MARKET ASSESSMENT FOR THERAPEUTIC MONOCLONAL ANTIBODIES AND THEIR FORECAST TO 2023

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree

of Master of Business Administration (MBA)

in

Pharmaceutical Management

by

Vicky Jain

Under the Supervision and Guidance of

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Engagement Manager
PharmaACE Analytics LLP

Dr Ashok Peepliwal
Associate Professor
IIHMR University

2021

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled 'market assessment for therapeutic monoclonal antibodies and their forecast to 2023' is the bonafide record of my original researchwork. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished workof others has been duly acknowledged in the text.

Signature: *Vicky Jain*

Name of the student: Vicky Jain

Date: 21-06-2021

Completion Certification

CERTIFICATE

This is to certify that Vicky Jain in partial fulfillment of the requirements for the awardof the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur has successfully completed his internship at PharmaACE Analytics Pvt. Ltd. during March 22, 2021 to June 19, 2021.

Place: Pune

Date: June 21, 2021

Pooja Cornelius

Pooja Cornelius
Lead- Talent Acquisition and Development
PharmaACE

CERTIFICATE

This is to certify that dissertation title 'market assessment for therapeutic monoclonal antibodies and their forecast to 2023 by using commercial analytics' is a record of the research work undertaken by Vicky Jain in partial fulfillment of the requirements for the awardof the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide
IIHMR University, Jaipur

Date

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IIHMR University, Jaipur

Date

ABSTRACT

Monoclonal antibodies are vital means for many molecular immunology research. Combined with methods such as epitope mapping and molecular modeling, monoclonal antibodies can perform antigen analysis and surface mapping of large molecules. They are widely used to detect and identify serum analytes, cell markers and pathogens, mainly due to the particularity of these unique reagents. The top ten therapeutic monoclonal antibodies in 2017-2020 include adalimumab, trastuzumab, rituximab, bevacizumab, cetuximab, denosumab, tocilizumab, ranibizumab and infliximab. Monoclonal antibodies, humanized monoclonal antibodies can obtain the highest yield. India's therapeutic monoclonal antibody market grew at a rate of 44%, the domestic market grew at a rate of 15%, and exports grew at a rate of 100%. India exported about $ 137 million in mAbs in 2020. India exports a huge amount of biosimilars. The market value of MAbs is projected to reach $ 349 million in 2023.

Keywords: Monoclonal antibody, mAbs, Adalimumab, Trastuzumab, Rituximab, Bevacizumab, Cetuximab, Denosumab, Tocilizumab, Ranibizumab, Infliximab, Forecast, ATC code.

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Vicky Jain

MBA PM 11

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Chapter 1: Introduction

Monoclonal antibodies have become a key component of various clinical laboratory diagnostic tests and therapeutic drugs(1). Monoclonal antibodies are used mechanically in many areas, though their use as healing for diseases, including, leukaemia, breast cancer, asthma, Crohn's disease, arthritis, transplants, macular degeneration, has been remarkable. Monoclonal antibodies are protein molecules produced by recombinant DNA technology within the laboratory from hybridoma-cells. In the past decade significant progress has been achieved in improving a couple of important aspects of the protection and effectiveness of primary antibodies in healing. Anticipated to their attributes, consisting of molecular-size, stability, & solubility, this kind of molecules is an extensive pharmaceutical company. In this bankruptcy we tried to identify the prevailing healing problems, formulate disadvantages and distribute antibody drugs, especially in the demanding situations and possibilities that the gifts will offer for the future.(2).

The record gives marketplace sizing and forecast throughout USD foreign money that the Worldwide Monoclonal Antibodies Sell is anticipated towards develop from USD ~89,650 Million in 2020 to USD ~153,700 Million through the ending of 2025(3).

India introduced the discharge of regulatory draft for ‘biosimilars’ on the B.I.O enterprise convention in Boston, USA, on 19 June 2012. Finalization points have been carried out on September-2012. Bodies of Regulatory liable for the approval of biosimilars in India are:

- *DB: Department of Biotechnology.*
- RCGM
- CDSCO(4).

In India top selling biosimilars are adalimumab, trastuzumab, bevacizumab, cetuximab, rituximab, denosumab etc.

Various companies are manufacturing the biologicals drugs like ZydusCadila, Dr.Reddy’s, Cipla, Hetero drugs, Reliance, RPG Life, Torrent Pharma, Glenmark, Biocon, etc.

Biosimilars are exactly what the name implies: it is a biological product that is "similar" to another biological drug (called a ‘reference product’).

Chapter 2: Review of Literature

In laboratory, mAbs are formed to serve as alternatives to antibodies capable of restoring, enhancing, or imitating the cell disease in an immune system. MAbs are constituted to bind with antigens which are commonly found on the cell receptor than healthy cells(5). MAb is a cell-binding protein manufactured in the laboratory. The monoclonal antibodies are numerous. Some cancer types are used for treatment. They can be utilized without help or transported directly to disease cells by medicines, contaminants or radioactive substances(6). The immune system reacts as foreign substances, including bacteria, viruses, and others. The body erroneously classifies natural cells as external and generates cell group antibodies. In the laboratory, scientists produce that reproduce the function of the immune structure. These man-made antibodies work out on proteins that harm tissues from auto- immune diseases. Synthetic human genes that produce from human genes in mice or other suitable mammals are synthetic antibodies. Then the antigen that the scientist wants to produce antibodies is vaccinated against the mice. This leads to human antibodies being produced by the immune cells of the mouse. The term "monoclonal antigens" refers to an artificial antibody that has cloned immune cells synthesized and that an antigen is binding to the same monoclonal antibody. Polyclonal antibodies are synthesized by various immune cells and are bound to several antigens by the produced antibodies(7).

History of monoclonal antibody development:

Production of the first monoclonal anti-body in 1975 and the first fully licensed monoclonal anti-body in 1986 which could target specific protein composition mutations and expression in a variety of disorders and defects and illnesses. The worldwide value of the antibody market place is roughly US ~$20 billion per year(8)(9).

Monoclonal antibody therapy is beneficial for cancer, autoimmune diseases, and neurological diseases that cause cell degeneration in the body (such as Alzheimer's disease). Monoclonal antibody therapy can help the immune system because the innate immune system responds to environmental factors by distinguishing foreign cells from somatic cells. Therefore, rapidly multiplying tumor cells or cell death in the body and then causing physiological problems are usually not a specific target of the immune system, because tumor cells are the cells of the patient. However, tumor cells are very abnormal, and many of them have unusual antigens. But they can weaken health.

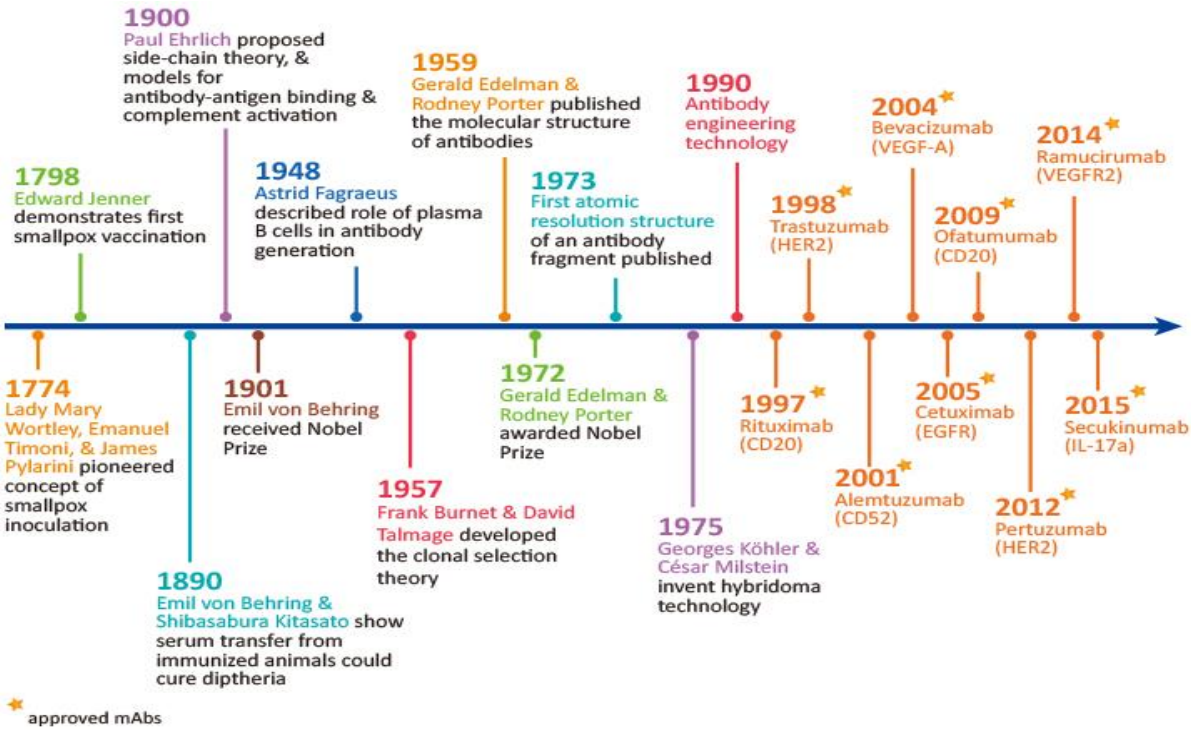

Figure 1: History of research and development for monoclonal antibody(10)

Monoclonal antibody are made of(6):

They are manufactured in 4 different ways and are named according to their ingredients:

- Murine: Made from mouse protein and treatment name ends with "omab".
- Chimeric: combination of some mice & people, and treatment named with "ximab".
- Humanized: formed by linking small portion of mice proteins with human-protein, and treatment named with "zumab".
- Human: completely human proteins, & treatment named with "umab".

Types of Monoclonal-antibody used to treatment(6):

- Naked monoclonal antibodies

Naked monoclonal-antibodies are without any drugs or radio-active substances attached. They work for self. Highly prevalent types of mAbs utilized to handle malignancy. Very naked monoclonal antibodies combine to cancer cell antigens, but several operate by attaching to antigens on more non cancer cells or similar free moving proteins. Naked monoclonal antibodies can operate in various approaches. Certain individuals enhance the human immune reaction to cancer cells through attachment to cancer cells and marking the destruction of human immune systems. One example is alemtuzumab,

Campath, used for some chronically lymphocytic leukemia patients. Alemtuzumab is linked to the CD 52 antigen in lymphocytic cells. The antimicrobial attracts immune cells when attached to it to destroy them. Additional naked monoclonal antigens primarily work by binding and blocking cancer cell antigens (or other cells nearby). This helps to spread or grow cancer cells. Trastuzumab (Herceptin), for instance, is an antibody aimed at the H.E.R. 2 protein. Sometimes, huge amounts of this protein are in the surface of breast and gastric cancer cells. HER2 will help these cells to expand when activated. Trastuzumab binds and prevents activation of these proteins.

- Conjugated monoclonal antibody

The conjugated MAb is combined with a chemo therapeutic agent or a radio active particle. These MAbs are used to deliver ingredients precisely to cancer cells. MAb spreads all over the body till it penetrates the target antigen and hardens. It provides toxic substances that are most necessary. This reduces damage in other parts of the body to normal cells. The combined mAbs can also be referred to as tagged,labelled or complete antibody.

Radiolycated antibody: Radio-active marked antibodies have small particles that are linked to it. This is an antibody against CD 20 antigen. The antibodies are direct radio-activity to cancer cells. Mab (Rituximab) medications and radioactive substances. Therapy with this kind of antibody can be well-recognized as radio-immune-therapy. Here, drugs and radiation are delivered to target cells which affects the target and almost close to cells.

Chemical labeling antibodies: These MAb have a chemotherapy drug (or another) attached to them, which is directed to a CD 30 antigen attached to chemicals called M.M.A.E. The antibodies aimed at the HER 2 protein attached to the chemical products called EM Tansine Ado-Trastuzumab, KADCYLA.

- Bispecific monoclonal antibody

A drug composed of 2 distinct mAbs be able to bind to 2 various proteins at the similar time. One example is blinatumo-mab, blincyto; Blinatumomab binds to CD 19 protein, which is present in certain leukemia and lymphoma cells; the other part binds to CD 3, which is a protein located on T cells. By combining to these two proteins, the medicine predicaments cancer and immune cells, triggering the immune structure to damage cancer cells.

Monoclonal antibody work(7):

Monoclonal Abs are structured to operate in various form. The role of drugs in supporting the immune system may include the following:

- Triggers cell membrane destruction. Some monoclonal antibodies can cause a reaction of the immune system, thus destroying cancer cells' outer wall.
- Cancer cells are marked. Some immune cells rely on antibodies to find their goals. The detection and destruction of cancer cells covered with monoclonal antibodies is easier.
- Directly attack cancer cells. Although designed for other purposes, some monoclonal antibodies may attack cells more directly. If some of this antibody's cling to the cell, it can be self-destructed by a set of events in the cell.
- Stop growing cells. Certain monoclonal antibodies obstruct the link between cancer cells and cell growing proteins that are necessary for the growth and survival of tumors.
- Chemotherapy is received. Likewise, some monoclonal antibodies attach chemotherapy drugs to treat cancer cells directly while healthy cells are avoided.
- Block inhibitors of the immune system.
- Prevent blood vessels from growing.
- Have treatment too for radiation. As monoclonal antibodies may connect to carcinogenic cells, antibody may be developed for further treatments as delivery vehicles. A small radioactive particle, cancer cells are directly treated and radiation effects on healthy cells are minimised. Radioimmunotherapy is called this variation in standard cancer radiotherapy.
- Combines cancer with cells in the immune system. Some drugs combine two monoclonal antibodies, one with cancer cells and one with certain immune system cells. This can encourage an attack on cancer cells by the immune system.

Side/Adverse effects of monoclonal antibody drug(7):

In general:

- Low blood pressure
- Nausea and vomiting
- Flu-like signs and symptoms

- Diarrhea
- Skin rash
- Allergic reactions

Serious side/adverse effects (rare side effect)

- High BP, heart-attacks , congestive heartfailure..
- Bleeding
- Low blood count
- Infusion reactions: serious allergic reactions can occur, which can lead to death in rare cases.
- Lung issues
- Skin problems: Skin sores & rashes may in some cases lead to severe infections.

Market overview of Monoclonal Antibodies:

In the early 1980s therapeutic monoclonal (MAbs) therapeutic development began. The earliest MAb invention was authorized in the United States for prevention of renal transplantation by muromonab-CD3 (Orthoclone OKT3 trademark, sold by Janssen-Cilag) in 1986.

Sales and approval growth in other MAb drugs was slow until the first chimeric antibody in the late 1990s had been approved. The approval of these products has dramatically increased the approval rate and sales of mono-clonal antibody products for humanised antibodies and antibodies over time. In 2019, worldwide revenue was almost USD 163 billion, signifying around 70 percent of the overall sales of all biopharmaceuticals (about USD 230 billion) for all single-clonal antibody medicines. This represents a substantial increase in sales and ratios compared to 75 billion US dollars in 2013 (approximately 50 percent). The renewed expansion in the sales of authorized MAb products and the current 1,200 MAb applicants (many of which are used for multiple indicators) will further increase the sales of MAb results and additional push the global sales of all biopharmaceuticals. The number of MAb creations permitted for profitable use in the United States and Europe has risen drastically, with 3 to 5 new products authorized each year from 2010 to 2014, trailed by 10 to 19 new products authorized each year from 2015 to 2019. The 119 MAb products in the mammalian system are full-size naked MAbs (60%), supported by full-length biosimilar MAbs (19%). The remaining 21% of MAb

products expressed in mammals consist of six other types of antibody products. Global MAb sales have increased more rapidly over the last five years than all other biopharmaceutical categories. Sales of all MAb products in 2014 rose from roughly US$84 billion (regardless of the type or production system) in 2019 to almost US$163 milliards, up by 93%. In 2019, the total annual sales of 36 single-clone antibody products were more than USD 1 bn, 5 of which achieved sales of over US$7 bn: AbbVie's Humira (adalimumab), Crete of the Merck, Eylea of the Regeneron (adflibercept), Squibbo of the Bristol Opdivo-Myers (nivolumab), and Genentech/Avastin. Rochez's (bevacizumab). For two consecutive years AbbVie (AbbVie) announced Humira sales of around US$19 billion, making it the best-selling drug product. As patents have expired, the interest of people in biosimilar development has increased with the granting of full rights to many high-level-profile and spectacular MAb results. The first monoclonal anticorruption biosimilars sold by Celltrion and Inflectra were approved in September 2013 for trade in Europe under the brands Remsima (sold by Pfizer) and Inflectra. In biosimilar versions of the popular MAb product from Janssen, Remicade (inflximab). There will be more biological similarities in the next few years(11)(12)(13).

The worldwide monoclonal antibody (MAb) market is expected to expand from US $ ~107 billion in 2020 to US $ ~114 billion in 2021, with a CAGR of 7%. The increase was primarily expected to the company rescheduling its actions and improving from the effects of COVID-19, which previously led to constricting suppression actions that consist of social isolation, remote work, and business closures, resulting in operational challenges. It is estimated that by 2025, the market will reach US $ ~180 billion, with a CAGR of ~12 %. The popularity of cost effective biosimilar is driving the growth of the market. The goal of biosimilars is to curb the rising cost of healthcare and respond to financial pressure from patient & government to reduce drug costs and increase access to treatment. Biosimilars are pharmaceutical products that have been developed to have properties like those of approved biopharmaceuticals. The cost of biosimilar monoclonal antibodies is 20% to 25% lower than that of original biological drugs. The number of clinical trials of biosimilar drugs is less than that of parent biologic drugs, which is also the reason for the low cost of biosimilar drugs. In India, a brand-new biosimilar policy called "Guide to Similar Biological Products" devised by the Central Drug Standards Control Organization is anticipated to greatly promote the biosimilar industry in India(14).

By 2027, MAbs therapy market will grow at a rate of 14 %; increased investment in product research and development will generate multiple prospects for market growth. The major companies in the MAbs therapy market research report are AbbVie, Merck & Co., Roche, BristolMyers Squibb, Johnson & Johnson, Daiichi Sankyo, Novartis AG, Alexion, Amgen, and other major market players(15).

Monoclonal Antibody in India

Biocon is the first Indian company to sell its product BIOMAb, MAbs, which received regulatory approval for marketing and production in India in September 2006. This product is a kind of tumor treatment based on monoclonal antibodies, such as head and neck cancer. The drug is specifically designed to target and block the epidermal-growth-factor-receptor that causes cancer cells to multiply. Nimotuzumab is a monoclonal antibody that specifically binds to the extracellular domain of E-G-F-R and prevents signal transmission. Treatment of advanced squamous cell carcinoma of the head and neck, concurrent chemotherapy and/or radiotherapy. Biocon is also cooperating with Mylan to develop a biosimilar mAb. In 2007, Dr. Reddy has developed a new concept for the biosimilar rituximab, a version of Roche's cancer therapy that allows more people to get the drug at half the original price. Reditux is Dr.'s second product. Reddy, he developed therapies for cancer and autoimmune diseases(16).

Anatomical Therapeutic Chemical (ATC) Classification

Active ingredients are divided into different category according to their respective organ or system and pharmacological, therapeutical, and chemical properties under the Anatomical Therapeutical Chemistry (ATC). The drug is divided into five groups.(17)

Structure

• The system has fourteen main anatomical/drug groups or first levels.

• Each main grouping of ATC is allocated into a second level, which can be a pharmacological or therapeutic group.

• Grades 3 and 4 are chemical, pharmacological, or beneficial subgroups.

• The fifth level is chemical substances(18).

Examples of various therapeutic monoclonal antibodies:

1. Adalimumab

Adalimumab is an anti-tumor necrosis factor alpha monoclonal antibody that is used to treat a variety of inflammations. Adalimumab is a biological disease regulator, administered subcutaneously. It was first released by Abbvie in United States and was approved in 2002. Adalimumab is also called 'Humira'(19). It is delivered by r-DNA expertise utilizing mammalian cell. This medicine comes in the form of a pre-filled syringe and pen, which is convenient for self-injection under the skin. The FDA approved a new biosimilar of adalimumab called adalimumab on October-2018. This biosimilar is called 'Hyrimoz' by Novartis(20).

Indication

The following are the conditions for adalimumab:

- Rheumatoid - arthritis
- Juvenile idiopathic – arthritis
- Psoriatic - arthritis
- Ankylosing - spondylitis
- Ulcerative - colitis
- Plaque – psoriasis

Mechanism of action

Adalimumab is specific for tumor necrosis factorα (TNFα) and prevents the effect of its cont act with TNF receptors on the face of p55 and p75 cells. When complement is present, adalim umab also lyses cells expressing surface tumor necrosis factor in vitro. TNF is a naturally occ urring cytokine that plays a role in normal inflammation and the immune reply. Elevated leve ls of TNF are detected in the synovial fluid of patients with rheumatoid arthritis, psoriatic arth ritis, and ankylosing spondylitis, and it plays an important role in pathological inflammation and joint destruction, the main complications of these diseases(20).

ATC Codes(21):

ATC Code	**Classification**
L04AB04	Adalimumab
L04AB	TNF-α inhibitors
L04A	Immuno-suppressants

L04	Immuno-suppressants
L	Anti-neoplastic & immune-modulating

Table 1 ATC Code of Adalimumab

2. Trastuzumab

Trastuzumab, an anti-human epidermal-growth-factor-receptor-protein. It is a r-humanized IgG-1-k monoclonal antibody that selectively binds to the extra-cellular domain of human EGFR(22).

In December 2017, the FDA approved the therapy of metastatic breast cancer or gastric cancer in which the tumour overexpresses HER2 patients for Ogivri (trastuzumab) as biosimilar for Herceptin (trastuzumab). Although "Ogivri" - the first US-approved biosimilar for breast or gastric cancer treatment, the second US approved biosimilar for cancer therapy. The biopsy of 'Herzuma' is approved in December 2018 (trastuzumab). The biosimilar FDA approved in June-2019, 'KANJINTI' (Trastuzumab).

Indications

- Indicates first-line treatment for breast cancer with paclitaxel
- Cisplatin/capecitabine/5-fluorouracil for treating gastric or gastroesophageal metastatic junction cancer
- Subcutaneous treatment with HER-2 positive breast cancer, combined with hyaluronidase and pertuzumab(23).

Mechanism of action

Trastuzumab is a r-humanized IgG1 mabs directed against the HER-2 receptor, which is part of epidermal growth-factor receptor of a photo-oncogene. Trastuzumab attach to the extra-cellular ligand and blocks the cleavage of the extra-cellular domain of HER-2 to induce antibody-induced negative receptor regulation and subsequently inhibit. (22).

ATC Codes(24):

ATC Code	**Classification**
L01XC03	Trastuzumab
L01XC	Monoclonal antibody
L01X	Anti-neoplastic

L01	Anti-neoplastic
L	Anti-neoplastic & immuno-modulating

Table 2 ATC Code of Trastuzumab

3. Rituximab

Rituximab is an anti CD 20 mabs. Rituximab is a transgenic chimeric mouse/human mabs that levels the CD 20-antigen present on the side of normal and malignant B lymphocytes. It was first approved by US-FDA in 1997 as a monotherapy for non-Hodgkin B cell lymphoma (NHL) patients. On November-2018, US-FDA supported the first Rituximab (Rituximab) biosimilar 'Truxima'(25)(26). 'Truxima' is suitable for the medication of grown patients(25).

Indication(25):

- Non-Hodgkin lymphoma
- Chronic lymphocytic leukemia
- With methotrexate to treat adult patients of rheumatoid arthritis
- Granuloma with polyangiitis
- Pemphigus vulgaris

Mechanism of action

In various parts of the autoimmune/inflammatory process, B cells can play a role, such as the production of RF and other auto anti-microbials, the presentation of antigen, activation of T cells and / or the production of pro-inflame-based cytokine tags(26).

ATC Codes(27):

ATC Code	**Classification**
L 0 1 X C 0 2	Rituximab
L 0 1 X C	Monoclonal antibodies
L 0 1 X	Anti neoplastic
L 0 1	Anti neoplastic
L	Anti-neoplastic & immuno-modulating

Table 3 ATC Code of Rituximab

4. Bevacizumab

Bevacizumab is an anti-vascular, endothelial developmental factor, used to treat several forms of cancer in combination with anti-tumor drugs. V.E.G.F. plays a major role in angiogenesis, lymph angiogenesis and growth of the tumour(28)(29).

In 2004, the FDA approved "Avastin" as the first anti-angiogenic substances to be commercialized for certain types of cancers. (29).

Indications

As an inhibitor of vascular endothelial growth factor (VEGF), bevacizumab is utilized in a variety of chemotherapy regimens to treat:

- non-small cell lung cancer
- metastatic colorectal cancer
- cervical cancer, peritoneal cancer, epithelial ovarian cancer, & fallopian tube cancer
- metastatic renal cell carcinoma
- recurrent glioblastoma(28).

Mechanism of actions

"Inducible hypoxia factors" transcription of V.E.G.F. proteins. The hypoxic cell-based micro-environment promotes the survival of harder tumour cells and creates an environment that is demanding to properly react to immune cells. VEGF has therefore developed a known anti-cancer mark for drugs as bevacizumab. Binding of mAb prevents VEGF from interacting with surface cell receptors and inhibits the promotion of angiogenesis. This prevents blood vessel formation, reduces tumour blood vessels and reduces the blood supply of the tumour. VEGF has also been upregulated in COVID-19 patients(29)(30)(28).

ATC Codes(31):

ATC Code	**Classification**
L01XC07	Bevacizumab
L01XC	Monoclonal-antibody
L01X	Anti-neoplastic
L01	Anti-neoplastic
L	Anti-neoplastic & immuno-modulating

Table 4 ATC Code of Bevacizumab

5. Cetuximab

Cetuximab is endothelial growth-factor receptor binding moieties used in the treatment of colorectal cancer and squamous cell carcinoma of the head and neck. Cetuximab is a recombinant chimeric human/mouse IgG1 antibody(32). Cetuximab was certified by the FDA under the trade name 'Erbitux' in February-2004. It is administered by intravenous infusion, as a monotherapy or in combination with other chemo-therapy(33).

Indications

- Squamous cell carcinoma of the head and neck in combination (Advanced)
- Squamous cell carcinoma of the head and neck, combined (Metastatic)
- Cetuximab is also suitable for wild-type K-Ras metastatic colorectal cancer that expresses EGFR, which is a test approved by the FDA in combination with FOLFIRI (a combination of leucovorin, fluorouracil, and irinotecan)(32).

Mechanism of Action

Epidermal Growth Factor Receptors: Transmembrane glycoproteins and type I receptor tyrosine kinases are stated on and in malignant cells that initiate a signal cascade involving cell differentiation, proliferation, migration, angiogenesis, and cell death. After binding to the EGFR domain, the EGFR time map suppresses EGFR activation. Inhibition of the EGFR signaling pathway ultimately suppresses cell cycle progression, cell survival pathways, tumor cell migration and invasion. Also induces cell death and reduces the production of substrate metalloproteinases and vascular endothelial growth factor (VEGF)(34)(33).

ATC Codes(35):

ATC Code	**Classification**
L01XC06	Cetuximab
L01XC	Monoclonal-antibody
L01X	Anti-neoplastic
L01	Anti-neoplastic
L	Anti-neoplastic & immuno-modulating

Table 5 ATC Code of Cetuximab

6. Denosumab

Denosumab is a RANK ligand inhibitor. Denosumab is a new type of fully human IgG-2 mabs which can inhibit a various of markers of bone-resorption with metastatic tumors. It was approved by the FDA on June-2010(36).

Indications

Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk of fracture.
- Reduces the incidence of vertebral, non-vertebral and hip fractures.
- to increase bone mass in women at high risk for fractures who are receiving adjuvant aromatase inhibitors for breast cancer.
- used for men with osteoporosis who are at high risk for fractures or for men who have received androgen deprivation therapy for non-metastatic prostate cancer to increase bone mass.

Xgeva:

- Avoidance of bone-related actions in patients with bone metastases from solid malignant tumor(36).

Mechanism of action

Denosumab is designed to target RANK Ligand, a protein used to promote bone removal and resorption as the primary signal. RANKL can overwhelm the natural bone defences of the body in many cases of bone loss. Denosumab avoids activation by RANKL on the surface and precursors of the RANK Receptor. Denosumab RANKL/RANK interaction prevention hampers the development and function of osteoclast and its survival, reducing bone resorption and increasing bone mass and corital bone strength and trabecular bone strength(37)(36).

ATC Codes(38):

ATC Code	**Classification**
M05BX04	Denosumab
M05BX	Bone- mineralization & structure

M05B	Bone- mineralization & structure
M05	Bone-diseases
M	Musculo-skeletal system

Table 6 ATC Code of Denosumab

7. Tocilizumab

Tocilizumab: interleukin-6 receptor-antagonist. Tocilizumab is a r-humanized mabs IL 6 receptor inhibitor. Roche, initiated developing in 2003. It is also used to treat severely ill-patients with COVID 19. Tocilizumab was approved by FDA on January 8, 2010(39)(40).

Indications

Tocilizumab is appropriate for the medication of slight to serious rheumatoid - arthritis, giant - cell arteritis, & cytokine release Syndrome(40).

Mechanism of Action

Interleukin 6 is an inflammatory cytokine and stimulates prompt reaction protein, serum amyloid A, fibrinogen, haptoglobin and α1 antitrypsin, while inhibiting the production of fibronectin, albumin and transferrin. IL 6 also stimulates antibody manufacture, produces cytotoxic T cell variant, and impedes controlling T cell differentiation. Tocilizumab combines to soluble and membrane-connected IL-6 receptors and impedes IL6 mediated inflammation(39).

ATC Codes(41):

ATC Code	**Classification**
L04AC07	Tocilizumab
L04AC	Interleukin-inhibitor
L04A	Immuno-suppressants
L04	Immuno-suppressants
L	Anti-neoplastic & immuno-modulating

Table 7 ATC Code of Tocilizumab

8. Ranibizumab

Ranibizumab: r-humanized MAbs and V.E.G.F-A antagonist. IgG-1-k iso-type MAbs moieties specifically created for intraocular use. Ranibizumab combine & hinders the biological movement of human vascular-endothelial-growth-factor A. Ranibizumab is marketed under the name 'Lucentis'(42)(43).

Indications

Cure patients with macular edema following retinal vein occlusion, age-associated (wet) macular deterioration and diabetic macular edema.

Mechanism of Action

The combination of ranibizumab & V.E.G.F. - prevents interaction of V.E.G.F. - with its endothelialcell surface-receptors, vascular-leakage and the formation of new blood-vessel, & reducing endothelialcell-proliferation (43).

ATC Codes(44):

ATC Code	**Classification**
S01LA04	Ranibizumab
S01LA	Anti-neo - vascularization
S01L	Ocular vascular - disorder
S01	Ophthalmological
S	Sensory – organ

Table 8 ATC Code of Ranibizumab

9. Infliximab

Infliximab is anti - tumor necrosis factor-alpha mAbs used to treat various inflammations. Infliximab is chimeric IgG-1 mAbs. Infliximab was first approved by the FDA as an intravenous injection in 1998, 'Remicade'. 'Inflectra' – 1st biosimilar was agreed in 2016. In December-2017, F.D.A. passed the 2nd biosimilar drug 'Ixifi' formed by Pfizer.(45)(46)

Indications

- Suitable for adults or children (≥ 6 years) with moderate to severe active Crohn's disease who do not respond to conventional treatments
- Suitable for drainage of intestinal cutaneous fistulas and recto - vaginal fistulas
- Suitable for adults or children (≥ 6 years) with moderate to severe active ulcerative colitis
- Suitable for moderate to severe active rheumatoid arthritis
- Suitable for active ankylosing spondylitis.
- For severe chronic plaque psoriasis

Mechanism of Action

Infliximab is the mabs IgG-1β that binds high affinity to soluble and transmembrane shapes of TNF α. The blocking effect of TNF - α further reduces local and systemic pro-inflammatory cytokine (i.e. IL - 1, IL - 6), reduces the migration of lymphocytes and leucocytes to inflammatory sites and induces apoptotic cells that produce TNF, enhances βB, and reduces endothelial adhesion molecules and acute cellular inhibitor levels(46)(45).

ATC Codes(47):

ATC Code	**Classification**
L04AB02	Infliximab
L04AB	TNF-α inhibitor
L04A	Immuno-suppressants
L04	Immuno-suppressants
L	Anti-neoplastic & immuno-modulating

Table 9 ATC Code of Infliximab

10. ABCIXIMAB

Abciximab is anti glycoproteinIIb/IIIa receptor mabs that is used to prevent thrombosis during percutaneous coronary intervention.

Indications

Abciximab can be used as an adjunct drug in percutaneous coronary intervention. It is used to prevent patients undergoing percutaneous coronary intervention and those who plan to undergo percutaneous coronary intervention within 24 hours and do not respond

to conventional medications Complications of cardiac ischemia in patients with unstable angina pectoris.

Mechanism of Action

Abciximab bind to complete platelet receptor GPIIb / IIIa. GPIIb / IIIa is a member of integrin adhesion receptor family and is the main platelet surface-receptor involved in platelet aggregation. By binding to the vitronectin re-ceptor, abciximab obstructs the integrin-mediated impacts, as well as cell adhesion. Abciximab blocks Mac-1 receptors on monocytes and neutrophils, suppressing the attachment of monocytes(48).

ATC Codes(49):

ATC Code	**Classification**
B01AC13	Abciximab
B01AC	Platelet aggregation inhibitor
B01A	Anti-thrombotic
B01	Anti-thrombotic
B	Blood and blood forming-organs

Table 10 ATC Code of Abciximab

Chapter 3: Methodology

RESEARCH METHODOLOGIES

Sample area: The study was carried out with Therapeutic Monoclonal Antibodies at PharmaACE Analytics Pvt. Ltd., Pune, Maharashtra.

Sample design: It is an analytic study to evaluate and assess potential customers and the future market using a prediction model in the treatment of therapeutic monoclonal antibodies drugs and brands. The product was expected to have a market share, volume and revenue. Qualitative and quantitative approaches to research have been adopted:

1) Qualitative Approaches:
    a) Data Cleaning
    b) Data Tagging
    c) Harmonization
2) Quantitative Approaches:
    a) Volume and projected Volume calculation.
    b) Unit rate in INR and USD calculation
    c) Value of product.

Study duration: The study was carried out for 3 months from 22 March 2021 to 19 June 2021.

Sample size: The entire Chapter 30 data and injectables domestic data was considered for estimation of volume and revenue of drug X. The year of the data is 2017 to 2020.

Data Collection Method: Primary data were received from the company.

Software Tools used: MS Excel (Advanced)

Chapter 4: Research objectives:

To record and calculate the past and future of market revenue of therapeutic monoclonal antibodies.

To study the top ten therapeutic monoclonal antibodies and calculate their market volume and market revenue.

To analyze percentage share of the type of therapeutic monoclonal antibody according to the nature of manufacturing types.

To study and calculate the top competitors of top five therapeutic monoclonal antibodies.

To study the different brands and their retail price analysis of top five therapeutic monoclonal antibodies.

Chapter 5: Results

1. Market size and estimation/forecast of therapeutic monoclonal antibodies from year 2017 to 2023.

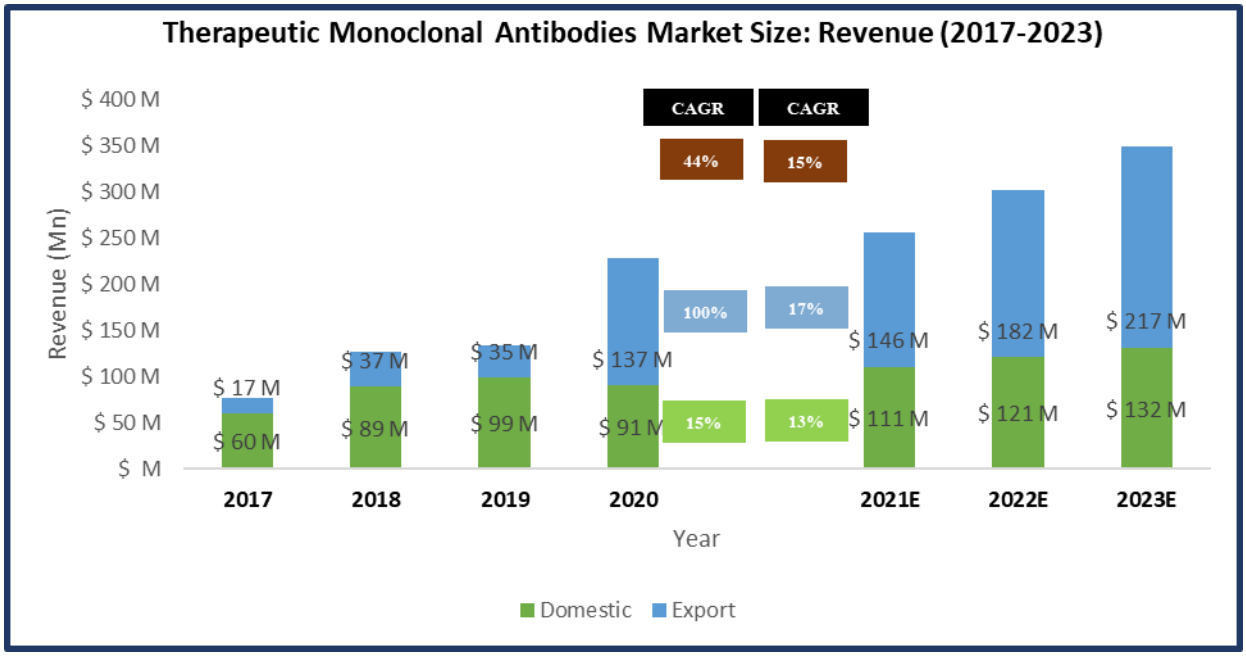

Chart 1 Market size (revenue) analysis of therapeutic monoclonal antibodies from year 2017 to 2023.

2. Based on market types: export or domestic, market volume and market value in percentage for year 2020.

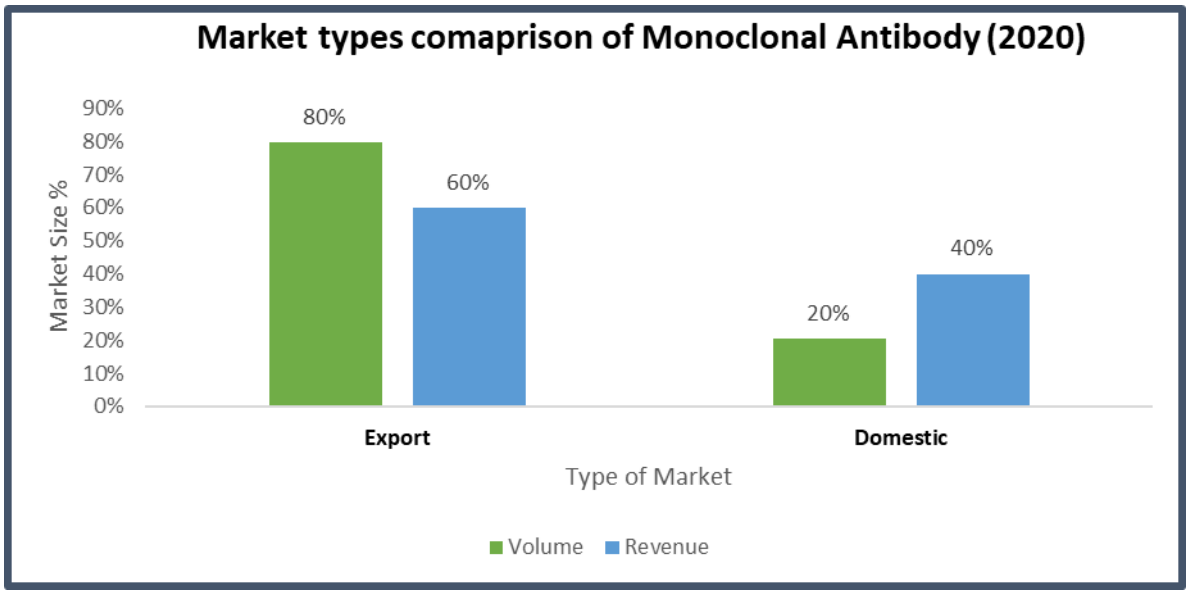

Chart 2 Market size analysis based on types of markets for therapeutic monoclonal antibodies in year 2020.

3. Based on different types manufacturing method, market size percentage is analyzed.

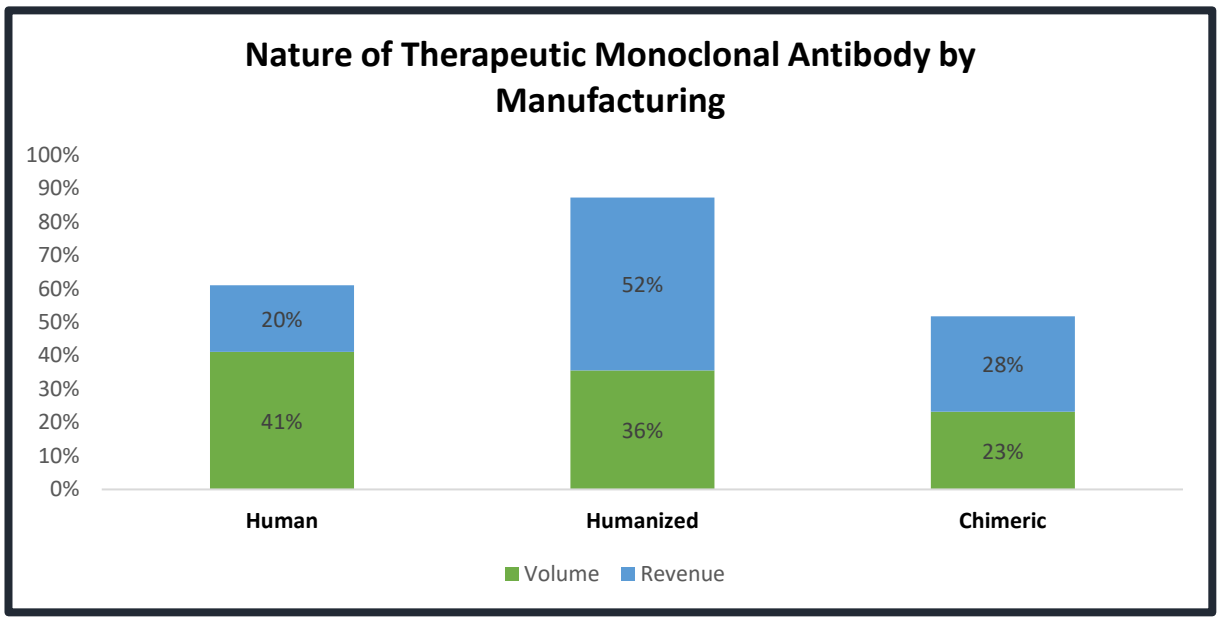

Chart 3 Market size analysis based on types of manufacturing for therapeutic monoclonal antibodies in year.

4. Sales generated in terms of volume and value by top ten monoclonal antibodies in Indian market from year 2017 to 2020.

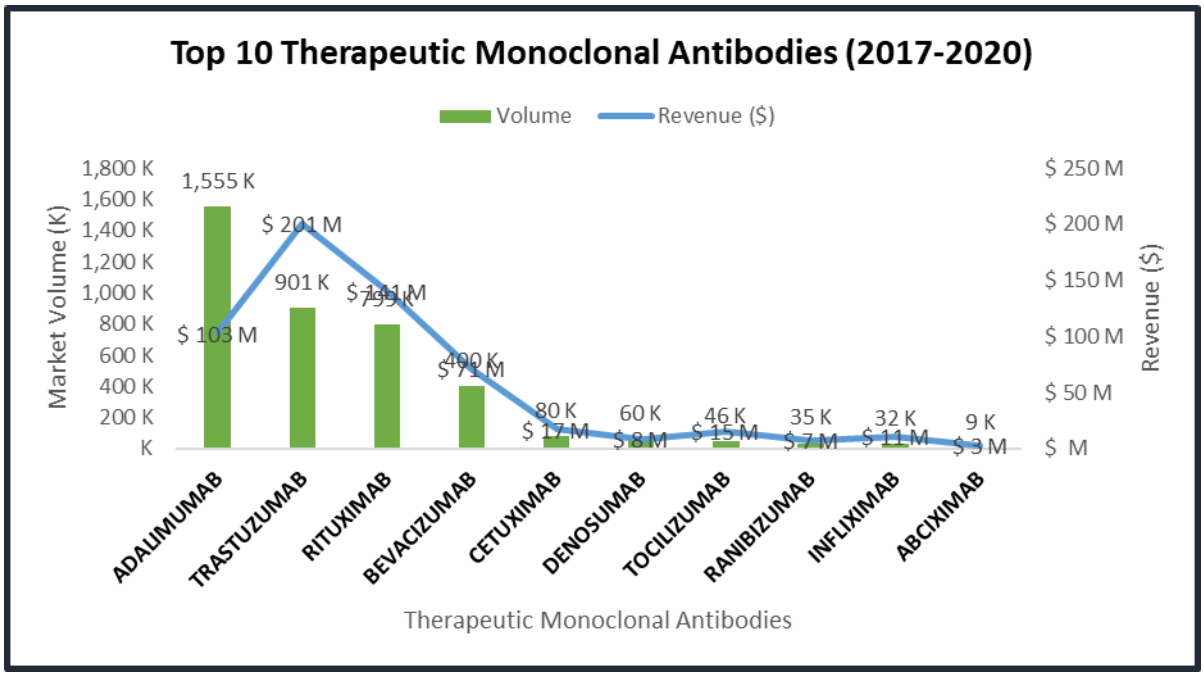

Chart 4 Market size (volume & revenue) analysis of top 10 therapeutic monoclonal antibodies from year 2017 to 2020.

5. Analysis of top 5 therapeutic monoclonal antibodies and their market volume and market value respective with manufacturing companies for year 2020 in domestic sales.

5.1. Domestic market analysis of top companies for overall sales of Adalimumab.

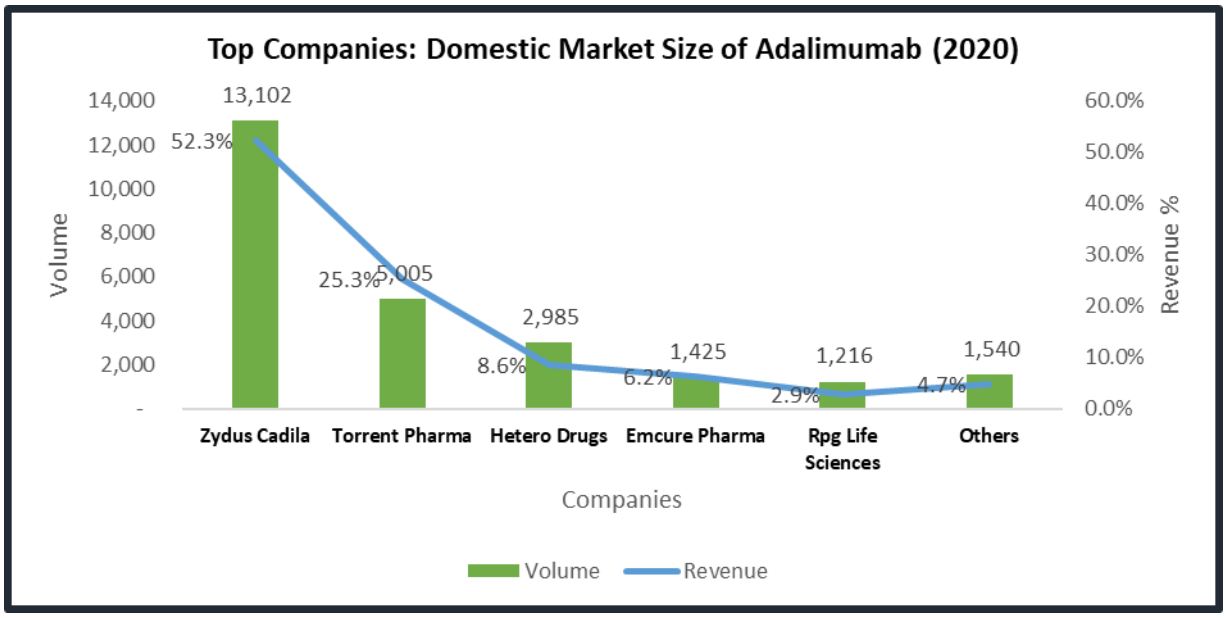

Chart 5 Adalimumab top companies and their market volume and market value.

5.2. Adalimumabs' brands retail price analysis respective with companies in Indian domestic market.

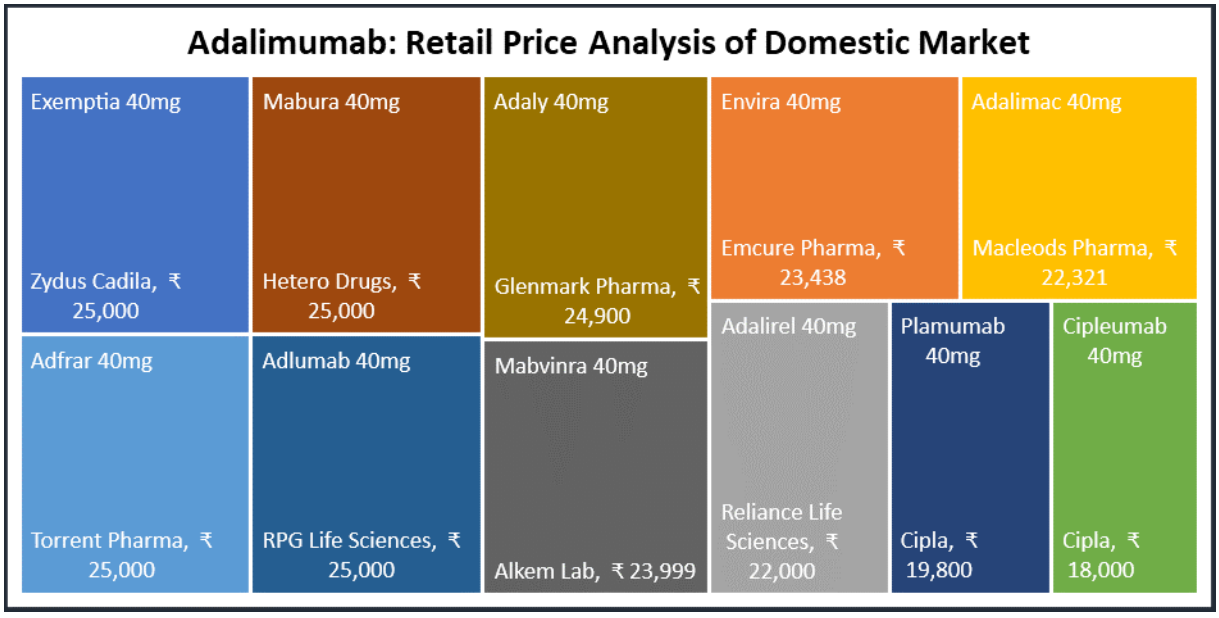

Chart 6 Adalimumab's brands retail price analysis with their companies in domestic market.

5.3. Domestic market analysis of top companies for overall sales of Trastuzumab.

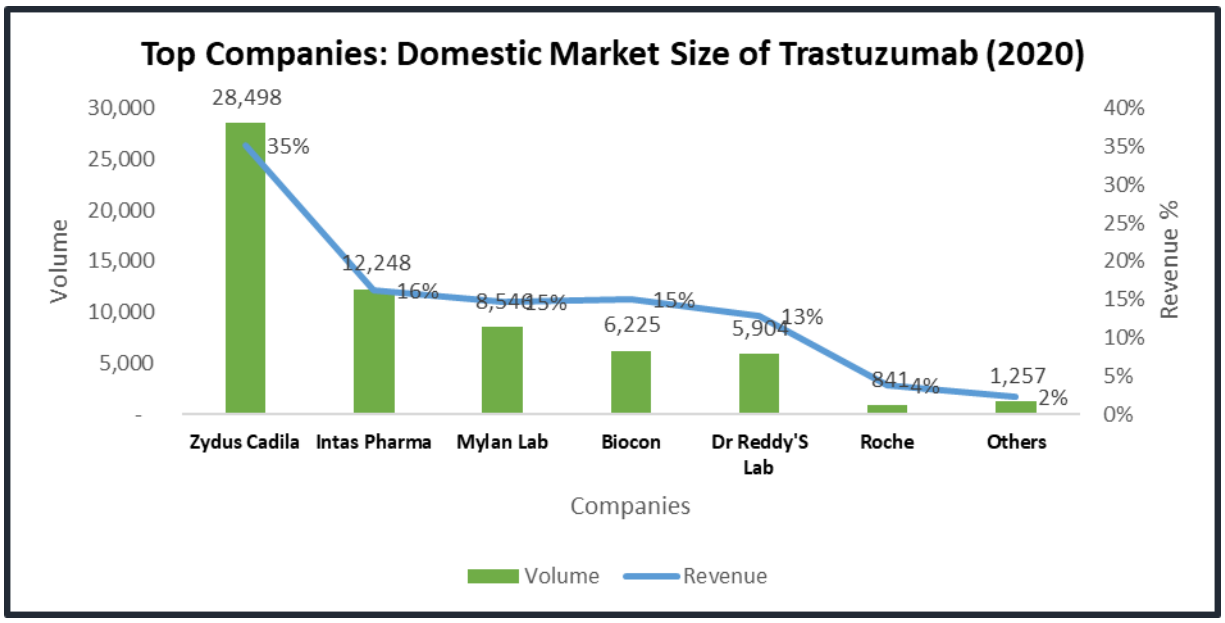

Chart 7 Trastuzumab top companies and their market volume and market value.

5.4. Trastuzumabs' brands retail price analysis respective with companies in Indian domestic market.

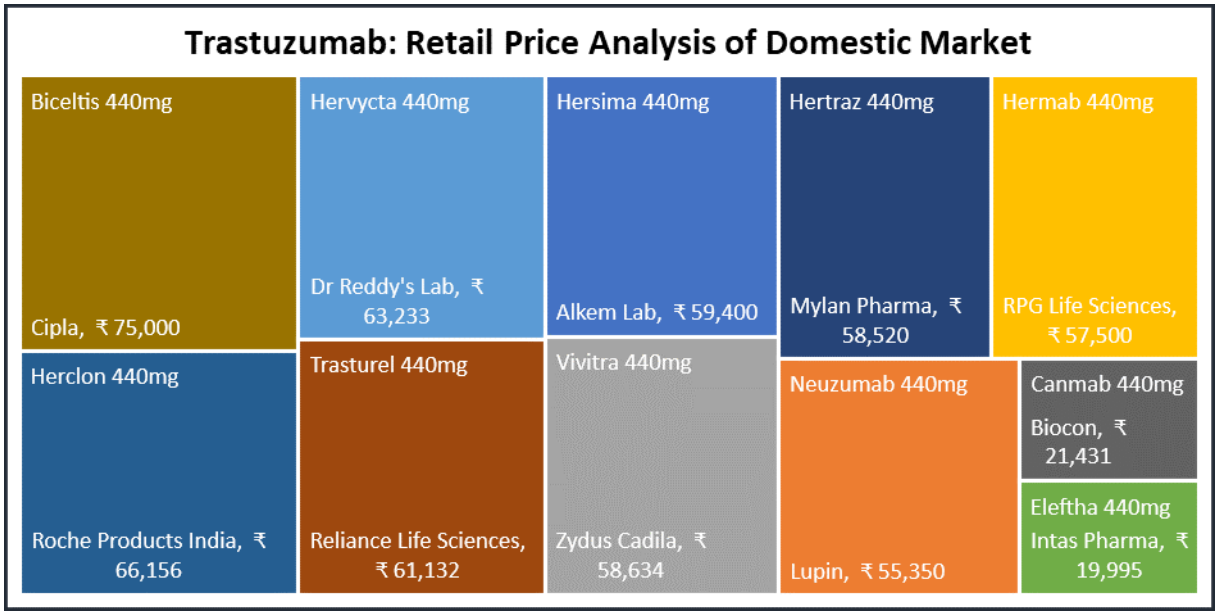

Chart 8 Trastuzumabs' brands retail price analysis with their companies in domestic market.

5.5. Domestic market analysis of top companies for overall sales of Rituximab.

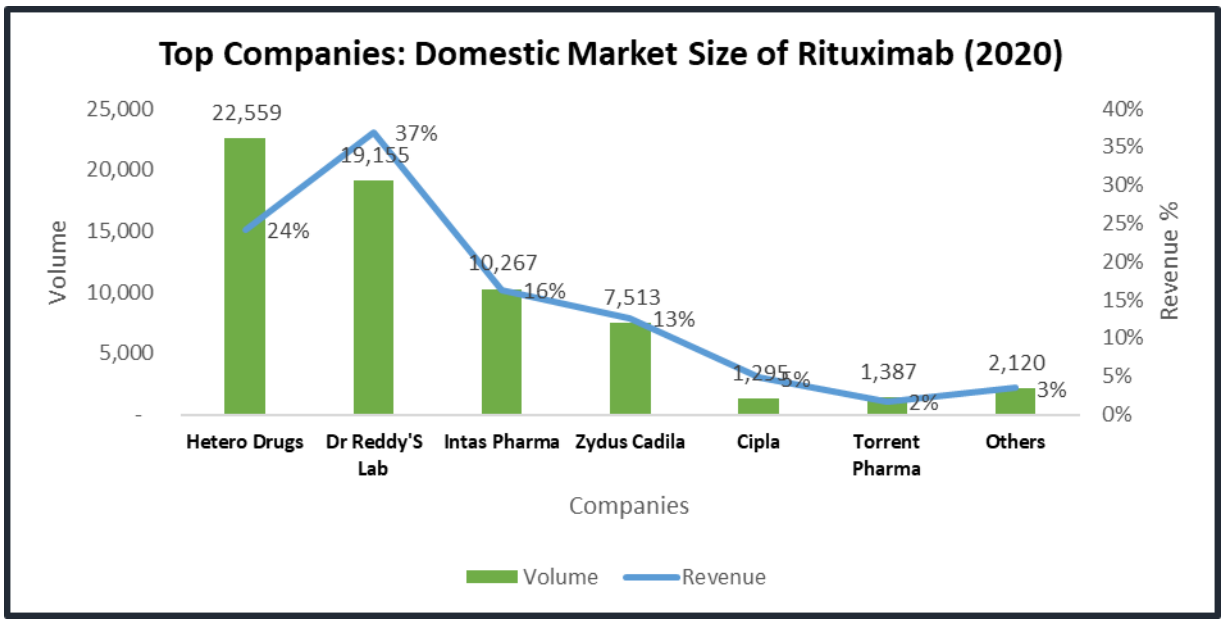

Chart 9 Rituximab top companies and their market volume and market value.

5.6. Rituximabs' brands retail price analysis respective with companies in Indian domestic market.

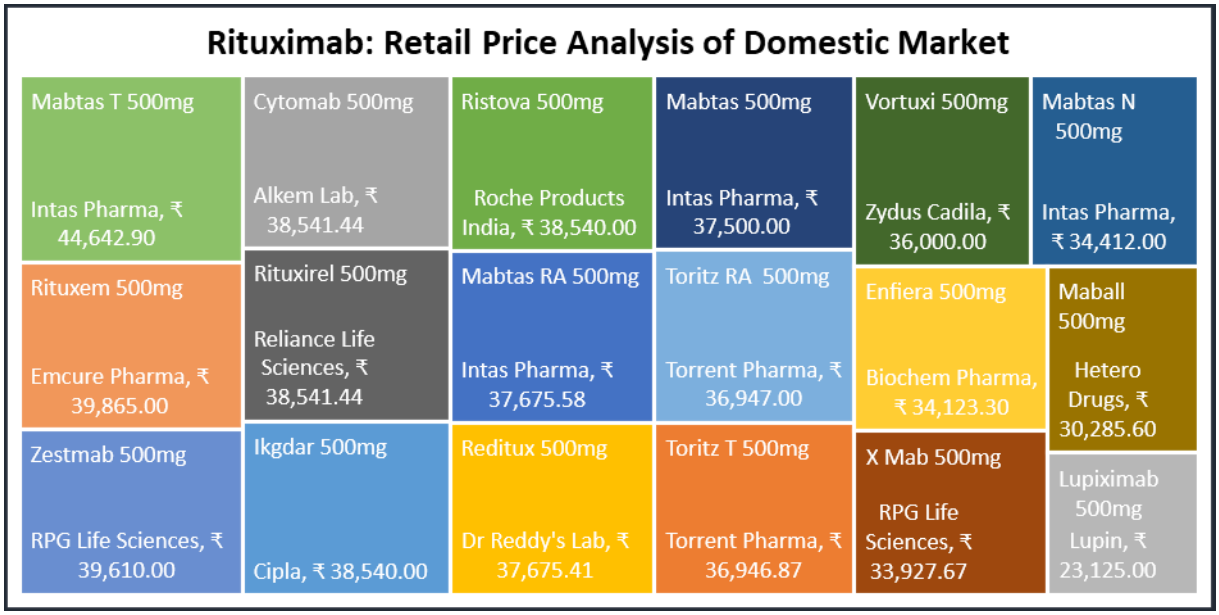

Chart 10 Rituximabs' brands retail price analysis with their companies in domestic market.

5.7. Domestic market analysis of top companies for overall sales of Bevacizumab.

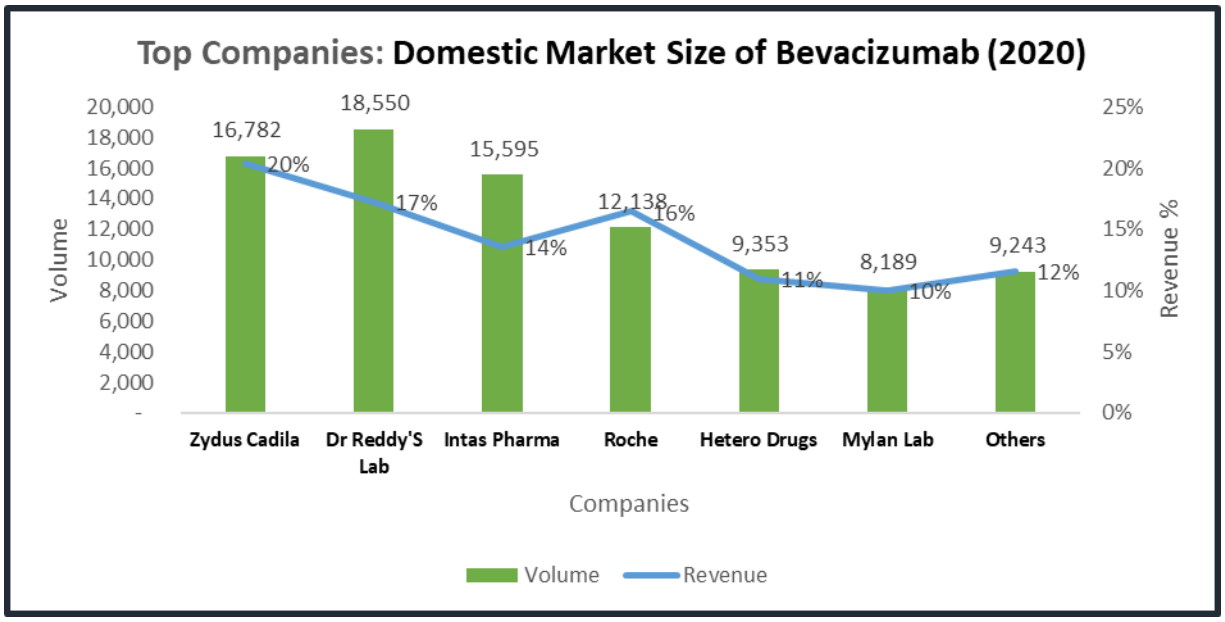

Chart 11 Bevacizumab top companies and their market volume and market value.

5.8. Bevacizumabs' brands retail price analysis respective with companies in Indian domestic market.

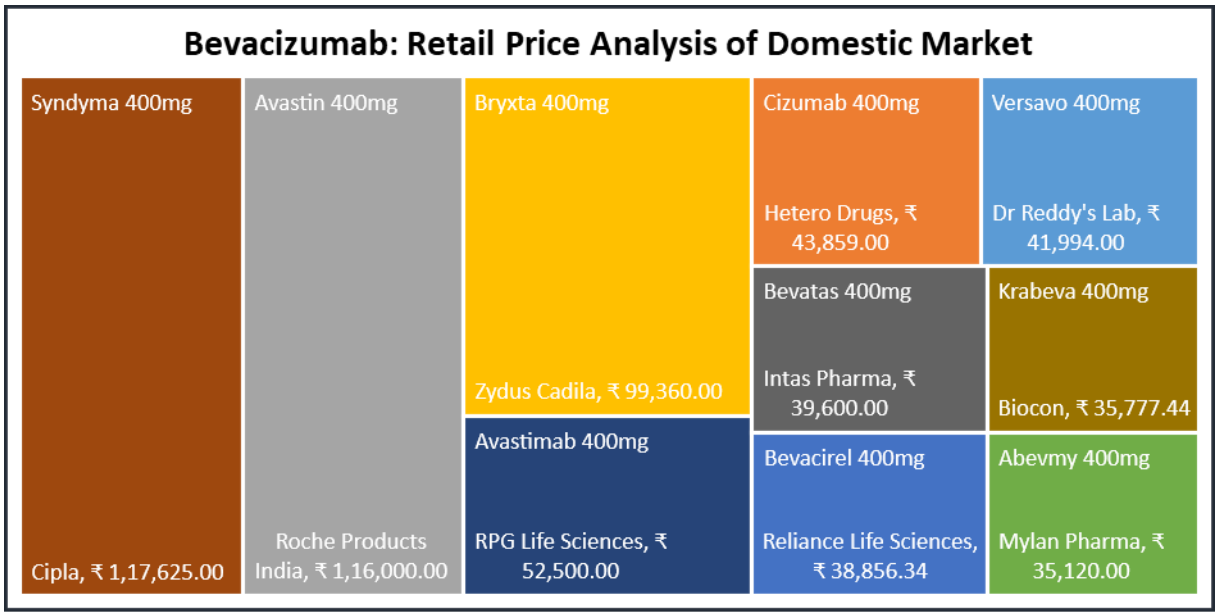

Chart 12 Bevacizumabs' brands retail price analysis with their companies in domestic market.

5.9. Domestic market analysis of top companies for overall sales of Denosumab.

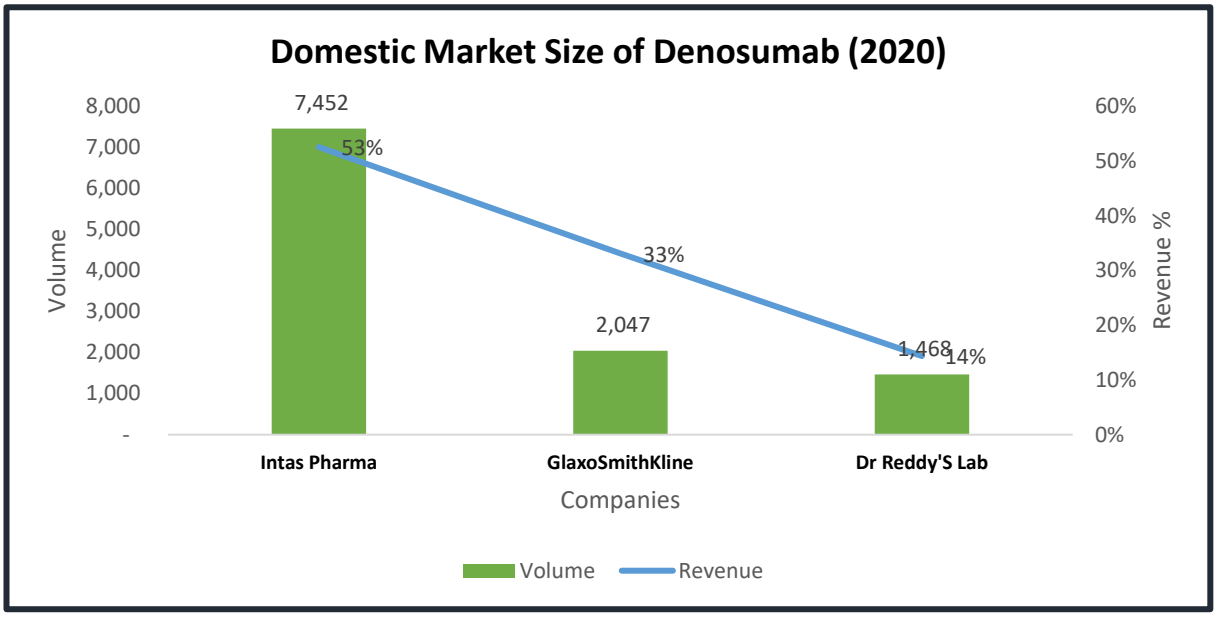

Chart 13 Denosumab top companies and their market volume and market value.

5.10. Denosumabs' brands retail price analysis respective with companies in Indian domestic market.

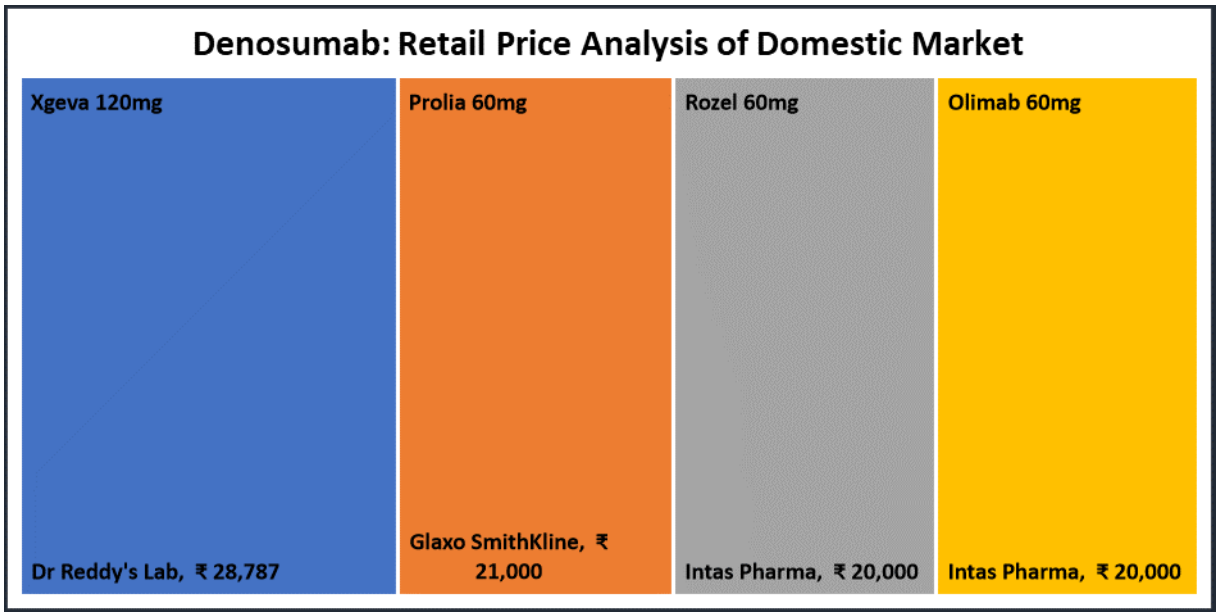

Chart 14 Denosumabs' brands retail price analysis with their companies in domestic market.

Chapter 6: Discussions

Therapeutic monoclonal antibodies are lab-made proteins that can bind to cells. Several monoclonal antibodies are available. They are used to treat some types of cancer. They can be used alone or to deliver drugs, toxins, or radioactive substances directly to diseased cells. Chart 1 shows the revenue in India by sales of therapeutic monoclonal antibodies from 2017 to 2023. India earned money from exports and domestic markets. The total market value of monoclonal antibodies for treatment in 2017 was $ 77 million, and the market value in 2020 is $ 228 million. From 2017 to 2020, India's therapeutic monoclonal antibody market grew at a rate of 44%, the domestic market grew at a rate of 15%, and exports grew at a rate of 100%. India exported about $ 137 million in mAbs in 2020. India exports a huge amount of biosimilars.

The use of monoclonal antibodies is increasing at a very rapid rate as the future is the biopharmaceutical and biosimilar market. The market value of MAbs is projected to reach $ 349 million in 2023. The CAGR of monoclonal antibodies used as therapeutic agents from year 2020 to 2023 would be increases at a rate of 15%. The export growth rate would be high as 17%, and the domestic market would see an average annual growth rate of 13%.

Indian Monoclonal Antibodies grew significantly from 2017 to 2020. In addition, sales of monoclonal antibodies in the domestic market are increasing year by year as the number of patients with cancer, bone disease, blood disease, etc. increases. With an increasing number of patients with high-acquaintance disease and cancer, this therapeutic monoclonal antibody provides the best results in terms of treatment, safety, and efficacy.

Sales and revenues in the therapeutic monoclonal antibody market are generated from the first export market and second domestic market. Chart 2 shows the main sales volumes and market value generated by the export market is higher than the domestic market in the year 2020. The export market size of monoclonal antibodies is 80%, and the domestic market size is 20% overall. Total revenue earning from exports of monoclonal antibodies is as high as 60%, while domestic markets total 40%. As a result, the export market size of monoclonal antibodies in 2020 is larger than the domestic market.

There are three types of therapeutic monoclonal antibodies in terms of manufacturing: human, humanized, and chimeric. Chart 3 shows the following figure. Total production by 'human' is 41%. The revenue earn from this is 20%. Mass production by ‘Humanized’ totals 36%, while revenue from ‘Humanized’ totals 52%. Mass production by ‘Chimeric’

is 23%, while revenue totals 28%. Most of the monoclonal antibody is manufactured by Human, and the largest revenue obtained by Humanized.

Chart 4 shows the top 10 therapeutic monoclonal antibodies from 2017 to 2020 were adalimumab, trastuzumab, rituximab, bevacizumab, cetuximab, denosumab, tocilizumab, ranibizumab, infliximab. Adalimumab's market volume is about 1,555 thousand, with revenues of $103 million. Trastuzumab's market size are about 901 thousand and revenue is 201 million dollars. The market size of rituximab is about 799 thousand and the revenue is 141 million dollars. Bevacizumab has a market size of about 400 thousand and a revenue of $71 million. The market size of cetuximab is about 80 thousand with sales of $17 million. Denosumab's market size is 60 thousand and revenue is $8 million. Tocilizumab's market size is about 46 thousand and revenue is $15 million. As a result, the market size of adalimumab is highest where the unit price is lower, and the revenues generated by trastuzumab are higher than that of adalimumab.

Chart 5 shows the results that in year 2020, the top five players in the domestic market for adalimumab are Zydus Cadila, Torrent Pharma, Hetero Drugs, Emcure Pharma and RPG Life Sciences. In the domestic market of adalimumab, the sales volume of Zydus Cadila is 13,102, and the profit from it is 52.3%. The company maintains the top position in quantity and sales in the domestic market of adalimumab. In the domestic market of adalimumab, Torrent Pharma's sales volume is 5,005, and the revenue from it is 25.3%, ranking second in the domestic market of adalimumab.

Chart 6 shows that there are 11 brands of adalimumab manufactured by 10 companies in the domestic market. The highest price of the manufactured brand is Exemptia40mg manufactured by Zydus Cadila at a price of Rs 25,000. Cipla manufactures two brands: Plamumab 40mg for Rs 19,800 and Ciplemumab 40mg for Rs 18,000. Therefore, the overall price range of all brands of adalimumab in the domestic market is between Rs 25,000 to Rs 18,000.

Chart 7 shows that the top 5 competitors for trastuzumab in 2020 are Zydus Cadila, Intas Pharma, Mylan Lab, Bicon and Dr Reddy`s Lab. In the domestic market of trastuzumab, the sales volume of Zydus Cadila is 28,498, with a revenue of 35%. The company has the best amount and revenue in the overall market for trastuzumab in the domestic market for trastuzumab. In the domestic market of trastuzumab, Intas Pharmaceuticals' sales volume is 12,248, with a revenue of 16%, ranking second.

The domestic market for trastuzumab has 11 brands manufactured by 11 different companies. Chart 8 shows that all brands are Biceltis, Hervycta, Hersima, Hertraz, Hermab, Herclon, Trasturel, Vivitra, Neuzumab, Canmab and Eleftha. Companies are Cipla, Dr Reddy`s Lab, Alkem Lab, Mylan Pharma, RPG Life Sciences, Roche Products India, Reliance Life Sciences, Zydus Cadila, Lupin, Bicon, Intas Pharma. The highest price of the manufactured brand is Biceltis manufactured by Cipla at a price of 75,000 rupees. The second highest produced brand Herclon 440mg is being manufactured by Roche Products India at a price of 66,156 rupees. Eleftha is manufactured by Intas Pharma at Rs 19,995. Therefore, the overall price range of all brands of trastuzumab is between Rs 75,000 and Rs 19,995.

Chart 9 shows that the domestic market of the leading companies of Rituximab are Zydus Cadila, Intas Pharma, Dr Reddy's Lab, Hetero Drug, Cipla and Torrent Pharma. The volume of Hetero Drugs on the domestic market of Rituximab is 22,559 and sales generated is 24%. The company holds the highest rank of volumes and revenue in Rituximab's domestic market. The volume of Intas Pharma on the domestic market of Rituximab is 10,267 and the turnover generated is 16%.

Chart 10 describes selling price analysis of Rituximab in domestic market. There are 18 brands that are manufactured by 13 different companies. The brand of the highest price is Mabtas T 500mg from Intas Pharma at a price of 44,642 rupees. The second high price brand is Rituxem 500mg, produced by Emcure Pharma for 39,865 rupees. Lupiximab 500 mg of Lupin is 23,125 rupees, the lowest brand price. Therefore, the general price range of all rituximab brands is within 44,642 to 23,125 rupees.

The domestic markets for the top Bevacizumab companies in 2020 are Zydus Cadila, Intas Pharma, Mylan Lab, Hetero Drugs, Dr Reddy`s Lab and Roche. Chart 11 shows that Bevacizumab has a market volume of 16,782 and a revenue of 20% in the domestic market of Zydus Cadila. Zydus Cadila ranks highest in Bevacizumab's domestic sales. In the domestic market of Bevacizumab, Intas Pharma has a market volume of 15,595 and a revenue of 14%.

Chart 12 shows an analysis of retail prices in the Bevacizumab domestic market. There are 10 brands manufactured by 10 other companies. The highest priced brand is Syndyma 400mg manufactured at Cipla's Rs 1,17,625 price. The second highest price brand, Avastin 400mg, is manufactured from Roche Products at a price of Rs 1,16,000. Bryxta 400mg is manufactured at Zydus Cadila at Rs 99,360 price. Mylan Pharma's Abevmy

400mg is Rs 35,120, lowest price. Therefore, the overall price range for all brands of bevacizumab is between Rs 1,17,625 and Rs 35,120. In year 2020 the domestic market of Denosumab’s top companies are Intas Pharma, Glaxo SmithKline, & Dr Reddy’s Lab.

Chart 13 shows that Intas Pharma's sales volume was 7,452 and its revenue was 53% in the domestic market of Denosumab. The company maintains the top position in volume and revenue in the Denosumab domestic market. In the domestic market of Denosumab, the sales volume of Glaxo SmithKline is 2,047 and the profit is 33%. Dr Reddy`s Lab has a volume of 1,468, which yields a return of 14%.

Chart 14 shows that there are 4 brands manufactured by 4 different companies in the Denosumab domestic market. The highest price brand is the Xgeva 120mg manufactured by Dr Reddy`s Lab at a price of Rs 28,787. The second highest price manufacturing brand, Prolia 60mg, is manufactured by Glaxo SmithKline at a price of Rs 21,000. Intas Pharma manufactures two brands, Rozel 60mg for Rs 20,000 and Olimab 60mg for Rs 20,000. Therefore, the full price range of all brands is between Rs 28,787 and Rs 20,000.

Chapter 7: Conclusion

India's therapeutic monoclonal antibody market grew at a rate of 44%, the domestic market grew at a rate of 15%, and exports grew at a rate of 100%. India exported about $ 137 million in mAbs in 2020. India exports a huge amount of biosimilars. The market value of MAbs is projected to reach $ 349 million in 2023. The CAGR of monoclonal antibodies used as therapeutic agents from year 2020 to 2023 would be increases at a rate of 15%. Most of the monoclonal antibody is manufactured by Human, and the largest revenue obtained by Humanized. The top 10 therapeutic monoclonal antibodies from 2017 to 2020 were adalimumab, trastuzumab, rituximab, bevacizumab, cetuximab, denosumab, tocilizumab, ranibizumab, infliximab. The market size of adalimumab is highest where the unit price is lower, and the revenues generated by trastuzumab are higher than that of adalimumab. In year 2020, the top five players in the domestic market for adalimumab are Zydus Cadila, Torrent Pharma, Hetero Drugs, Emcure Pharma and RPG Life Sciences. There are 11 brands of adalimumab manufactured by 10 companies in the domestic market. The highest price of the manufactured brand is Exemptia40mg manufactured by Zydus Cadila at a price of Rs 25,000. The overall price range of all brands of adalimumab in the domestic market is between Rs 25,000 to Rs 18,000. The sales volume of Zydus Cadila is 28,498, with a revenue of 35%. The company has the best amount and revenue in the overall market for trastuzumab in the domestic market for trastuzumab. The overall price range of all brands of trastuzumab is between Rs 75,000 and Rs 19,995. Monoclonal antibodies (mAbs) have been one of the fastest-developing class of pharmaceutical drugs. As greater ability objectives are diagnosed thru a more expertise of molecular mechanisms underlying disease, it gives possibilities for the improvement of recent mAb-primarily totally based drugs. Key regions have covered most cancers, immunotherapy, inflammatory diseases, and autoimmune diseases.

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