case Study of India and Russia. American Society of Clinical Oncology Annual Meeting, USA. Retrieved from https:// am.asco.org/biosimilars-low-and-middle-income-markets-case-study-india-and-russia

Md. Abu Zafor Sadek. (2016, June). Growth Potential of Biosimilar Products in Bangladesh. 5th European Biosimilars Congress, Valencia, Spain. Retrieved from http://biosimilars-biologics.pharmaceuticalconferences.com/europe/ppt/2016/growth-potential-of-biosimilar-products-in-bangladesh

Mizik, N., Jacobson, R. (2004). Are Doctors 'Easy Marks'? Quantifying the Effects of Detailing and Sampling on New Prescriptions. Management Science, 50 (12): 1704-1715.

Monique Ellis. (2017). "Who are the top pharmaceutical companies in the world", ProClinical Life Sciences. Eldon House: 2-3 Eldon St, London, UK.

Nick, C. (2012). The US Biosimilars Act: Challenges Facing Regulatory Approval; Pharm Med 26 (3): 145–152. doi:10.1007/bf03262388

Nitin Naikn., & Sanjeev Kumar. (2016, April): 6 Factors Driving Global Biosimilar Market Growth. Life Science Connect, Philadelphia, USA. Retrieved from www.biosimilar development.com/doc/factors-driving-global-biosimilar-market-growth-0001

Philip Kotler, Gary Armstrong. (2011). Principles of Marketing, Pearson Prentice Hall, Business & Economics-651 pages

Parvez M Chowdhury. (2011). An overview of the pharma sector in Bangladesh. A BRAC-EPL report

Research Report PricewaterhouseCoopers (PwC) International Limited. (2011). Industry, Strategies & Trends analysis. Research & Market report on Pharma 2020

Pricewaterhouse Coopers (PwC) International Limited. (2013). Global Pharma Industry 2013-18. Trend, Profit & Forecast Analysis

Pharmaceutical Product Development Report (2013, March). Developing Biosimilars in Emerging Market: Regulatory & Clinical Considerations.

Patricia M. Danzon. (2018). Differential Pricing of Pharmaceuticals: Theory, Evidence and Emerging Issues. PharmacoEconomics. (https://doi.org/10.1007/s40273-018-0696-4)

ppd Report. (2016, May). World biosimilars market to hit $26.3M by 2020. Pharmaceutical Product Development (ppd). USA.

Phillip Miller. (2012). China: Tipping the Balance: Risks and Opportunities in Biosimilars. Deallus Consulting Ltd., UK. Retrieved from http://www. Dealllusconsulting .com/china-tipping-balance-risks-opportunities-biosimilars

Peter Loftus and Denise Roland (2018). Drug maker Keeps Cheaper Humira Copies out of U.S. The Wall Street Journal. Oct. 16

Quintiles IMS. (2016). Intercontinental Marketing Services, Health, USA. Retrieved from www.quintiles.com/microsites/biosimilars-knowledge-connect/biosimilars-by region/europe

Rajiv Kumar., & Jagjit Singh. (2014, July). Biosimilar drugs; Current status. International Journal of Basic and Applied Medical Research, Vol-4, Issue-2

Research & Market report. (2012). Industry, Strategies & Trends analysis: Pharma2020

Ralf Otto., Alberto Santagostino & Ulf Schrader. (2014, December). The Rapid Growth in Biopharma: Challenges & Opportunities. Insights & Publications.

Rolando Y. Wee. (2017). “Biggest pharmaceutical markets in the world by country”, Worldatlas. Transcanadienne, Suite 100, St. Laurent, QC, Canada.

Rodeina Chlland. (2011). Biosimilars in Emerging Markets Is It a Level Playing Field? PRA Health Sciences, Green Park, UK

Raj Kumar, V., Ishita, S., Ayush, G. Biosimilars. (2018). A Review of Regulatory Perspective in Indian Context. Bull. Pharm. Res. 2017, 7, 139. Biomolecules, 8, 89 21 of 21

Ranjit Shinde, Divya Rajagopal. (2019). Understanding the biosimilars opportunity for Indian pharma. ET Markets

Riaz, Ali, Rahman, Mohammad Sajjadur. (2016). Routledge Handbook of Contemporary Bangladesh. Routledge. p. 165. ISBN 978-1-317-30876-8.

R&D. (2018). Next Generation of Biosimilars and Biobetters: Challenges and Opportunities. Drug Discovery & Development. **(**www.drugdiscoverytrends.com**)**

Saunders, M., Lewis, P. & Thornhill, A. (2012). "Research Methods for Business Students" 6 6th edition, Pearson Education Limited

Steinberg FM., & Raso J .(1998, May). Biotech Pharmaceuticals and Biotherapy: An Overview. Journal of Pharmaceutical Science.;1(2):48-59.

Science News. (1978, September). Human Insulin: Seizing the Golden Plasmid. Magazine Issue, Vol:114-12.

SMi. (2016, September). SMi Group's 7th Annual Biosimilars Europe Conference, London, UK. Retrieved from https://www.smi- online.co.uk/pharmaceuticals/uk/biosimilars-europe

SRM. (2018). Social Research Method. Retrieved from https://www.socialresearchmethods.net/kb/sampprob.php

Salim Afzal Shawon. (2011, June). Pharma Industry of Bangladesh; Finance research report.

Schutt, R. (2006). Investigating the Social World. Sage Publications. p423-426,412-416

Simon Mundy., & Andrew Ward. (2015, June). South Korea pushes to be new force in Pharmaceuticals. The Financial Times, London, UK. Retrieved from https://www.ft.com/ content/0d1367ac-09a9-11e5-8534-00144feabdc0

Surbhi S. (2016). Difference Between Questionnaire and Interview. Key Differences. Retrieved from https://keydifferences.com/difference-between-questionnaire-and-interview.html

Sarker, M.M., Rashid, M.S., Raju, A.A., Rana, M.; Karim, M.F., Akter, R., Howlader, A.N., Ming, L.C., Ismail, N.E. (2016). Evaluation of the Pharmaceutical Quality of Different Brands of Ranitidine Tablets Manufactured in Bangladesh: A Pharmaceutical and Public Health Prospective. J. Appl. Pharm. Sci. 6, 055–061.

Schutt, R. (2006). Investigating the Social World. Sage Publications. p423-426,412-416

Schiffman. & Kanuk. (2000). "Consumer Behavior," 7th Edition, Prentice Hall, Upper Saddle River.

Thulasi Lakshmi K., Sreekanth Reddy CP., Alagusundaram M., & Jayachandra Reddy. (2014). Regulatory Approvals of Biosimilar: Indian Market Perspective. International Journal of Advanced Pharmaceutics, Vol-4, Issue-4, 245-258

T. Sayandhan., SS Kodithuwakku., & LHP Gunaratne. (2010). Influence of Marketing in Prescribing Pharmaceutical Products by Ophthalmologists in Sri Lanka, Tropical Agriculture Research Vol. 20, 260-268

Tina Valbh, BS Pharm, RPh. (2016, February). The Value Potential of Biosimilars in the United States, Axium Healthcare Pharmacy. New Jersey, USA. Retrieved from http://www.Specialty pharmacytimes.com/ publications /specialty-pharmacy-times/2016/february-2016/the-value-potential-of-biosimilars-in-the-united-states/P-2)

Talgeri, N., Chiplunkar, S. S. (2002). Marketing and Distribution of Pharma Goods. Retrieved from www.Pharmabiz.com/Chronicles

Trifiro G, Marciano I, Ingrasciotta Y. (2017, November). Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018 Mar;18(3):309-315. doi: 10.1080/14712598.2018.1410134.

The Biotech Effect (2008, August): Pharmaceutical Technology Market & Customer Insight.

Tomas Gabriel Bas., & Carolina Oliu Castillo. (2015). BioMed Research International. USA. Volume 2016, Article ID 5910403, 12 pages. Retrieved from http://dx.doi.org /10.1155/ 2016/ 5910403 Biosimilars in Developed and Developing East and Southeast Asian Countries: Japan, South Korea, and Malaysia-Overview, Evolution, and Regulations Assessment

The World Bank Databank. (2015). Retrieved from http://data.worldbank.org/

TGA. (2016). Biosimilars in Pharmaceutical Price Benefit Scheme. Therapeutic Goods Australia (TGA). Retrieved from http://www.pbs.gov.au /info/general /biosimilars.

The Economic Times. (2016, July). Cipla to invest Rs 590 crore for a biosimilars plant in South Africa. The Economic Times, India. Retrieved from: http://economictimes. indiatimes.com /industry/healthcare/biotech/pharmaceuticals/cipla-to-invest-rs-590-crore-for-a-biosimilars-plant-in-south-africa/articleshow /53113643.cms)

The Pharma Letter. (2016, June). FDA approves Inflectra, the first biosimilar MAb in the USA. Putney, London, UK. Retrieved from http://www.thepharma letter. com /article/fda-approves-inflectra-the-first-biosimilar-mab-in-the-us

UK Trade Briefing. (2011, September). UK trade & investment sector briefing: Pharmaceutical Opportunity in Bangladesh.

U.S. Food and Drug Administration. (2012). Guidance for Industry: Quality considerations in demonstration biosimilarity to a reference protein product. Washington DC: U.S. Food and Drug Administration.

World Health Organization (2012, March). Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization World Health Organization. (2010, April). Retrieved from http://www. who.int/biologicals/areas/biological_therapeutics /BIOTHERAPEUTICS_ FOR_WEB_22APRIL2010.pdf.

World Health Organization. (2017, April). Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). Retrieved from http://apps.who.int/medicinedocs/en/d/Js19941en

World Health Organization. (2017, July). Similar biotherapeutic products. Retrieved from http://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en

World Health Organization. (2018). Public Spending on Health: A Closer Look at Global Trends

Vakratsas, D., Kalyanaram, G. (2010). Price Effects on Physician Prescription Behavior and the Role of HMO Orientation. Retrieved from http://nmims.edu/wp-content/ uploads/ 2012/ w3/ SPTM/

Zafar Momin, Calvin Wijaya and Paul Bernardo. (2017). Will Asia Go Big In Biosimilars Adoption and Manufacturing? L.E.K. Consulting Article. May 18.

Website Based References

www.businessdictionary.com/definition/growth-potential.html

www.merriam-webster.com/dictionary/potential

www.searchcio.techtarget.com/definition/growth-potential

www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

www.businessdictionary.com/definition/growth-potential.html

www.merriam-webster.com/dictionary/potential

www.searchcio.techtarget.com/definition/growth-potential

www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

www.globenewswire.com/news-release/2017/08/14/1084378/0/en/Global-Generic-Drug-Market-Size-Share-Will-Reach-USD-380-60-Billion-by-2021-Zion-Market-Research.html

www.acmeglobal.com/acme/investors/financial-reports/annual-reports/

www.archive.dhakatribune.com/bangladesh/2013/jul/03/local-api-base-key-pharma-future

www.pharmajogot.com/api-in-open-market-behind-drug-manufacturers/

www.dgda.gov.bd/index.php/2013-03-31-05-16-29/list-of-valid-source

www.bangladesheconomy.wordpress.com/2008/06/01/api-park-to-give-pharma-industry-a-major-boost/

www.today.thefinancialexpress.com.bd/trade-market/construction-work-of-factories-set-to-begin-by-february-1514569707

www.today.thefinancialexpress.com.bd/trade-market/construction-work-of-factories-set-to-begin-by-february-1514569707

www.prnewswire.com/news-releases/global-238-bn-active-pharmaceutical-ingredients-api-market-2017-2025-300533088.html

www.businessdictionary.com/definition/growth-potential.html

www.merriam-webster.com/dictionary/potential

www.searchcio.techtarget.com/definition/growth-potential

www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

https://en.wikibooks.org/wiki/Research_Methods/Types_of_Research

https://blog.euromonitor.com/8-ways-identify-market-opportunities-business-growth/

www.pharmaceutical-technology.com/news/global-biosimilar-market-forecast-reach-99-28bn-2024/

Business Jargon. (2018). Business Jargon. Available from

https://businessjargons.com/judgement-sampling.html

Investopedia. (2018). Investopedia LLC. Available from
https://www.investopedia.com/terms/stratified_random_sampling.asp

Thesaurus. (2018). Available from https://www.dictionary.com/browse/parenthesis

www.dhakatribune.com/business/stock/2018/11/03/bangladesh-s-burgeoning-pharmaceutical-sector-ruling-local-market-stock-business-and-expanding-abroad

www.policygenius.com/health-insurance/what-is-a-specialist-physician/

www.thepharmaletter.com/article/is-there-a-future-for-biobetters

www.blog.marketresearch.com/the-growing-pharmaceuticals-market-expert-forecasts-and-analysis

www.biosimilardevelopment.com/doc/the-china-biosimilars-market-rise-of-a-potential-powerhouse-0001

www.wsj.com/articles/biosimilar-humira-goes-on-sale-in-europe-widening-gap-with-u-s-1539687603