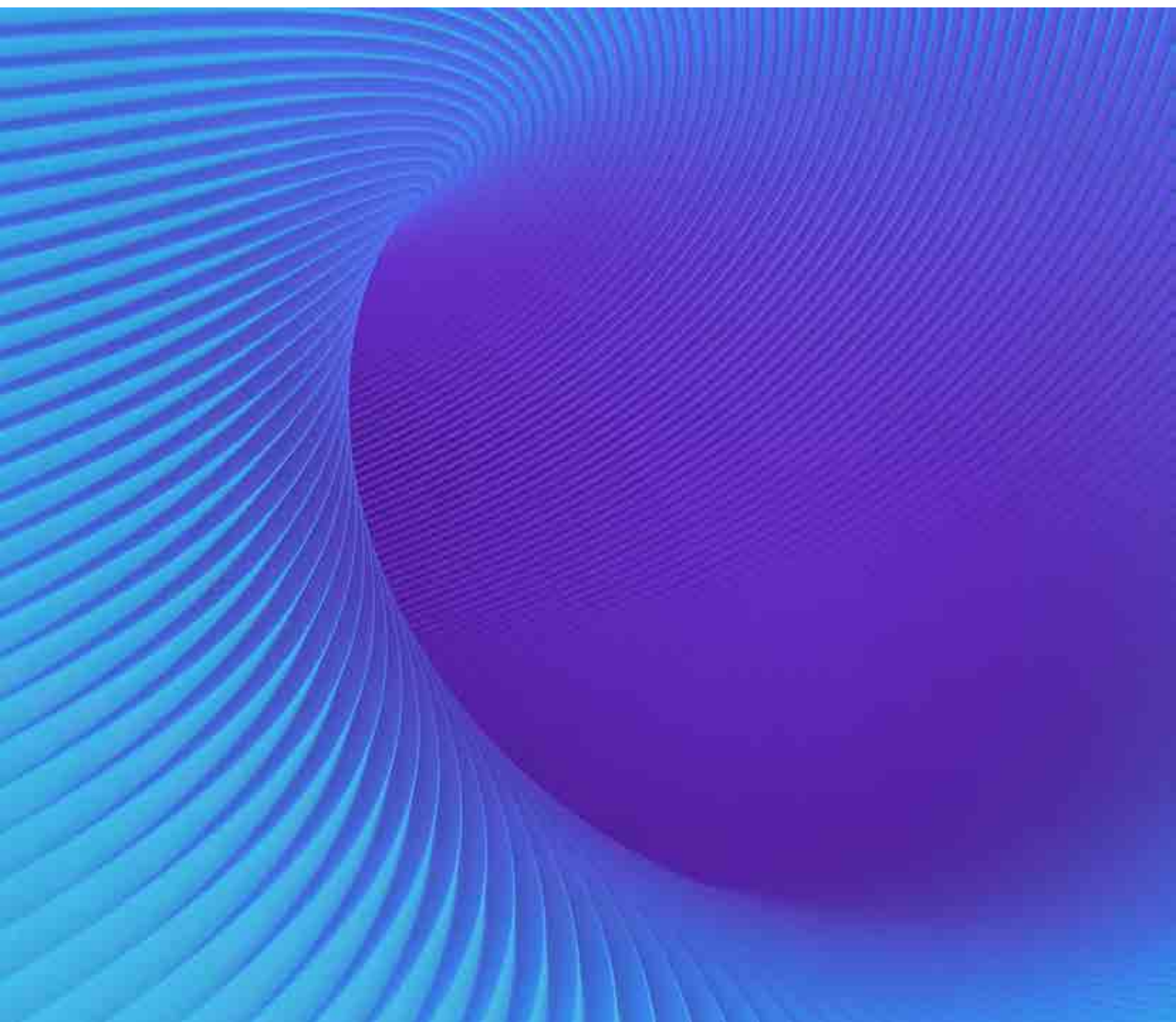




Biotechnology Industry Research Assistance Council  
(A Govt. of India Enterprise)

Special report

# India: The emerging hub for biologics and biosimilars



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# **Global Bio-India 2019** **Power to Transform Lives**

November 21- 23, 2019

# Foreword



**Dr. Renu Swarup**

Secretary, Department of Biotechnology

Ministry of Science & Technology, Government of India

India is predicted to be one of the world's 'fastest-growing bio-hub' in recent years. India's growing biosimilars industry is the primary driver of growth, with respondents citing 'India's rising domestic demand, bio investments, and the potential for increased exports to advanced markets.' India has over 95 approved biosimilars in the domestic market more than any other country and market penetration, which is currently relatively low and is expected to increase quickly in coming years with the increase in demand by middle class. The pipeline for biosimilars in India is also robust, in part fueled by the Indian government's initiative to offer subsidies to Indian biosimilar manufacturers, and the expiration of existing biologics patents and India's Central Drugs Standard Control Organisation aligning guidelines closely with global regulators including US FDA, MHRA and others. Recent reports indicate, that more than 40 biosimilars were in the clinical development stage in India which is a similar number to those in development in the European Economic Area (EEA), and far more than in development in the United States.

Department of Biotechnology (DBT) and its public sector enterprise Biotechnology Industry Research Assistance Council (BIRAC) have made sustained efforts through funding, policy advocacy, new initiatives, capacity building, human resource development, promoting innovation and infrastructure creation in Research Institutions, Small and Medium size Industries, Large Industries as well as nurturing emerging enterprises. National BioPharma Mission a joint initiative of World Bank and DBT is further strengthening the base in the country. Collectively, these initiatives are well placed to catapult Indian Biotech Sector in the next growth phase.

I see that there is a great potential for Indian Biotech Sector to become a global hub for manufacturing of biologics; innovating globally competitive, novel, affordable - vaccines, biosimilars and advanced immunotherapeutics, that is accessible to all for India and the World.



## India: The emerging hub for biologics and biosimilars

“India’s emerging biopharma sector aims to emulate the global leadership of generic drugs and vaccines with Biosimilar Biologics with a focus on providing affordable access through technology innovation coupled with economies of scale. Over the past decade India has seen the largest number of approved Biosimilars which are serving the needs of patients globally. The Biopharma sector has delivered a robust 5 year CAGR of greater than 50% and is the fastest growing healthcare segment. The Department of Biotechnology along with the Ministry of Health have built an enabling foundation with a clear regulatory pathway that assures safe and efficacious Biosimilars with an underlying objective of being the most affordable in the world. Many of these are being supplied to the highly regulated and advanced markets of North America, Europe and Japan. With the advent of Ayushman Bharat, India’s Universal Healthcare program, these life transforming Biosimilars are now accessible to the poorest patients in our country afflicted with cancer, diabetes and other immune mediated diseases. Global Bio India provides a showcasing platform for India’s growing stature as an emerging hub for Biologics and Biosimilars.”

Kiran Mazumdar-Shaw, Chairperson & Managing Director, Biocon Limited

“Serum Institute of India, in addition to the 24 already WHO pre-qualified vaccines, is focused on significant investment in disease elimination with global access strategies by developing new vaccines like PCV, HPV, Malaria, rBCG, and biosimilars as well as novel monoclonals for treatment of Dengue, HIV, Antimicrobial resistance and recombinant Anti-snake venom with strong support from the Govt. of India through Dept. of Biotechnology, Ministry of Health and Indian Council of Medical Research by effective translation through seamless regulatory and funding processes.

India’s growing contribution and heft in the health sector through novel technologies and innovative science, supported by economies of scale and cutting edge manufacturing infrastructure to drive new frontiers in health science will be showcased by Global Bio India.”

Dr. Cyrus S. Poonawalla, Chairman and Managing Director, Serum Institute of India

# India: The emerging hub for biologics and biosimilars

**“India is on the cusp of a biotech revolution. We have already embarked on building world class manufacturing facilities wherein just like generics we would be the high quality and affordable biosimilar producer for the world.”**

Dr. Cyrus Karkaria, President – Biotechnology, Lupin limited

**“India’s BioPharma sector has emerged as a key global player offering numerous advantages in terms of faster market entry, skilled manpower, large captive consumption due to burgeoning population and facilitation provided by the Government of India thus enabling it to compete with major players in the Industry.**

**With an experience of 15 years in the Biopharma sector, USV is now vertically integrated for which it has made substantial investment to develop and manufacture products that meet Regulatory requirement of all major markets.”**

Prashant Tewari, Managing Director, USV

**“Innovation in bio-manufacturing technologies are critical for the success of the Indian Biotech Industry and Gennova has made significant in-roads in this space. Global Bio India is going to provide a forefront space for discussion between researchers, industry players, regulators and policymakers to define the future of Indian Bio-economy.”**

Sanjay Singh, Ph.D., Chief Executive Officer, Gennova Biopharmaceuticals Ltd

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# Introduction

The global life science industry is facing a shift from chemical-based drugs to biologics and biosimilars. While biosimilars received their first approval in the EU in 2006 and in the United States in March 2015<sup>1</sup>.

India approved its first biosimilar in as early as 2000. Now India leads with over 98 biosimilars approved till September 2019 (source: CDSCO). Approvals of biosimilars in regulated markets have further motivated Indian pharma companies to invest in the large and growing biosimilars market to increase their market share globally. Additionally, product patents of more than 10 blockbuster biologics with total revenue of USD 60bn are set to expire within two to three years, providing a further boost to the biosimilars market.<sup>2</sup>

**Table 1: Biologics and Biosimilars approved in India (2014 – 2018)**

Year	Biologics (r-DNA derived drug product)	Biosimilars (r-DNA derived drug product)
2019	01	03
2018	42	18
2017	17	05
2016	24	08
2015	28	15
2014	23	12
98 biosimilars have been approved in India till date		

Source: Biologics Division, CDSCO

In response to the high commercial potential and the need for development of indigenous drugs to cater to the large Indian population pool, the Government of India has taken steps to encourage India's development as a hub for biotechnology-based drugs.

The Department of Biotechnology (DBT) and Biotechnology Industry Research Assistance Council (BIRAC) are working in close collaboration with the industry and academia on multiple initiatives to promote research and manufacturing in biotechnology-based drugs. Initiatives include:

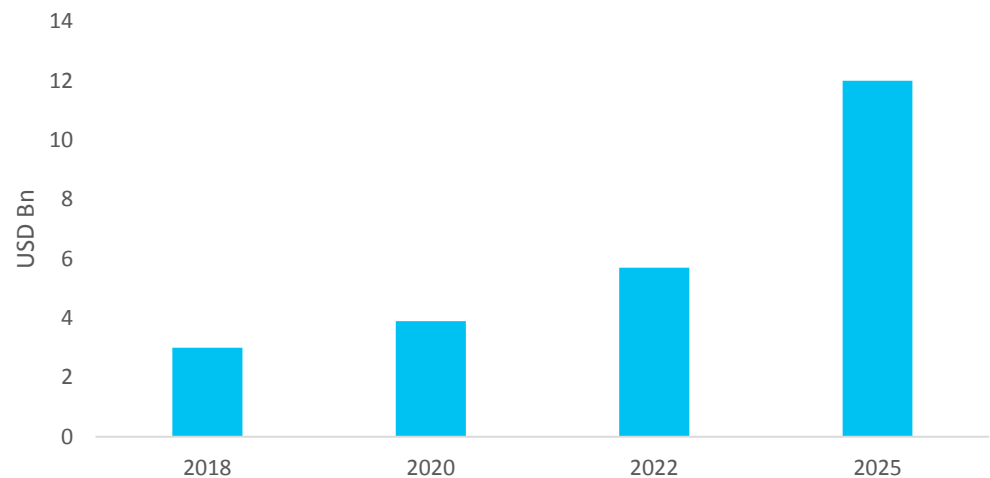
- New policies to ease business development
- Revised Guidelines of Similar Biologics released by DBT & Central Drugs Standard Control Organization (CDSCO) on 15<sup>th</sup> August 2016 have simplified the regulatory pathway to enable faster approvals, cGMP manufacturing processes assuring safety, efficacy, and quality
- Skill development and infrastructure capacity building for research in novel biologics and biosimilars
- Promotion of entrepreneurship and start-ups through National Biopharma Mission, and partnerships with national research and academic institutions and incubators

The number of approvals in India in the last 5 years represent a robust opportunity for biologics and biosimilars. Association of Biotechnology Led Enterprises (ABLE) in India estimates the size of the broader economic impact for biologics, biosimilars and vaccines, to grow at a compounded annual growth rate (CAGR) of 22% to become USD 12bn by 2025.

Contract research services in early discovery and clinical development for biologics and biosimilars in India is estimated to be USD 200Mn and growing at a CAGR of 40% (source: ABLE).

The current push for R&D in biotechnology research will establish India as one of the top biotechnology destinations across the globe.

**Figure 1: Market size for Biologics, Biosimilars, and Vaccines in India**



Source: ABLE

NOTE: Market size includes indigenous manufacture, import and exports from India

## Changing dynamics of the pharmaceutical market

### Small molecule therapeutics vs biologics

Small molecule therapeutics have inherent advantages such as their low molecular weights (0.1 - 1 kDa); tendency to be chemically and thermally stable; wide range of polarity; and ability to bind with targets like G-protein-coupled receptors (GPCRs), ligand-gated ion channels and receptor tyrosine kinases. They can access targets in intracellular regions, cytosols, nuclei and even CNS targets, separated by the tight blood-brain barrier (BBB), which are not accessible to biologics due to the large size. Additionally, most are suitable for oral delivery and have a simpler drug discovery/development process.

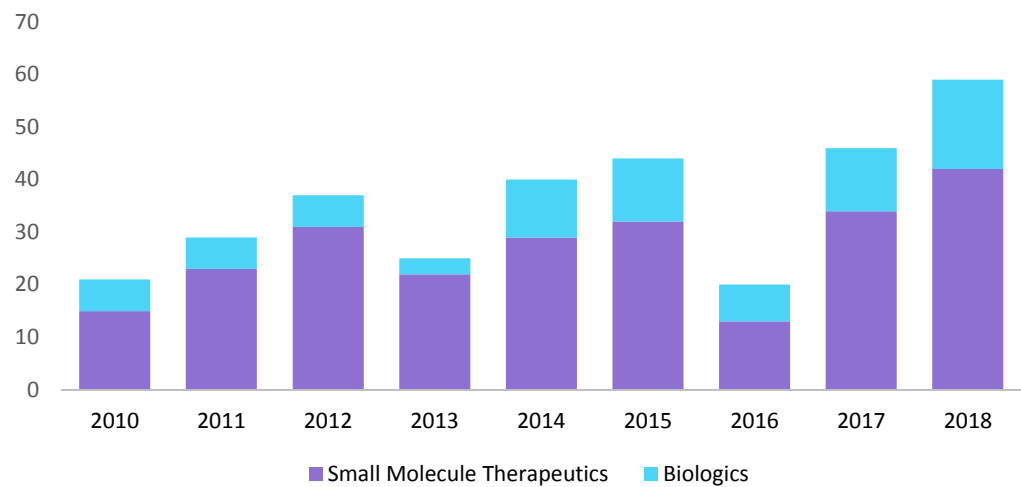
Biologics on the other hand are excellent for targeted delivery and less prone to drug-drug interactions, but have complex structures and less stability.<sup>3</sup>

The advent of the first biologic drug 'humanized insulin' in the 1980s introduced a new era in the pharmaceutical industry. Biologics development began with large peptides and recombinant proteins, but now include a wide range of other entities, such as antibodies, monoclonal antibodies, and more recently, nanobodies and related objects, soluble receptors, recombinant DNA, antibody-drug conjugates (ADCs), fusion proteins, immune-therapeutics and synthetic vaccines. Pharmaceutical industry analysts and investors are focusing more on the biologics industry, which remains relatively nascent when compared to 100+ years of the small molecule therapeutics' industry. This interest is largely due to the commercial potential, physicians' preference and enhanced patient compliance for biologics. New entrant biologics and this alternative drug discovery regime pose a substantial business challenge to the established small molecule therapeutics discovery regime, which has defined the pharmaceutical industry so far.



Biologics also have significant untapped potential in disease areas such as asthma, allergy and dyslipidemia. There has been a surge in USFDA small molecule therapeutics and biologic license application (BLA) approvals of biologics in the last 8 years (2010-2018).<sup>4</sup>

**Figure 2: USFDA small molecule therapeutics/BLA approvals (2010-2018)**



Source: Cortellis Competitive Intelligence

The pharmaceutical market is changing rapidly as biologics gain major market share in terms of both revenue and total market, which was USD 200.6bn in 2013 and is expected to grow to USD 386.7bn by the end of 2019 at a compounded annual growth rate (CAGR) of 10.6%.<sup>5</sup>

Currently, the market for biologics is very condensed in terms of the number of indications in which they can be used, and is dominated by indications such as autoimmune diseases, oncology and diabetes, which have a high incidence and prevalence rate. Among these, oncology was valued at USD 136bn in 2018 and is estimated to be valued at USD 220bn by 2024, growing at a CAGR of 8.4%.<sup>6</sup> Top 10 biologics contribute to more than 35% of the total biologic market, whereas top 20 small molecules contribute to ~20% of the small molecule therapeutics market. Oncology dominated the biologic market as a result of a high number of strong launches into high unmet-need indications. Leading molecules have generated substantial revenue in 2018 such as Humira (adalimumab – USD 20bn), Opdivo (nivolumab – USD 7.5bn), Keytruda (pembrolizumab – USD 7.2bn) and Revlimid (lenalidomide – USD 9.8bn).<sup>7</sup>

Considering the huge market potential and unmet clinical need, we expect growth to continue in the future.

## What are biologics and biosimilars

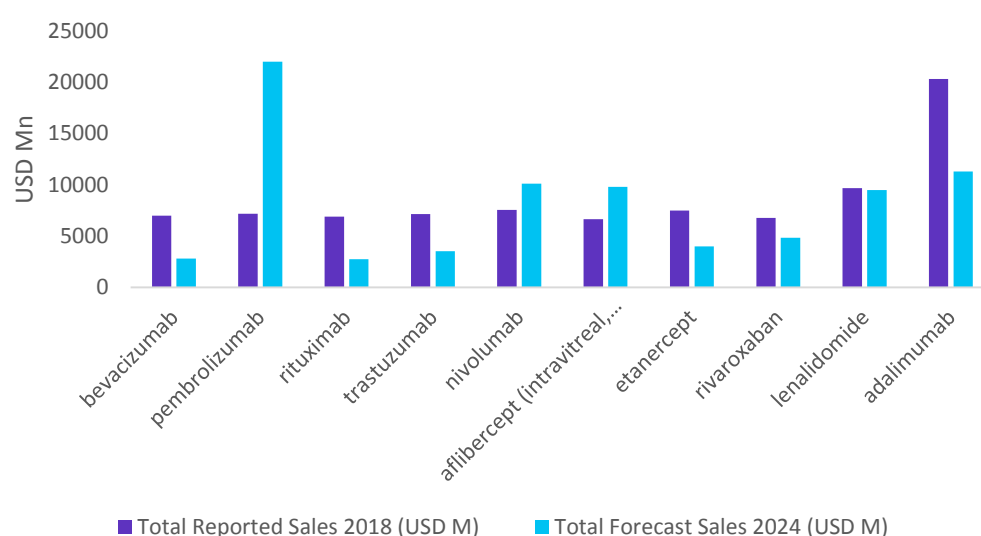
A biologic drug (biologics) is a product that is produced from living organisms or contains components of living organisms. Biologic drugs include a wide variety of products derived from human, animal or microorganisms using biotechnology. Follow-on-biologics and biosimilars as a class of drugs have emerged as an effective alternative to reduce the cost of biologic therapies. A biosimilar is a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.<sup>8</sup> Biosimilars are highly like the reference product in terms of safety, purity and potency, but may have minor differences in clinically inactive components. We make a distinction between biosimilar and follow-on biologics in that biosimilars are slightly modified versions of the original biological molecule, whereas follow-on biologics are the same molecule by innovator post patent expiry.

## Innovation in biotechnology focused on biologics and biosimilars: need of the hour

Biologics are one of the fastest growing classes of therapeutic compounds, given their promise of targeted treatments for multiple conditions with reduced side effects. Biologics are forecasted to make up more than one fourth of the total revenue of the pharmaceutical market by 2020.<sup>9</sup> Biologics also offer less likelihood of the adverse side effects associated with small molecule therapeutics and invasive surgeries. Biologics have proven potential to treat a wide range of conditions, provided technological challenges are overcome. They can reach targets that were considered 'undruggable' using small molecule therapeutics and reduce side effects to increase patient compliance.

Research and innovation on pharmacologically active compounds originating from small molecule therapeutics has declined in the last decade due to lower profitability and fewer blockbuster small molecule candidates. Based on the sales data of 2018, out of the top 10 blockbuster molecules, only two were small molecule therapeutics and eight were biological

**Figure 3: Top 10 blockbuster molecules based on 2018 sales data**



therapeutic as shown in Figure 3.<sup>7</sup>

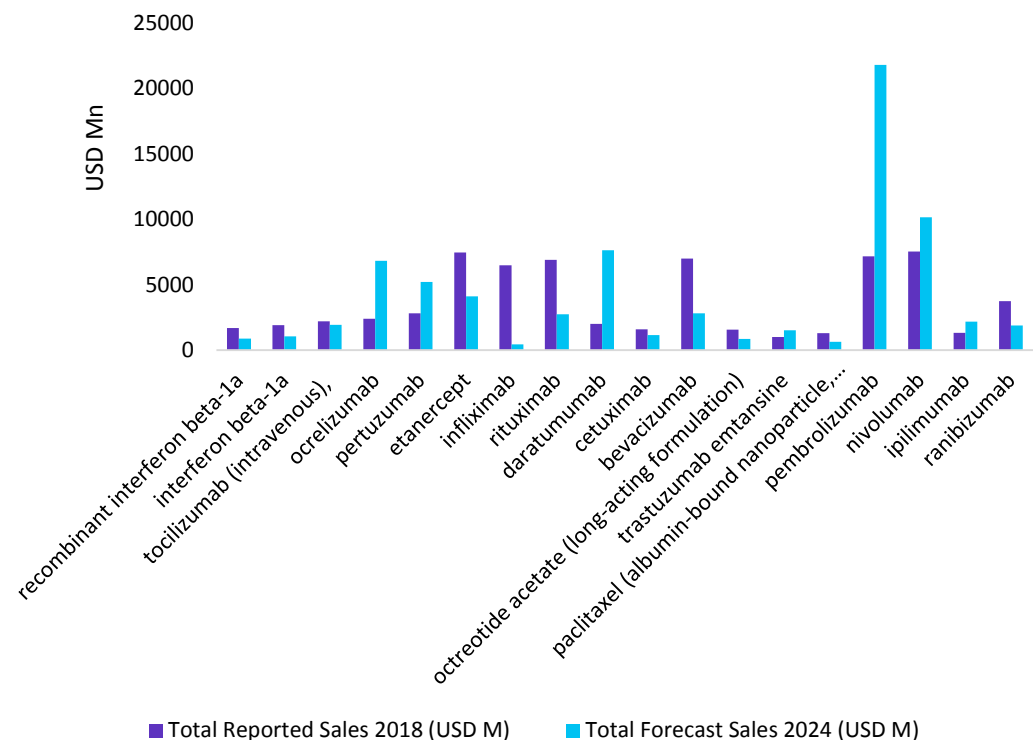
Source: Cortellis Competitive Intelligence

Novel research is now more focused on treating niche indications in homogeneous smaller patient groups. In the area of orphan diseases (defined by the USFDA to include rare diseases affecting fewer than 200,000 people)<sup>10</sup> three first-in-class drugs entered the market in 2018 with the potential to achieve sales of over USD 1bn by 2022. Roche/Chugai launched Hemlibra (emicizumab) for the treatment of hemophilia A with factor VIII inhibitors. For treatment of hereditary angioedema, Shire entered the market with lanadelumab. Alnylam and Genzyme also launched patisiran for treatment of hereditary transthyretin amyloidosis. Each of these orphan drugs is set to become the new standard of care in its respective disease area. Similar trends continued in 2019, when companies invested more in rare diseases, unmet needs and conditions with current treatments hampered by safety, efficacy, convenience or other issues.

Most of the targeted diseases were characterized by genetic disorder and/or excessive immune response (including autoimmunity). AveXis/Novartis's Zolgensma (onasemnogene abeparvovec) is an injectable gene therapy that uses a viral vector to introduce DNA for a functional SMN protein into a patient's cells; it is expected to generate sales of USD 2.09bn by 2023. Another niche indication is Paroxysmal nocturnal hemoglobinuria (PNH), which is a rare, potentially fatal blood disorder. Alexion's Ultomiris (ravulizumab) is a next-generation follow-up to its blockbuster PNH drug Soliris (eculizumab), which leveraged ultra-orphan drug pricing to achieve blockbuster sales of USD 3.14bn in 2017, and USD 3.78bn forecast for 2023. Bluebird bio's LentiGlobin (betibeglogene darolontivec) corrects the defect causing beta thalassemia, a blood disorder that causes life-threatening anemia, and is expected to generate USD 1.12bn.<sup>7</sup>

In addition to niche indications, biologics are of utmost importance for targeting widespread diseases with an increasingly higher incidence rate and profound implications. One such indication is cancer. Small molecule therapeutics are used for treatment but produce debilitating side effects because small molecules affect normal healthy cells along with target tumor cells. This limits tolerability and becomes a major concern for patients and physicians. In response, 171 biologics/biosimilars have been launched globally versus 151 small molecule therapeutics for treatment of different types of cancers. Examples of blockbuster biologics (reported sale > USD 1bn) for treatment of cancer are summarized in the following graph with current sales and sales forecast for 2024.<sup>7</sup>

**Figure 4: Sales of blockbuster biologics used in the treatment of cancer**



Source: Cortellis Competitive Intelligence

## Biologics vs biosimilars

As innovation increases, biologics are paving the way in the market but represent the most expensive of treatments. There is global consensus on the need to reduce the price of treatment. It is estimated that global biosimilars market opportunity would grow to over USD 70bn by 2027<sup>11</sup>. Biosimilars play a role parallel to generic drugs with respect to innovator small molecules, as they similarly enter the market after the monopoly period and are intended to drive down prices through competition.

Two competing filgrastims (one of which was a Biologics Price Competition and Innovation Act (BPCIA)-governed biosimilar) entered the United States market in 2013 and 2015 but merely flattened Neupogen's price trajectory. Despite the launch of biosimilars, Neupogen continued to retain the largest share of the filgrastim market due to inherent challenges with biosimilars such as the evolving regulatory environment and lack of automatic substitution. Infliximab (USD 3.6bn in sales in 2018) faced competition from a biosimilar entry to the market which was priced 15% less than branded infliximab (Remicade). It is estimated that prices may decline up to 20-30% as more biosimilars enter the market, leading to potential projected saving of ~USD 54bn in ten years (2017-2026). Similarly, in Europe, an average of 3.5% per year can be saved with biosimilars entry to the market.<sup>12</sup>

Though this percentage may seem low, it represents substantial savings given that annual treatment with biologics can reach USD 100,000 per patient per year. For example, Ilaris (canakinumab) costs between USD 379,000 and USD 462,000 per patient per annum in Sudden

Juvenile Idiopathic Arthritis. Similarly, Soliris (eculizumab), a monoclonal antibody that treats a rare, chronic blood disease called atypical hemolytic uremic syndrome (aHUS) and prevents the breakdown of red blood cells in people with paroxysmal nocturnal hemoglobinuria (PNH), costs more than USD 600,000 per patient, per year.

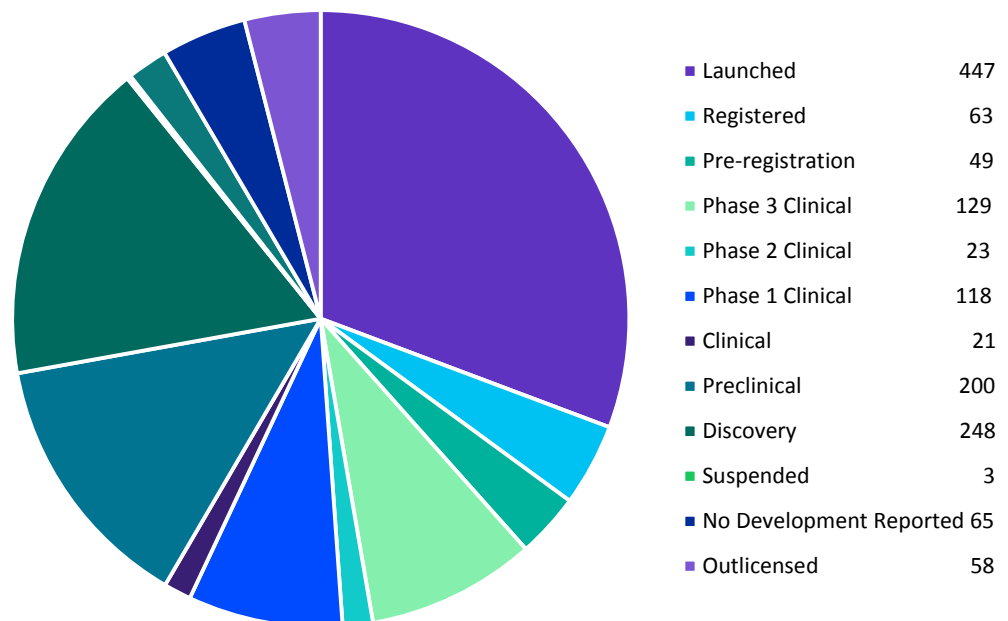
The substantial prices of novel biologics are expected to drive innovation and adoption of biosimilars, increasing competition and supporting price reduction and patient access. Advancements in scientific technology have expedited research and development of biosimilars, enabling improvements to biologics designed around 15 years ago. However, regulatory approvals and the time from regulatory approval to actual market entry of biosimilars remain challenges.

Neither of the two FDA-approved biosimilar competitors of Humira (adalimumab), Boehringer Ingelheim's Cyltezo (adalimumab-adbm) and Amgen's Amjevita (adalimumab-atto) have entered the market despite gaining regulatory approval. Amgen has announced a delay in the launch of its biosimilar in the United States until January 2023. Similarly, biosimilar Erelzi (etanercept-szzs) for Enbrel, Mvasi (bevacizumab-awwb) for Avastin, and Ogivri (trastuzumab-dkst) for Herceptin, are yet to enter the United States market although approved by FDA.

### Current environment for development of follow-on biologics and biosimilars

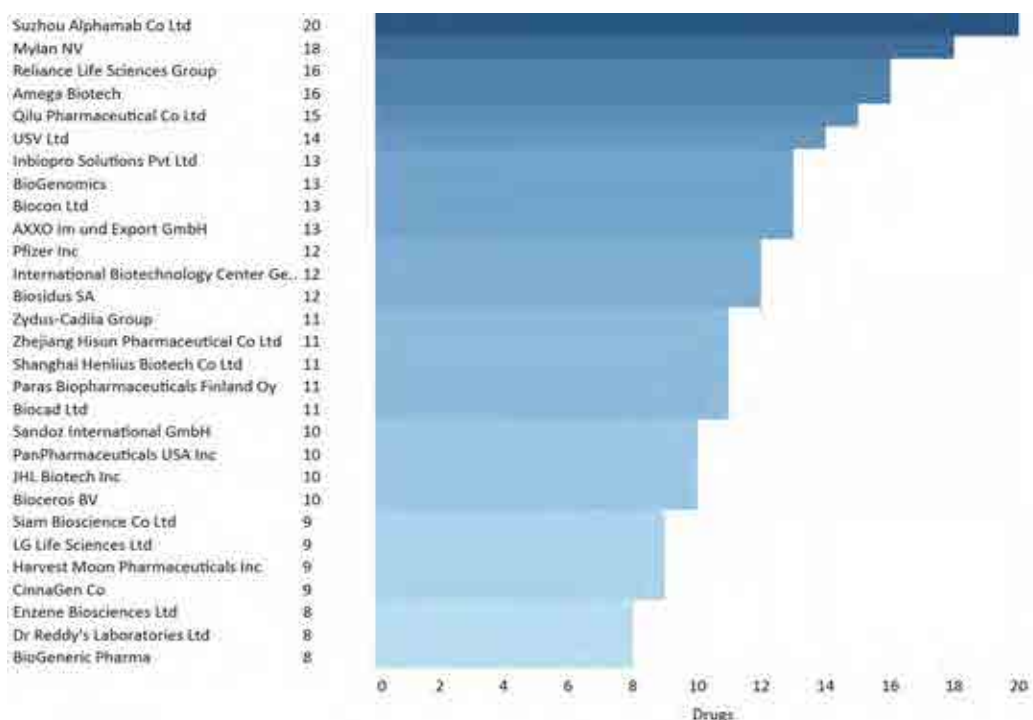
Biosimilars as a class of drugs have emerged as an effective alternative to reduce the cost of biologic therapies. Globally 1,015 biosimilars/follow-on biologics are under development for various therapy areas such as rheumatoid arthritis, neutropenia and cancer, by 475 companies, which are actively developing these follow-on biologics owing to a huge commercial potential.<sup>7</sup>

**Figure 5: Biosimilars and follow-on-biologics drug launched and in pipeline**



Source: Cortellis Competitive Intelligence

**Figure 6: Top global companies by biosimilars and follow-on-biologics drugs launched and in pipeline**



Source: Cortellis Competitive Intelligence

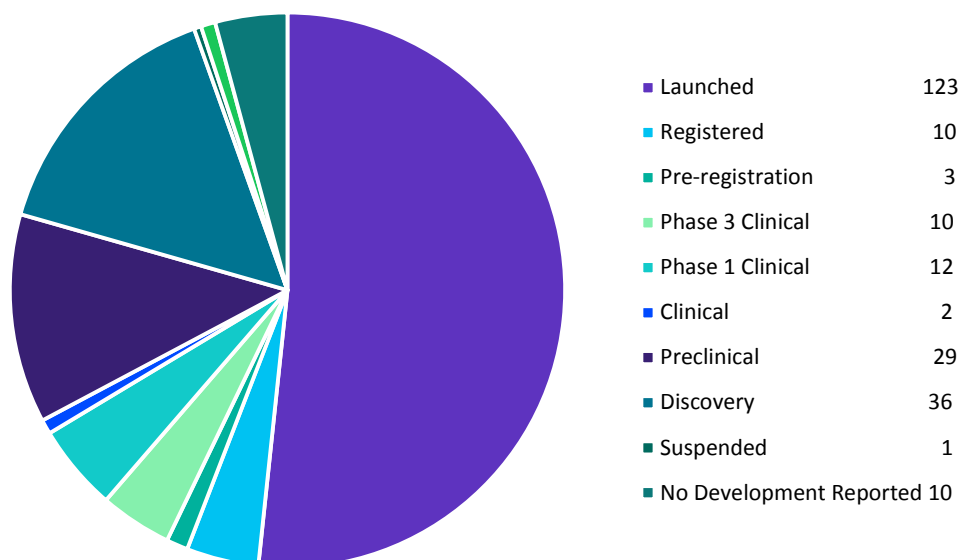
Note: This table includes companies with more than 8 biosimilars and follow-on biologics launched and under development. The other active companies include Samsung Bioepis and Celtrion.

Reviewing the biosimilars pipeline, we see 201 active biosimilars in the pipeline of 52 Indian pharmaceutical companies.

India's first novel biologic, a monoclonal antibody, BIOMab EGFR for head and neck cancer was launched for patients in India in 2006. CANMab, biosimilar Trastuzumab launched in India in 2014 was the world's first biosimilar Herceptin to be developed by Biocon and Mylan, followed by other biosimilar versions. In 2016, Biocon's Insulin Glargine became the first biosimilar from India to be commercialised in Japan. Ogivri, biosimilar Trastuzumab, co-developed by Biocon and Mylan, became the world's first biosimilar Herceptin to be approved in the US in Dec 2017. Fulphila (Pegfilgrastim) another biosimilar co-developed by Biocon and Mylan became the first biosimilar Neulasta to be approved in the US in 2018. Subsequently Fulphila also became the first biosimilar developed in India to be commercialized in the US in 2019.

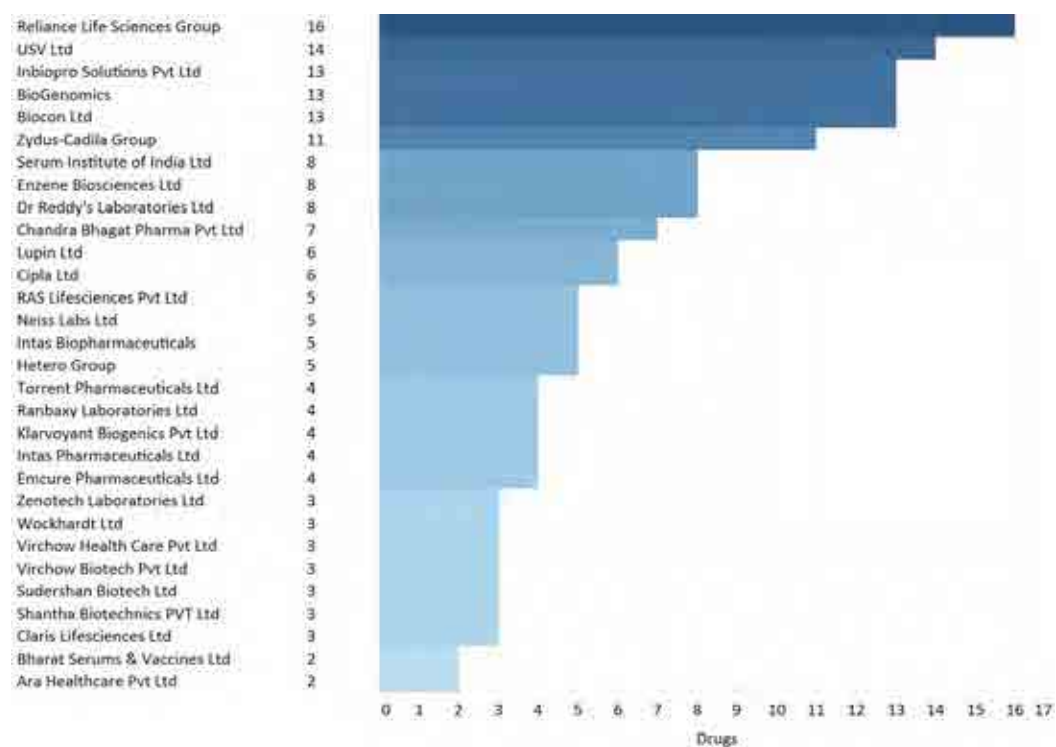


**Figure 7: Pipeline of biosimilars for Indian pharmaceutical companies**



Source: Cortellis Competitive Intelligence

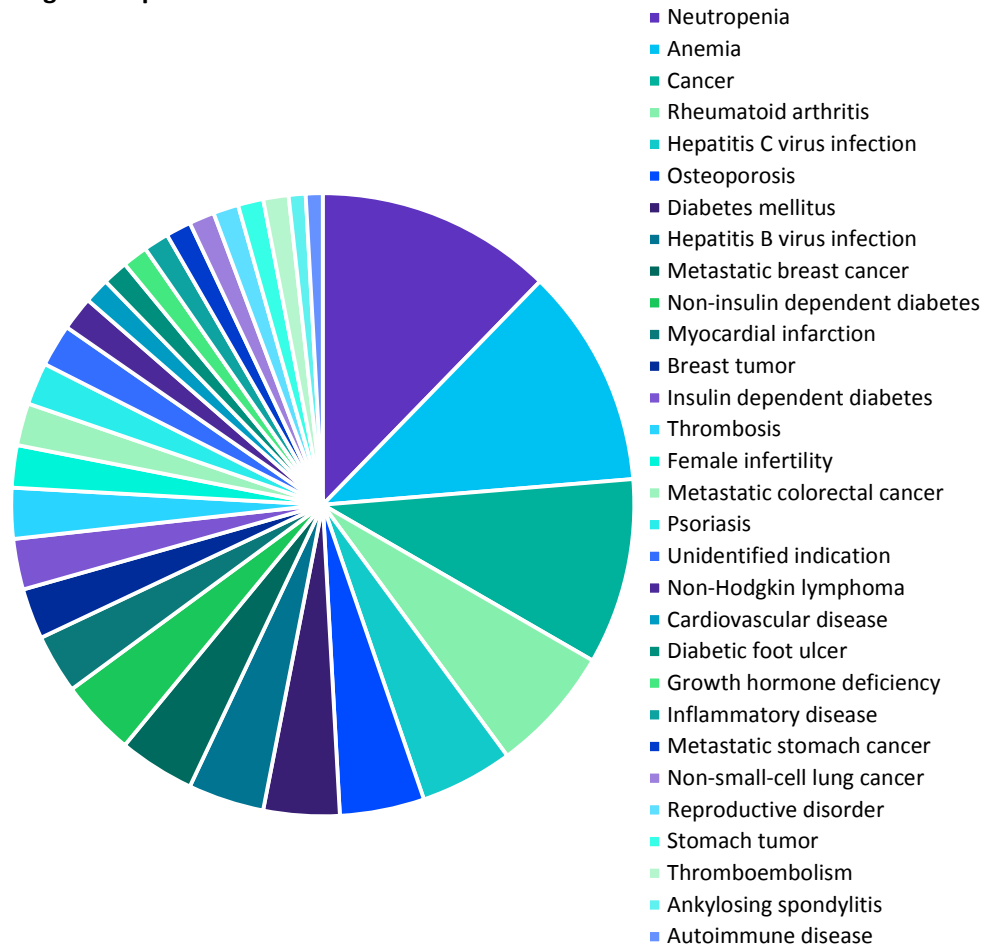
**Figure 8: Top Indian companies by biosimilars and follow-on-biologics launched and under active development**



Source: Cortellis Competitive Intelligence

Biologics and biosimilars have been used in many chronic and specialty therapy areas such as diabetes, multiple sclerosis, rheumatoid arthritis, cancer and autoimmune disorders with extensive clinical success. Monoclonal antibodies tend to dominate the pipelines of large Indian pharma companies active in biosimilars. Cancer and autoimmune disorders are among their focus areas, as seen in Figure 9.

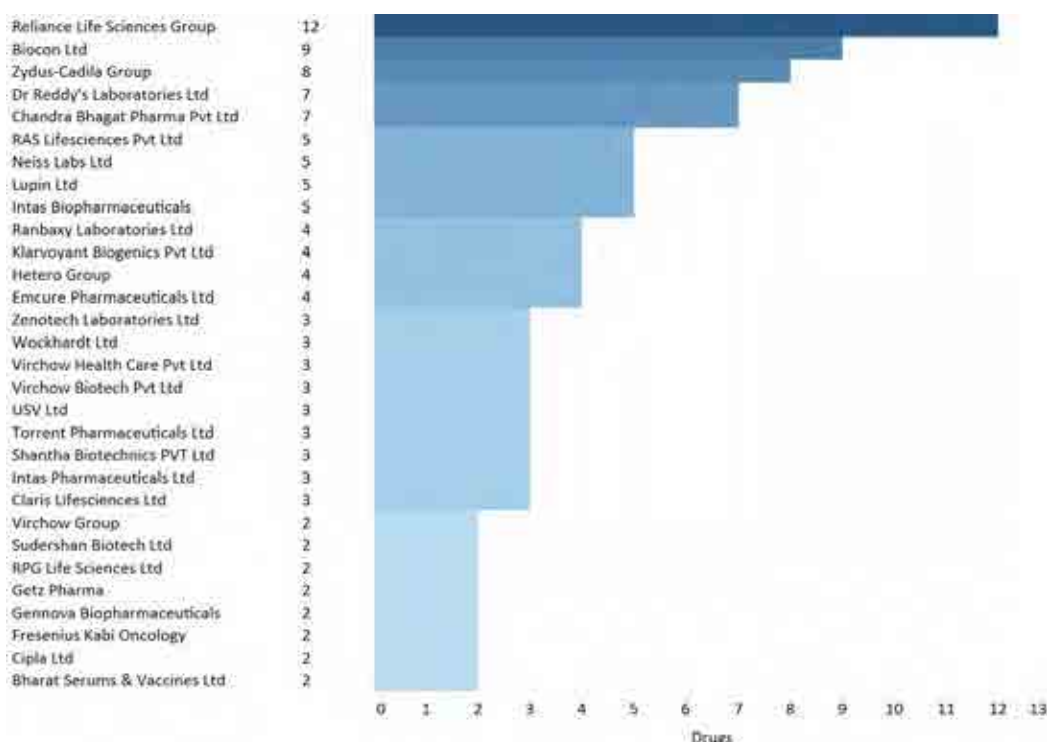
**Figure 9: Targeted Indications for biosimilars and follow-on biologics being developed**



Source: Cortellis Competitive Intelligence

Indian pharma companies are well positioned to tap into biosimilar segments and take a significant market share in the next decade. If played well, this could be the next success story for the Indian pharma market following the generics story in the United States. This potential is highlighted by the growing list of biosimilars already launched by Indian companies.

**Figure 10: Top Indian companies by biosimilars and follow-on biologics launched**



Source: Cortellis Competitive Intelligence

Sixteen follow-on biologics and biosimilars have been launched in India since 2015 in multiple indications, but primarily in cancer. The following table summarizes launches in India from 2015 onwards.

**Table 2: Biosimilars and follow-on biologics launched by Indian pharmaceutical companies in India since 2015**

Drug name	Originator company	Active companies	Active indications	First launched date
teriparatide	Zyldus-Cadila Group	Zyldus-Cadila Group	Osteoporosis	February 28, 2015
ranibizumab, Viropro	Axxiom Inc	Axxiom Inc; Intas Pharmaceuticals Ltd	Age related macular degeneration	June 19, 2015
rituximab	Hetero Group	Hetero Group	Chronic lymphocytic leukemia; non-hodgkin lymphoma; rheumatoid arthritis	August 5, 2015
erythropoietin	Serum Institute of India Ltd	Serum Institute of India Ltd	Anemia	Dec. 17, 2015
trastuzumab	Zyldus-Cadila Group	Zyldus-Cadila Group	Breast tumor	January 9, 2016
adalimumab	Reliance Life Sciences Group	Reliance Life Sciences Group; Torrent Pharmaceuticals	Ankylosing spondylitis; Inflammatory bowel disease; psoriasis; psoriatic arthritis; rheumatoid arthritis;	January 12, 2016

			ulcerative colitis	
<b>rituximab</b>	Reliance Life Sciences Group	Reliance Life Sciences Group; Torrent Pharmaceuticals	Non-hodgkin lymphoma; rheumatoid arthritis	January 12, 2016
<b>bevacizumab</b>	Hetero Group	Hetero Group	Metastatic colorectal cancer	June 27, 2016
<b>bevacizumab</b>	Reliance Life Sciences Group	Lupin Ltd; Reliance Life Sciences Group	Cancer	Sept. 6, 2016
<b>bevacizumab</b>	Zydus-Cadila Group	Zydus-Cadila Group	Cancer; non-small-cell lung cancer	Sept. 30, 2017
<b>bevacizumab</b>	Biocon Ltd	Biocon Ltd; Mylan NV	Brain tumor; cancer; metastatic colorectal cancer; non-small-cell lung cancer; ovary tumor; renal tumor; uterine cervix tumor	Nov. 23, 2017
<b>adalimumab</b>	Hetero Group	Hetero Group	Rheumatoid arthritis	January 3, 2018
<b>pegfilgrastim</b>	Biocon Ltd	Biocon Ltd; Mylan NV	Neutropenia	June 30, 2018
<b>pegfilgrastim</b>	Lupin Ltd	Lupin Ltd	Neutropenia	July 25, 2018
<b>trastuzumab</b>	Dr Reddy's Laboratories Ltd	Dr Reddy's Laboratories Ltd	Breast tumor; metastatic breast cancer; metastatic stomach cancer	July 26, 2018
<b>bevacizumab</b>	Dr Reddy's Laboratories Ltd	Dr Reddy's Laboratories Ltd	Fallopian tube cancer; glioblastoma; metastatic breast cancer; metastatic colorectal cancer; metastatic non-small cell lung cancer; metastatic renal cell carcinoma; ovary tumor; peritoneal tumor; uterine cervix tumor	Aug. 19, 2019

Source: Cortellis Competitive Intelligence

## The global emerging biotherapeutics landscape

'Emerging biotherapeutics' refer to changing industry trends impacting established biologics as well as biologics being developed with new technologies and innovative approaches to clinical treatments. Recombinant proteins and antibodies have dominated the biologics clinical indications list, and this continues to be the case, especially in autoimmune and oncology diseases. In the case of protein biologics, innovative changes in sequence and chemical modifications are being applied that add safety or stability, or modify specific functions. Antibodies have also seen innovation in such areas as altered structural sequences and chemical conjugates that modify their functional impact on biological systems.

More recently, innovations in clinical testing of antibodies in combination therapies or as bi-specific antibodies have led to improved treatment paradigms in many areas. New technology advances in RNA as drugs and viral vector delivery systems have also begun to make an appearance in the clinic. For brevity, we will confine our discussion here to antibody biotherapeutics, which represent the largest biotherapeutic area in terms of both the number of launched and development stage entities.<sup>7</sup>

Antibodies as biotherapeutics represent the largest single group of agents and is one of the largest growth areas. Today there are 336 launched antibody therapeutics representing 208 companies worldwide. The potential for future expansion of approved antibody therapeutics becomes evident when looking at the much larger number of entities in clinical development, which in order of most advanced to earliest clinical stages are: phase 3 clinical (312), phase 2 clinical (532), phase 1 clinical (784), and pre-registered (96). The top five countries and regions with registered antibody biotherapeutics are: United States (133), Mainland China (106), EU (102), Japan (78) and Canada (77). The top five countries/ regions with the most clinical development stage antibody biotherapeutics are similar to the previous list except that Japan leaves the list (183) and Australia joins the ranks: United States (783), Europe (283), Mainland China (266), Australia (245) and Canada (232). Taken together, these numbers demonstrate the worldwide trend towards increased application of antibody biotherapeutics in clinical trials.<sup>6</sup>

Within the antibody biotherapeutic landscape, immune disease indications dominate, but clinical development stage activities show oncology applications taking over in terms of development. The top biotherapeutics launched in autoimmune indications are rheumatoid arthritis (35), psoriasis (29), psoriatic arthritis (26), ankylosing spondylitis (18), Crohns disease (17) and ulcerative colitis (16). Oncology applications follow with chronic lymphocytic leukemia (15), metastatic breast cancer (14), breast tumor (13), metastatic colorectal cancer (12) and non-Hodgkin lymphoma (12). When looking at clinical development trials in progress, however, oncology indications dominate with nine of the top 10 development trials. Rheumatoid arthritis is the lone autoimmune indication in that group at number three. The top 5 indications are: advanced solid tumor (188), solid tumor (88), rheumatoid arthritis (84), metastatic breast cancer (82) and non-small-cell lung cancer (79).

While not a new concept, antibody drug conjugates (ADC) is a recent area of increased activity as follow-on to the successful launch of three oncology drugs: trastuzumab emtansine, brentuximab vedotin, and polatuzumab vedotin. This has spurred new efforts involving 39 companies in all stages of clinical development: phase 3 clinical (6); phase 2 clinical (19); phase 1 clinical (40); and pre-registration (4). All of the ADC trials are in the area of oncology with the top five countries involved being: United States (41), Europe (15), Mainland China (11), Canada (10), and Japan (9).<sup>7</sup>



# Initiatives by Government of India to promote biotech-based drug development

The Government of India is keen to promote biotech-based drug development under the 'Make in India' campaign. Multiple reports have summarized initiatives introduced by the Department of Biotechnology (DBT), the Biotechnology Industry Research Assistance Council (BIRAC) and the government of India to support the vision of making India a hub for biotechnology-based innovation and research.<sup>14,15,16,17</sup> These efforts focus on policy initiatives and investments, promotion of industry-institute partnership, creating entrepreneurship cells to promote biotech start-ups and skill development.

BIRAC supports innovative translational research from ideation to commercialization. Public Private Partnership is also encouraged to attract investments from Industry, Investors and other agencies, philanthropic agencies. BIRAC has created a provision of demising investment ideas by supporting startups with funding from 50 Lakhs (70,000 USD) up to 7 crores (1 M USD) per Startup. Fund of Funds called Biotechnology Innovation Fund – AcE has mobilized more than INR 300 Crores for specific investments in the biotech innovation start-up ecosystem to scale-up R&D and innovation.

The Department of Biotechnology (DBT) in collaboration with World Bank, initiated an industry-academia collaborative mission 'National Bio-Pharma Mission' with a corpus of USD 250 Mn which is implemented by BIRAC. The objective of the mission is to enhance research and development of biopharmaceuticals. The mission accelerated the preclinical development of many biotherapeutics such as Insulin Glargin (Vitane Pharmaceuticals), Herceptin (Serum Institute of India), and Plasma fractionation (BIBCOL). This mission also supported development of a few vaccines such as, Universal Flu vaccine (MynVax), Pneutgar-15 (Tergene), TV003/TV005 (Indian Immunologicals), DSV4 and DSV4+2E VLP (Sun Pharma). It also supports skills development by providing necessary mentoring and trainings in domains of technology transfer, IP filing, Management of intellectual property, business plan development, etc.

There are about 2700 + Biotech Start-ups in the country & this number is expected to grow to 10,000 by 2025. BIRAC intends to nurture 300-500 start-ups every year. It has created a network of world class Bioincubation Centre under BioNEST scheme which will grow to 50 by FY 2020. BIRAC's flagship ideation to PoC scheme - Biotechnology Ignition Grant (BIG), which is one of the largest early stage programs and has supported more than 440 entrepreneurs, start-ups. Noticeably, after initial funding by BIRAC, such grantees are able to generate follow-on funding of approximately INR ~250 Crores from public and private sources. In addition to start-ups and biotech companies, BIRAC also supports research institutes and small and medium scale enterprises (SMEs). Importantly, among the 1000+ entrepreneurs, startups directly supported by BIRAC there are 130+ products and technologies that are in the market in India and other countries.

As enable, revised Guidelines on Similar Biologics released by DBT & CDSCO in August 2016 have provided a simplified efficient regulatory pathway for manufacturing processes assuring safety and efficacy with quality as per cGMP standards. This regulatory enabler has led to Indian patients to get access to world class biosimilars at the most affordable prices prevailing in the world.

The government of India has also collaborated with many foreign universities to bridge the knowledge and technology gap and promote early stage biotech-based drug discovery.

As the ease of doing business promotes start-ups and incubator centers, BIRAC extended exemption on the service tax provided by BIRAC approved biotechnology incubators to incubated companies with effect from April 1, 2016. It also ensured that mandatory requirements of export/import license for biological samples were removed w.e.f. August 4, 2016. Now, organizations can give self-certification to customs authorities to ensure they are/will follow all applicable rules, regulations and procedures for the safe transfer and disposal of biological samples. BIRAC also worked on extending start-up status for new entities up to 10 years, instead of the original seven. Greenfield pharmaceutical projects can now avail 100% FDI and up to 74% FDI is permitted under the automatic route for brownfield pharmaceutical projects.

DBT and BIRAC have introduced multiple skill development initiatives in the biotechnology sector as well, such as the Indo-EU, Indo-France, Indo-UK, Indo-Sweden, Indo-Australia several G2G collaboration driven funding, mentoring provisions, which encourages researchers to undertake a collaborative research project at a leading science institute besides facilitating Startups and entrepreneurs. DBT has now trained more than 7,000 personnel in biotech industries under the Biotechnology Industrial Training Programme (BITP). Additionally, there are capacity building training and mentorship workshop including business, IP, legal mentorship, Entrepreneurship Development (ED), Grant Writing & conducted routinely and already covered > 10,000 candidates.

Today there are about 2700+ Biotech startups in the country, 600+ Biotech companies, 100+ Biotech incubators. These numbers are expected grow to 4-5 times in next 5 years. India now has reached a critical mass of Biotech Entrepreneurs, Startups in the country with 130+ products commercialized in the market. It is anticipated to see an exponential growth in the next 5 years – a huge value proposition for investors, industries and scaling of the ecosystem integrating as a recognized nucleus to contribute to the global Biotech Ecosystem.

## Conclusion

The pharmaceutical industry faces many changes both within India and globally. While small molecule therapeutics had previously dominated research and captured major market share, the advent of large molecule therapeutics (biotherapeutics/biologics) has rapidly transformed the pharmaceutical industry.

Small molecule therapeutics have certain inherent advantages; however, biologics' targeted approach and substantial reduction of side effects in therapeutic areas such as oncology, have made them the more promising therapeutics. Biologics have therefore become the treatment of choice by physicians and patients and are thus generating significant revenues and enjoying larger market share. Rituximab and Trastuzumab are on the WHO list of recommended drugs. Most of the recent blockbuster drugs (generating revenue of > USD 1bn) are novel biologics. Follow-on-biologics/biosimilars are gaining huge traction in the research and development community and pharmaceutical industry. As a comparatively cheaper version of novel biologics, they have potential for huge cost savings depending on the size of the patient pool.

The Indian pharmaceutical/biotech industry is well placed to tap into the huge opportunity offered by biologics and biosimilars and already has an extensive pipeline of biosimilars under development. Steps taken by government of India to support the pharmaceutical industry with the necessary infrastructure, funding and global collaboration to bridge the technical knowledge gap, and further development of regulatory guidelines will help capture this opportunity.

Given innovation in technology and economies of scale, India is likely to achieve USD 12Bn market size for biologics, biosimilars, and vaccines by 2025.

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