Major biosimilars contributing to the economy of pharma industry in US and impact of COVID-19 on the uptake of biosimilars globally

By-

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Introduction

Biologics, are known since the nineteenth century, and the first bacteria-generated biologic, human insulin, was approved by the US FDA in 1982.

Examples of biologics- Vaccines such as the human papillomavirus for cervical cancer, gene therapies, tissues for transplant like tendons and ligaments, blood and blood products

Biologic therapies have transformed the treatment of a wide range of diseases, including cancer and autoimmune disorders.

Patents and other exclusivity periods for a number of biologics are about to expire or have already expired, paving the way for the development and approval of biosimilars that are comparable to licensed biologics

What are Biosimilars?

- The FDA defines a biosimilar as a biological product that has been approved based on evidence that it is highly similar to an FDA-approved biological product known as a reference product and that the biosimilar and reference product have no clinically significant differences

- To be approved for use in the United States, biosimilars must demonstrate that they:
  - Have the same mechanism of action, have the same strength and dosage, and can thus be taken in the same way as the original biologic medication.
  - Do not have any clinically meaningful differences in safety or effectiveness when compared to the original biologic medication
  - Maintain the same high manufacturing standards as the originals

Biosimilars market is divided into 3 categories

Product Class

- Monoclonal antibodies
- Recombinant hormones
- Immunomodulators
- Anti-inflammatory drugs
- Others

Application

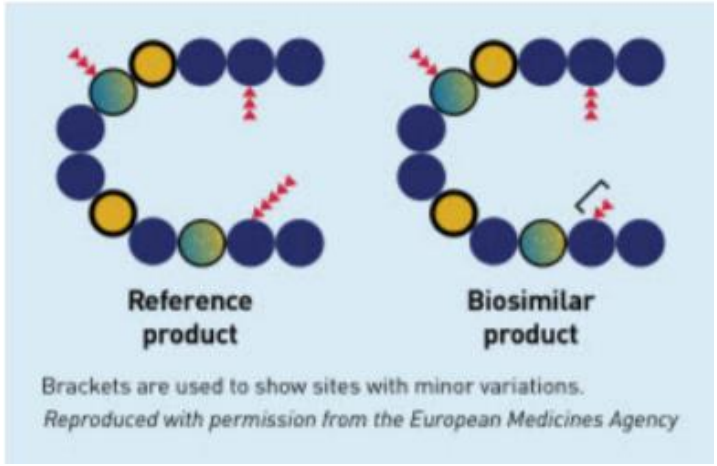
- Blood diseases
- Growth hormone deficiency
- Chronic and autoimmune diseases
- Oncology
- Other

Geography

- North America
- South America
- Europe
- Asia Pacific
- Middle East and Africa

Terms used to describe a biosimilar-

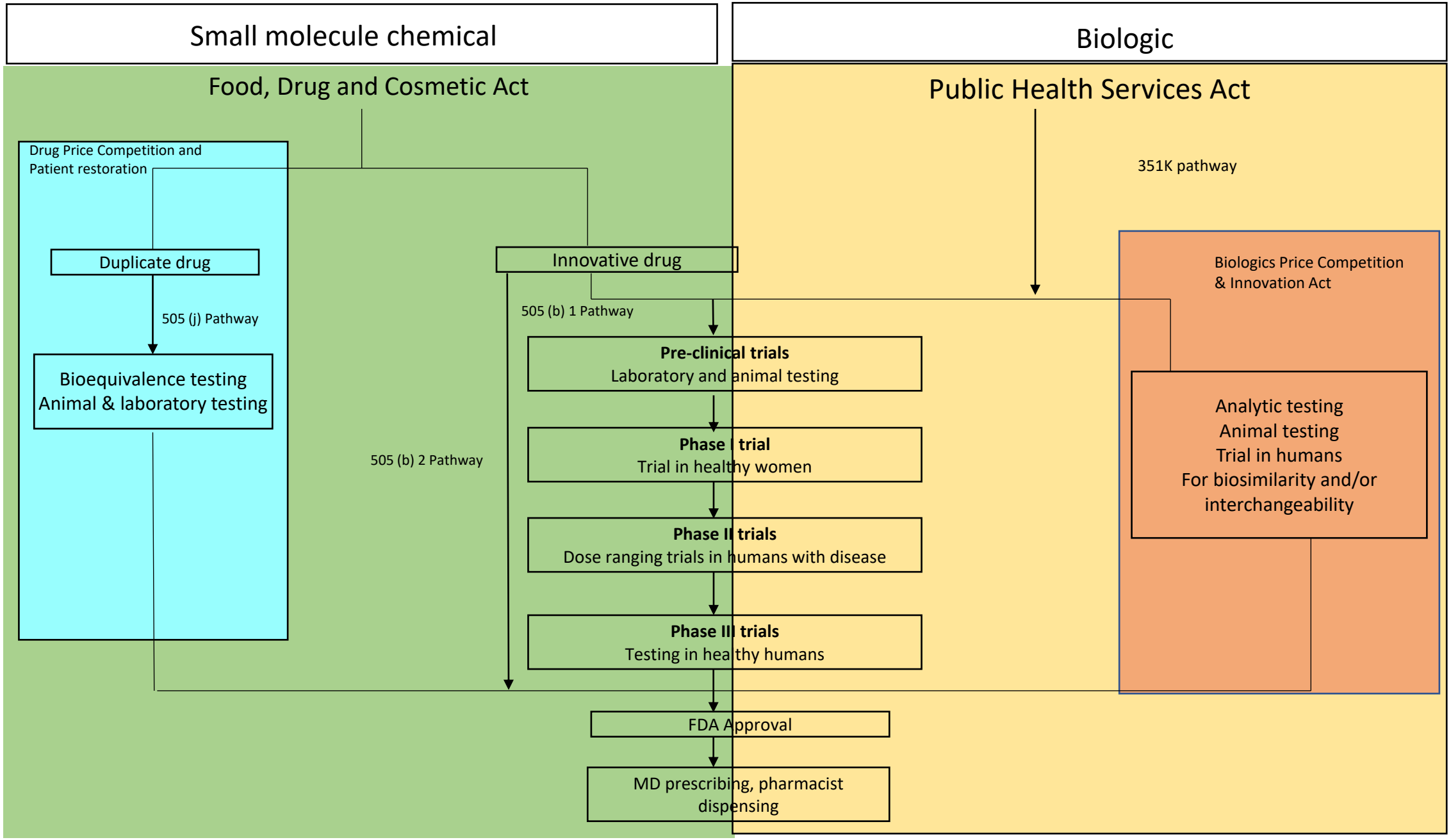
- **Biological product-** Larger, more complex molecules than others. Example: therapeutic proteins (e.g. filgrastim), monoclonal antibodies (e.g. adalimumab), and vaccines
- **Reference drug**- A single biological product already approved by FDA, for which a biosimilar product is comparable, is a reference product
- **Interchangeable product-** An interchangeable product is a biosimilar product that meets additional requirements stipulated by the Biologics Price Competition and Innovation Act
- **Generic drug-** Generic drugs are made up of small molecules that are easy to duplicate and reproduce. A generic drug's active component is the same as a brand-name drug's active component



Research objectives

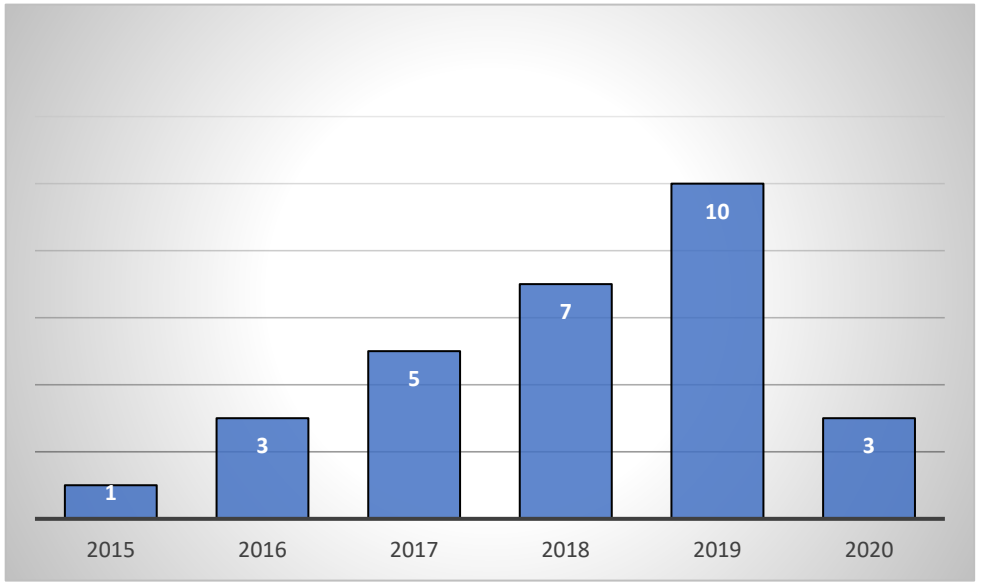
- To analyze the current market scenario of biosimilars in USA
- To study the regulatory pathway for the approval of biosimilars in USA
- To identify the key differences in the USA and EU biosimilars market
- To identify the challenges and opportunities that lie in the acceptance of biosimilars in USA
- To study the effect of COVID-19 on the uptake and adoption of biosimilars globally

Regulatory pathway for approval of biosimilars in US

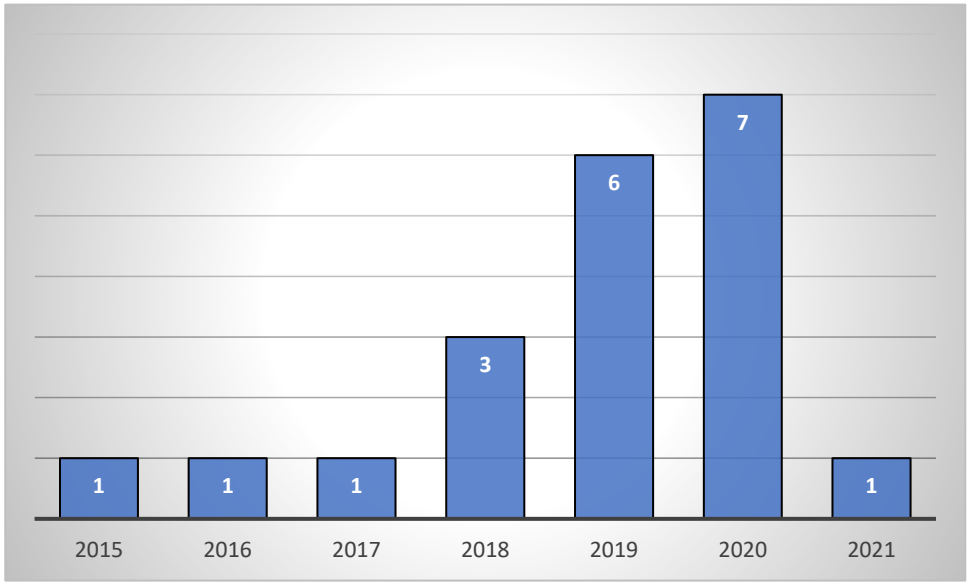

Small molecule chemical
Biologic
Food, Drug and Cosmetic Act
Public Health Services Act
Drug Price Competition and Patient restoration
Duplicate drug
505 (j) Pathway
Bioequivalence testing
Animal & laboratory testing
Innovative drug
505 (b) 1 Pathway
505 (b) 2 Pathway
Pre-clinical trials
Laboratory and animal testing
Phase I trial
Trial in healthy women
Phase II trials
Dose ranging trials in humans with disease
Phase III trials
Testing in healthy humans
FDA Approval
MD prescribing, pharmacist dispensing
351K pathway
Biologics Price Competition & Innovation Act
Analytic testing
Animal testing
Trial in humans
For biosimilarity and/or interchangeability

Market scenario of biosimilars in US

- The first biosimilar approved by the US FDA - **Zarxiso** (filgrastim), by Sandoz Inc. on March 6, 2015, having reference product Neupogen
- Recent biosimilar approval by US FDA- **Riabni** (rituximab-arrx) of Amgen Inc. on December 17, 2020. Riabni is the third biosimilar to Rituxan
- 29 biosimilars approved by US FDA so far, but only 20 of the 29 approved biosimilars have been launched so far
- Biosimilars currently account for only 2.3 percent of the biologicals market in the US
- Despite the fact that the United States sells 60% of all biologicals, Europe accounts for 90% of worldwide biosimilars sales

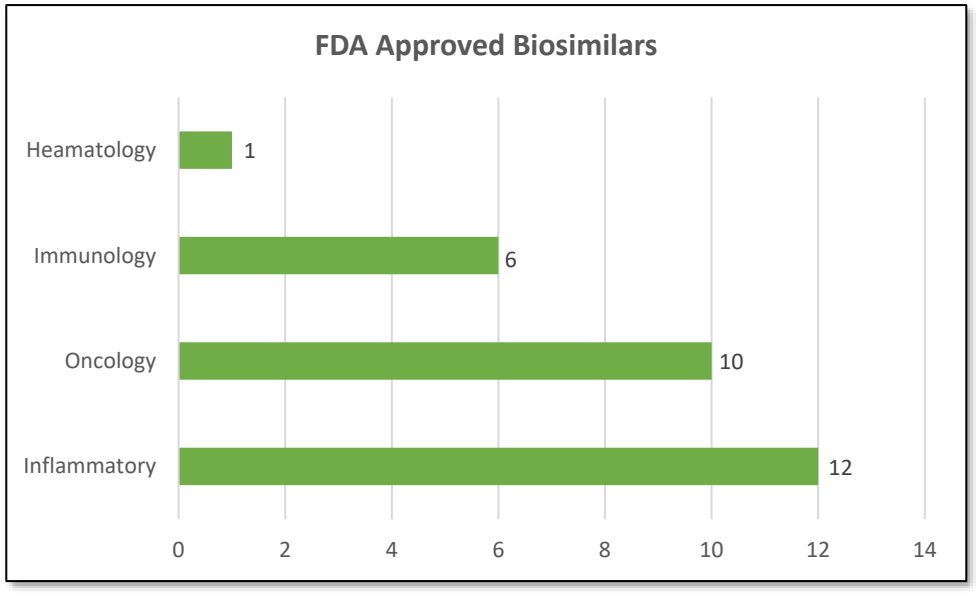


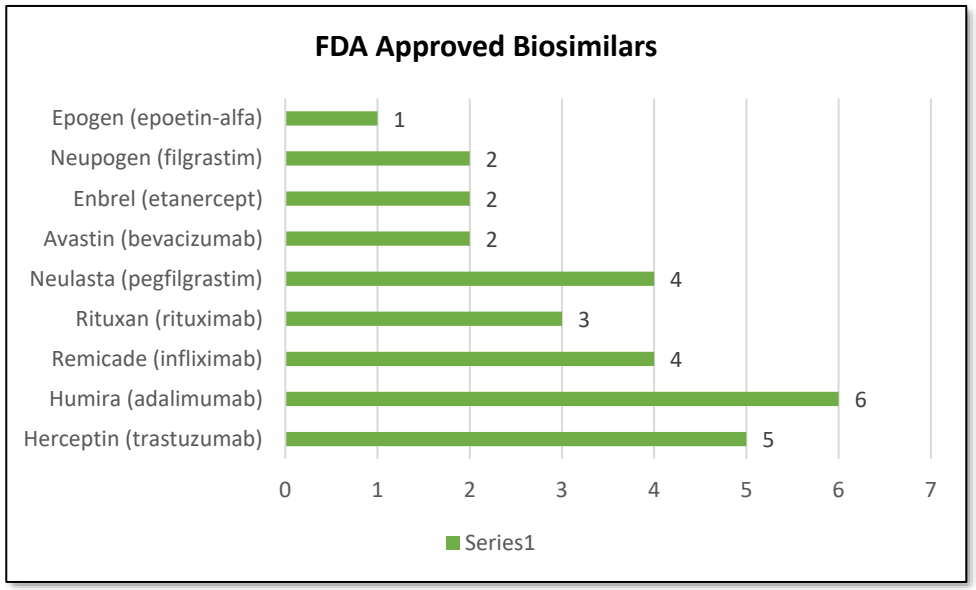
Number of biosimilars approved in US, per year



Number of biosimilars becoming available in the US, per year

When a biosimilar is approved in the United States, it does not become instantly available to patients, and only one biosimilar became available each year between 2015 and 2017. However, six biosimilars were accessible to the patients starting in 2019 and continuing through July 2020. Patients have access to 20 biosimilars as of June 2021





There are **9 reference products**

- Herceptin (trastuzumab)
- Humira (adalimumab)
- Remicade (infliximab)
- Rituxan (rituximab)
- Neulasta (pegfilgrastim)
- Avastin (bevacizumab)
- Enbrel (etanercept)
- Neupogen (filgrastim) and
- Epogen (epoetin-alfa) in

4 therapeutic areas

- Oncology, Oncology supportive care/ Immunology, Inflammatory and Hematology for which biosimilars have been approved in US

- The global biosimilars market was estimated at USD 28,235 million in 2020, and revenue of USD 103,638 million is predicted in 2026, representing a CAGR of 24.2 percent during the forecast period
- The key biosimilar companies operating in the US biosimilars market are Amgen, Mylan, Sandoz, Coherus Biosciences, Pfizer, Celltrion, Samsung Bioepsis, Boehringer Ingelheim Pharmaceuticals, and Hospira
- Kanjinti of Amgen Inc., Udenyca of Coheru Biosciences, Retacrit of Pfizer and Zarxio of Sandoz are the successful products which have more than 10% of market share in the US biosimilars market

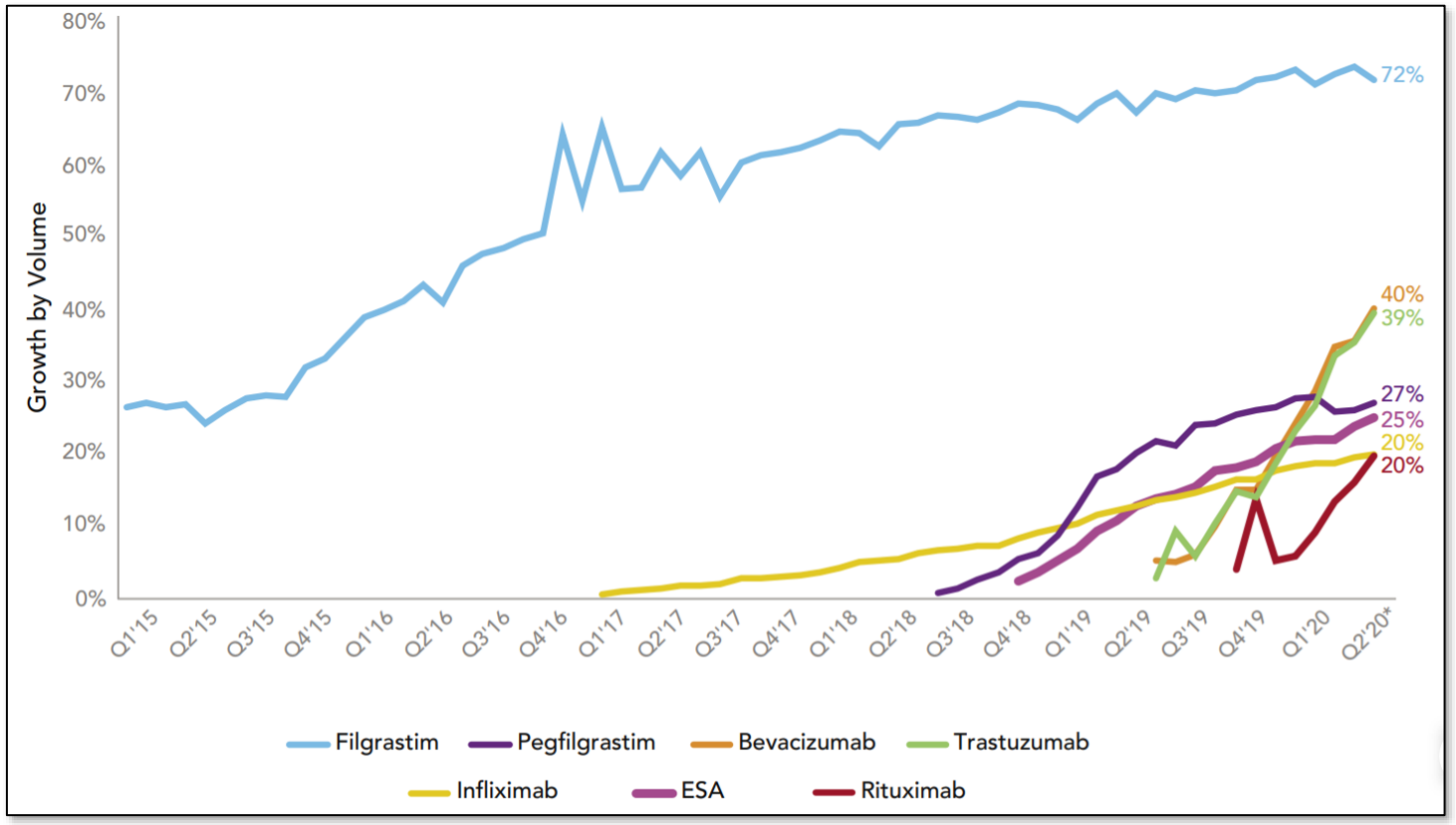
Company	**Successful products based on >10% market share**
Amgen	Kanjinti
Coherus	Udenyca
Pfizer	Retacrit
Sandoz	Zarxio

Biosimilars pricing in US

- Biosimilars lower healthcare costs by offering considerable wholesale acquisition cost (WAC) and average sales price (ASP) savings at launch, as well as through price competition
- Manufacturers introduce biosimilars at a WAC price that is generally **15% to 37%** cheaper than the WAC of the reference product and
- Almost all biosimilar manufacturers launch at a WAC price that is **3% to 24%** lower than the reference product ASP
- Now, the ASP of reference products is beginning to decline due to competition from biosimilars
- For example- The ASP for the infliximab reference product (Remicade) has decreased by over 30%, while the ASPs for the biosimilars, Inflectra and Renflexis, have decreased by roughly 40%. After 5 years, Neupogen (filgrastim) biosimilars account for over 75% of the market.

Biosimilars growth uptake curve in US

The rate of biosimilar acceptance is generally increasing over time. In the majority of therapeutic areas where biosimilars have been introduced, they have gained a large share of the market

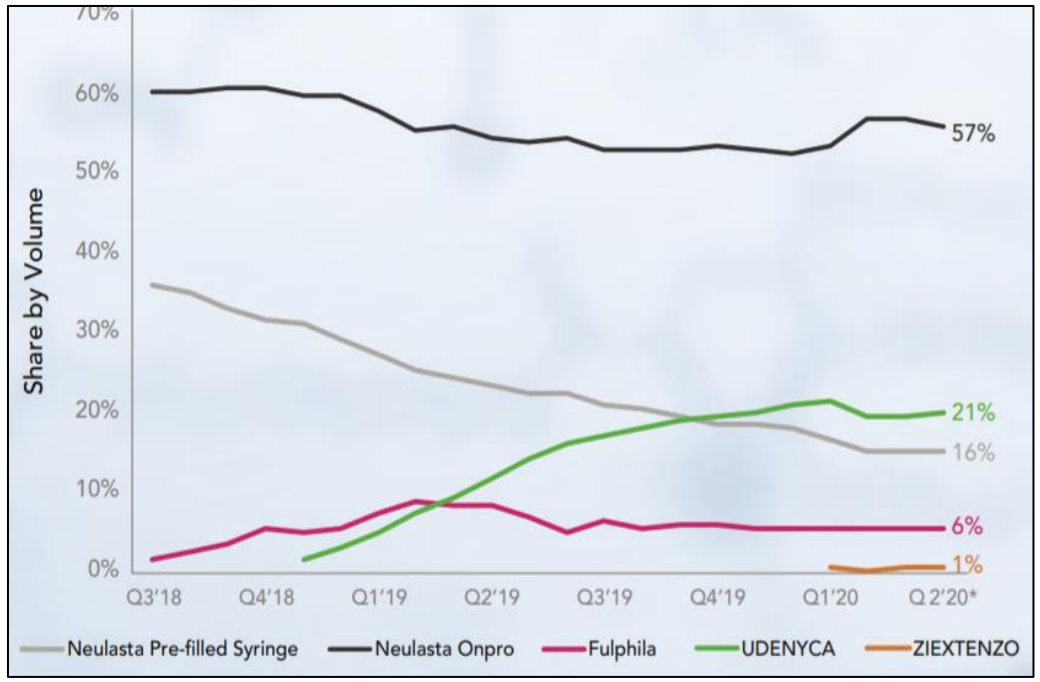


Oncology biosimilars

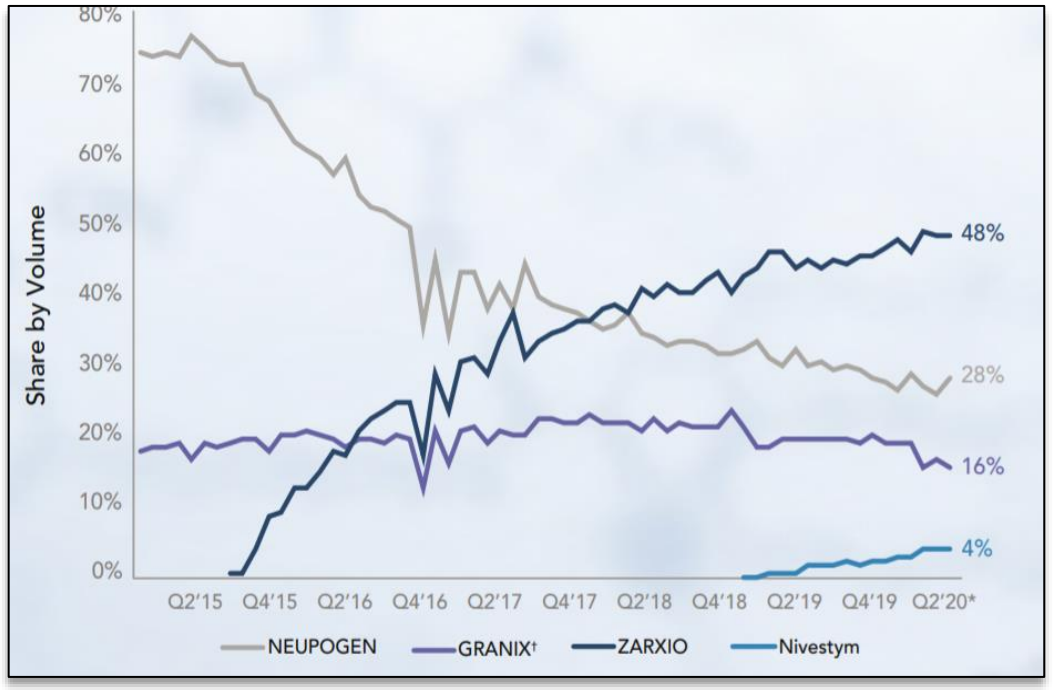
- Trastuzumab, bevacizumab, and rituximab are the biosimilars available for oncology therapies in the US
- Biosimilars for oncology therapies have shown significant growth since their launch in the biosimilar market
- Biosimilars of trastuzumab and bevacizumab, for example, account for at least 40% of total revenues
- Although rituximab biosimilars are relatively young, they account for 20% of sales by volume
- As of 2021, five trastuzumab biosimilars have been approved in the US for HER2-positive breast cancer: Ogivri, Herzuma, Ontruzant, Trazimera, and Kanjinti, and all five are on the market
- All trastuzumab biosimilars were marketed at a 7 percent to 20% lower price than Herceptin's ASP
- Bevacizumab biosimilars (Mvasi and Zirabev) have seen rapid uptake, with Mvasi taking 38 percent of the market in just nine months
- Among the rituximab biosimilars, Truxima had a 17 percent market share, whereas Ruxience had a 3 percent market share

Oncology supportive biosimilars

- **Pegfilgrastim, filgrastim,** and **epoetin alfa** are the biosimilars available for oncology supportive treatment. The most developed biosimilar category in the United States is oncology supportive care



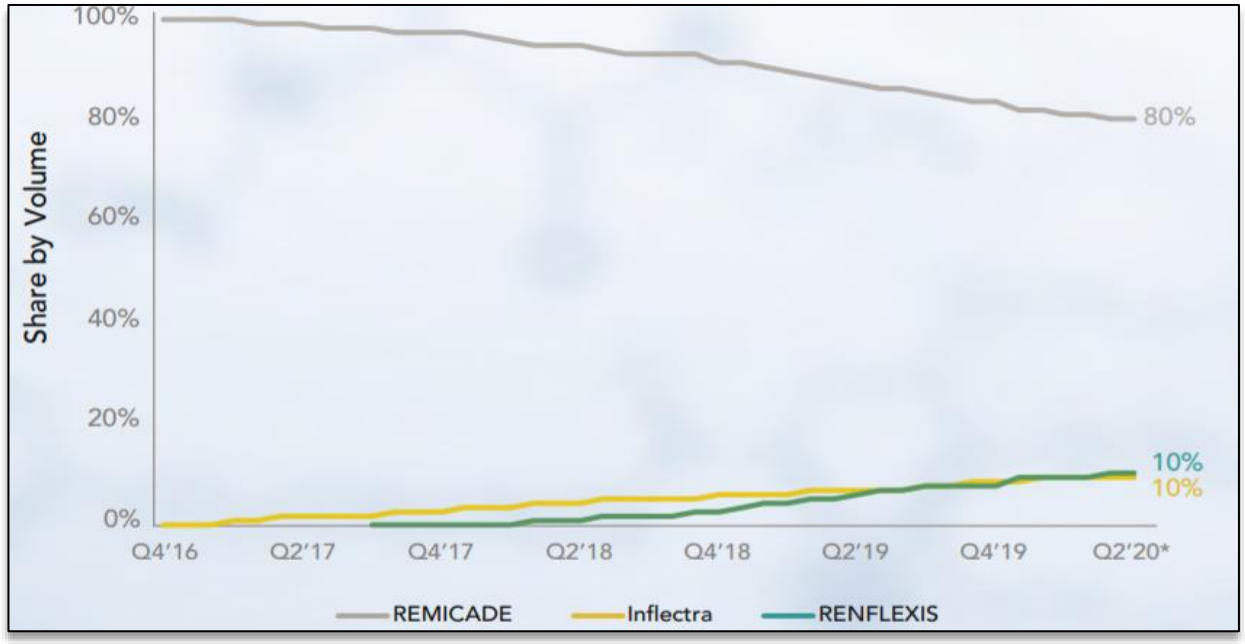
Biosimilar Uptake Curve for Pegfilgrastim Products



Biosimilar Uptake Curve for Filgrastim Products

Inflammatory biosimilars

- Inflammatory biosimilars include Infliximab, adalimumab and etanercept. These are used for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, etc.
- Anti-inflammatories account for 3 of the main six top-selling biologics (Remicade is the third best-selling anti-inflammatory), which could contribute to significant cost savings for biosimilars in this class



Biosimilar Uptake Curve for Infliximab Products

Challenges in the adoption of biosimilars in US-

Biosimilars are hampered by issues like as manufacturing methods, interchangeability, and nomenclature, which hinder them from doing what they were supposed to do-

1) Approximately 50% or more of the data contained in biosimilar drugs approval applications concerns manufacturing processes
2) Biosimilars face competition from at least two sources: branded companies' biologics and consumer brand awareness
3) Interchangeability is another important challenge for biosimilars in the future
4) Persuading stakeholders that the US is at a tipping point that will determine whether the biosimilars market in the US is perceived as a success or failure
5) Nomenclature for biosimilars has also been problematic

There are various misconceptions about biosimilars. These are some of them:

- Patients refuse to take them
- Physicians are unaware of them
- Doctors won't prescribe them because they're not as effective as the originals
- Biosimilar naming suffixes and CMS coding are suffocating growth
- Biologics are "natural monopolies" that prevent biosimilars from entering the market

For example-
Challenges for the adoption of trastuzumab biosimilars in oncology primarily related to cost of care, limit the acceptance of oncology biosimilars, including drug pricing, patient access, formulary inclusion, and treatment management algorithms.

Opportunities for biosimilars in US

- Growing geriatric population
- Preference over traditional biologics because of lower costs
- Increasing promotion by government and private organizations as an alternative to traditional biologics and synthetic medicinal products
- Innovator price reductions with significant discounts
- Strategic partnerships by biosimilars manufacturers and outsourcing biosimilar production
- Potential profitability of producing numerous biosimilar drugs in the same facility
- Biosimilars are increasingly being chosen by private and public insurers as preferred items for their plans above their reference products

Differences in the US and Europe biosimilars market

- Disparity in the patent environment- certain EU patents expiring faster and some original businesses in the US placing greater patent hurdles
- Faster approval process in Europe- In Europe, 69 biosimilars have been approved, with practically all of them going on the market right once. In comparison, the US FDA had only approved 29 biosimilars as of January 2021, with only 18 having been released in the country thus far
- Market disparities-

1. Market maturity
2. Number of Competitors
3. Biosimilar market share

Impact of COVID-19 on the uptake of biosimilars

- The COVID-19 pandemic has posed significant hurdles for the pharmaceutical industry, particularly biosimilar makers
- The pandemic has had an impact on supply and demand, making it difficult for manufacturers to predict.
- On the supply side, worldwide lockdowns have disrupted supply chain procedures in hubs such as China, India, and the United States
- The impact of COVID-19 on the global biosimilars market has been multifaceted

- **Healthcare providers (HCP) and other medical decision-makers' inaccessibility-** Lack of availability resources to continue evaluating complex biosimilar-related decisions during this time.
- **Shortages in supply-** On the supply side, worldwide lockdowns have disrupted supply chain procedures in hubs such as China, India, and the United States.
- Businesses relying on facilities in Europe and Asia may be the most vulnerable in terms of supply.
- For instance, Pfizer/Celltrion biosimilar product Inflectra, whose manufacturing facility is in South Korea, is exposed to supply risk

Company	Biosimilar Products	Manufacturing Locations
Pfizer/Celltrion	Inflectra	South Korea
Mylan/Biocon	Fulphila and Ogivri	India
	Semglee	Malaysia
Sandoz/Novartis	Prefilled syringes and devices for Sandoz biosimilars and Novartis reference biologics	Austria
	Binocrit	Slovenia

- **Low demand of biosimilars-** On the demand side, patients postpone seeking therapy, especially for less convenient delivery such as infusions, resulting in decreased patient volume and reduced demand
- **Delays in clinical trials and approvals of biosimilars:** Due to issues monitoring protocols, deprioritization in favor of more immediate acute care needs, and patients' incapacity to travel to appointments, most clinical studies have been postponed

Despite the challenges faced by the global biosimilars market due to COVID-19, there is a hope for biosimilar market to rise and have a significant share in the biologics market-

- Increased budgetary pressure can hasten the post-crisis adoption of biosimilars
- With government support, local biosimilar production is likely to rise by 8-10% in the next 3-4 years, resulting in more MNC-domestic collaboration
- Biosimilars that come with robust patient support programmes will gain maximum traction in the region
- Virtual interactions between pharmaceutical companies and physicians will be the new norm post-COVID-19-

Recommendations

Biosimilar value proposition

The value proposition for adopting biosimilars must connect with payers, providers, and patients in order to maximize commercial potential.

The long-term worth of biosimilars must be understood by payers

Payers have a tendency to make coverage and reimbursement decisions with a short term approach

Physicians must develop greater experience and confidence in biosimilars

- Raise physician awareness of the benefits of biosimilars
- Develop evidence to seek interchangeability to promote utilisation and remove obstacles to biosimilar adoption

Biosimilars must become much more well-known among patients

- Help patients understand how to reduce their out-of-pocket costs by increasing patient awareness of biosimilars

Recommendations

Recommendations to increase post- COVID uptake of biosimilars

- ✓ Selecting free economic zones and hotspot regions with the most incentives to produce locally
- ✓ Collaborating with local pharmaceutical enterprises that meet high quality and technological criteria
- ✓ Providing comprehensive and holistic patient support programmes
- ✓ Planning a soft launch and using digital tools and technologies to engage Key Opinion Leaders in their marketing efforts (KOLs)

Conclusion

- Biosimilars are crucial in continuing to provide clinicians and patients with choice in their care plans while also lowering overall healthcare expenditures, as we've seen over the last five years in US
- Biosimilar adoption has advanced in recent years, the United States is on course to save $100 billion in drug expenses over the next five to ten years
- According to research, embracing biosimilars and patient choice will result in the necessary competition to expand access to biosimilars and biologics for 1.2 million patients
- COVID-19, without a doubt, threw the entire healthcare business into a loop. As a result, one of the top concerns among responders is how regulatory authorities, pharmaceutical companies, treatment locations, and patients will adjust as the pandemic continues.
- Some experts predict that 2021 will be the “year of the biosimilar,” when many stakeholders finally resolve the access constraints that are hindering biosimilar adoption
- Biosimilars will eventually account for a significant chunk of the US biologics market

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