A Journey **of Self-Belief**

BIOSIMILARS
Insulins, mAbs and Other Biologics

15+

We have over 15 years of expertise in providing biosimilar insulins to patients globally.

Biocon realized the potential of biosimilars very early on and decided to invest in developing them for global markets at the turn of the millennium. It was early days, India had just approved its first biosimilar, a vaccine for hepatitis B. It took a special kind of fortitude to foray into a complex therapeutic space where the regulatory pathway was still evolving and the international landscape was complex and dynamic.

Biological medicines are playing a critical role in the treatment of serious illnesses such as diabetes, cancer and immune-mediated inflammatory diseases. These innovator drugs, launched in the late 1990s and 2000s, are expensive and hence not accessible to all patients. The top nine branded biologic drugs generated global sales of USD 62 billion in 2018, as per a recent Morgan Stanley research report. As patents on these drugs have either expired or are about to expire by 2025, their biosimilar versions have either hit the market or are currently under development.

As the term suggests, biosimilars possess similar medicinal properties to the original biologics they are referenced to, with similar expected patient outcomes. Targeted as alternatives to existing patented and approved biologics, they have little structural variance, and comparable safety and efficacy to the originator biologic. Unlike small molecule generics, biosimilars require huge investments in research and manufacturing infrastructure as they are more complex, have less-established regulatory pathways and face intellectual property hurdles.

Nonetheless, biosimilars are relatively inexpensive when compared to originator biologics and hence more affordable for patients. Governments and regulatory agencies have recognized the role of biosimilars in addressing issues of access and affordability. They have introduced several measures to support biosimilar development and approval, encourage uptake across multiple indications and foster reimbursement.

The Biosimilars Opportunity

Having realized the biosimilars potential very early on, Biocon decided to invest in biosimilars development for global markets at the turn of the millennium. It was early days, India had just approved its first biosimilar, a vaccine for hepatitis B.

It took a special kind of fortitude to foray into a complex therapeutic space where the regulatory pathway was still evolving and the international landscape was complex and dynamic.

Europe introduced a biosimilars regulatory framework in 2005 leading to the first biosimilar approval in 2006. Since then many biosimilars have received approvals and witnessed good market penetration in the EU region. These biosimilars generated savings of over EUR 1.5 billion in the five largest EU markets alone between 2006 and 2017 *(Medicines for Europe report).*

Biocon, along with partner Mylan, has received approvals for three biosimilars, Trastuzumab, Pegfilgrastim and Insulin Glargine, and commercialized two of them in Europe.

The U.S. was a late entrant in this area, approving its first biosimilar only in 2015. Till June 2019, 20 biosimilars, have been approved by the U.S. Food and Drug Administration (FDA). Biocon is the only company from India to have obtained U.S. approvals for two of its biosimilars, Trastuzumab and Pegfilgrastim, co-developed with Mylan.

With Morgan Stanley estimating the U.S. and EU biosimilar markets to grow at a CAGR of 24% to USD 13.3 billion by 2025 from USD 2.9 billion in 2018, a number of companies worldwide are pursuing biosimilar development despite the prohibitive costs and complexity involved.

An Indigenuous Insulin for Diabetes Patients in India

In the 2000s, India was home to a quarter of the world's then 120 million people with diabetes, and they only had access to expensive imported insulin brands sold by global innovator companies.

Biocon started a biosimilar insulins program in the early 2000s to indigenously develop

2+ Bn

We have cumulatively provided over 2 billion doses of our biosimilar insulins to patients in several countries.

a safe, effective and affordable alternative to this life-saving therapy for Indians who needed insulin to manage their diabetes.

While the product patent on human insulin had long expired, it continued to be protected by strong process patents. Most of the patented processes were using the yeast, Saccharomyces cerevisiae or the bacteria, Escherichia coli to manufacture recombinant human Insulin (rh-Insulin).

As a part of our differentiation strategy, we chose to develop our own proprietary technology based on the methylotropic yeast, *Pichia pastoris,* to produce insulin which was not explored before, hence it was not patent protected.

Pichia as a production system was familiar to us as we had used it in the past to make recombinant phytase, an enzyme used in human health and animal nutrition.

Our rh-Insulin underwent extensive clinical trials in India before we obtained regulatory approval to launch the product as Insugen® in 2004. We compelled the innovator companies to drop prices of their brands by launching Insugen® at a fraction of prevailing insulins prices.

Today, our rh-Insulin is registered in over 40 countries worldwide and has been commercialized in many emerging markets.

Moving to Modern Insulins

The 1990s saw the advent of insulin analogs, which mimicked the body's own insulin production. Insulin Glargine was the first long-acting analog to become commercially available. It allowed better metabolic control, thereby ensuring a better quality of life and improved treatment satisfaction. Having made a difference to people with diabetes in India with our rh-Insulin, we took up the challenge of developing biosimilar Insulin Glargine.

The completion of the process and analytical development, non-clinical and clinical studies for Insulin Glargine in India culminated in its approval and subsequent launch under the brand name Basalog® in 2009, providing diabetes patients with an advanced, affordable insulin therapy.

To take biosimilar Insulin Glargine to people with diabetes worldwide, Biocon initiated a global development program in 2010. The program got a fillip in 2013, after Mylan, a global leader in generic medicines, came forward to partner us for co-developing a basket of insulin analogs, including Insulin Glargine, Insulin Aspart and Insulin Lispro. It was an extension of an earlier agreement to jointly develop monoclonal antibodies and other biologics with Mylan for global markets.

Introducing Patient-Friendly Insulins Devices

As insulins use increased globally, insulin makers across the world began replacing syringe delivery with novel delivery devices like insulin pens, which were less painful and provided people with diabetes an easy-to-use, convenient-to-administer and accurate method of insulin delivery.

2015

Our biosimilar Insulin Glargine was the first insulin to be approved as per the new bio-comparable guidelines of COFEPRIS, Mexico, in 2015.

In 2011, we introduced INSUPen®, a reusable insulin device manufactured with high precision German technology, which offered metered dosing of Insugen® & Basalog®.

Biocon's reusable pens are today available in India, Malaysia and a few other emerging markets, where they have made a significant impact on the quality of life of patients who need treatment for their diabetes.

To take our insulins to the maximum number of people with diabetes we added disposable pens to our portfolio in 2015 since most of the patients on insulin in the Western world preferred this option. We partnered with one of the world's leading medical device makers, Becton Dickinson, to design a pre-filled, disposable insulin pen for both the Indian and global markets. This was the first product to roll out from our Bengaluru-based devices facility set up for manufacturing new generation, patient-friendly insulin devices. The pen, Basalog One®, strengthened our Insulin Glargine portfolio comprising vials, refills and reusable devices.

Making a Difference in Diabetes Management Worldwide

In line with our commitment to make global impact we forged strong regional partnerships in many key emerging markets to provide access to our high-quality yet affordable recombinant human insulin.

For instance, in Mexico, along with our partner Lab PiSA, we have been providing access to our affordable rh-Insulin therapy for over a decade. In 2015, our Insulin Glargine became the first insulin to be approved as per the new bio-comparable guidelines of COFEPRIS, the Mexican Health Authority.

The debut of our insulins in the developed markets happened in 2016 with the approval of our Insulin glargine pen in Japan. This was a landmark achievement for us. While Biocon did the product development, the Japanese partner FUJIFILM Pharma conducted the local clinical studies and commercialized our product.

We had finally entered a regulated market with our own biosimilar, and in doing so became the first company from India to commercialize a biosimilar in Japan.

The approval of our product enabled access to an affordable, world class, pre-filled, disposable pen for the 7.2 million people with diabetes in Japan in 2016 *(IDF)*. Till then, only seven biosimilars had received approvals in Japan, including one biosimilar version of Insulin Glargine. Given Japan's reputation of high product quality expectations and stringent manufacturing standards, the commercialization of our product enhanced our global credibility manifold.

Our partner Mylan submitted a Marketing Authorization Application (MAA) for biosimilar Insulin Glargine with the European Medicines Agency in 2016. It culminated in the approval of Semglee® (Insulin Glargine) in March 2018 and its commercialization in late 2018. Mylan also obtained approval for Semglee® in Australia subsequently.

Our biosimilar Insulin Glargine has been approved in over 60 countries and is commercialized in several key emerging markets like Mexico, Malaysia, South Korea, and UAE, where it is offering an affordable treatment option to millions of people with diabetes.

Even as we make a difference globally with our biosimilars for rh-Insulin and Insulin Glargine, we are working on widening our basket with Insulin Aspart. This rapid-acting insulin analog is currently progressing well in Phase III clinical studies.

Looking to Address the Insulins Crisis in U.S.

We are sensitive to the plight of insulin-dependent diabetes patients in the U.S., where prices of this essential medication have tripled between 2002 and 2013 and many patients are spending hundreds, sometimes thousands, of dollars out of their pockets every month to buy innovator brands *(JAMA)*.

As a company driven by its mission to provide affordable access to high quality, life-saving therapies, we are committed to enable access in the U.S. to our insulins for patients with diabetes.

40+

Our rh-Insulin is registered in over 40 countries worldwide and has been commercialized in many emerging markets.

Our strategy of disruptive pricing helped increase insulin access for diabetes patients in India 15 years ago. Since then we have built one of Asia's largest integrated insulins manufacturing facilities in Malaysia and India to drive economies of scale, enabling us to provide millions of doses of insulin at affordable prices in emerging and developing countries, including Japan and some countries in the European Union.

In fact, we have been providing our insulins in Mexico through our partner for over a decade at a fraction of the price patients pay in the U.S. Through rh-Insulin and Insulin Glargine we have been helping people with diabetes in Mexico manage their condition better by providing affordable access to these critical insulin therapies.

We initiated global development for Insulin Glargine to address patient needs in the U.S. in 2010 and our partner Mylan made a regulatory submission in 2017. However, a 30-month stay was triggered on the approval of the biosimilar due to a patent litigation initiated by the innovator. We believe the final approval of Insulin Glargine is linked to the end of stay period which is expected in March 2020.

Furthermore, we have initiated development of rh-Insulin for the U.S. market. We are greatly encouraged by the positive actions taken by the U.S. FDA in clarifying the path to approval of biosimilar insulins through the transition from the 505 (b)(2) to the 351(k) legislations and in terms of specifying requirements for an interchangeable designation.

Targeting Cancer & Autoimmune Diseases

Our multi-disciplinary technological capabilities combined with a growing expertise in clinical development enabled us to enter the complex territory of mammalian cell culture technology as early as 2003. Mammalian cell culture is key to developing monoclonal antibodies (mAbs), which are complex biomolecules that display specific affinity towards the target antigen or receptor on a tumor cell and initiate a complex set of events that leads to tumor regression and in some patients, complete remission.

Though these molecules stood at the steep end of the learning curve, we leveraged our cutting-edge science and technology capabilities in process development and analytical characterisation to develop in-licenced humanized antibodies for life threatning diseases like cancer and autoimmune conditions like psoriasis. Our path-breaking work in the field led to the launch of India's first novel mAb in 2006. It also drew global attention to our R&D capabilities in the realm of complex biologics. Mylan partnered with us in 2009 to develop a high value portfolio of biosimilars, comprising Trastuzumab, Pegfilgrastim, Bevacizumab, Adalimumab and Etanercept. In 2018, we agreed to expand our collaboration and added two new next-generation biosimilar programs.

Bringing World's 1st Biosimilar Trastuzumab to India

Our collaboration with Mylan witnessed its first success in India in 2013, when our molecule became the first biosimilar

Trastuzumab to win approval anywhere in the world. Trastuzumab was hailed as a path-breaking targeted therapy for HER2-positive breast cancer patients. The aggresive cancer cells spread more rapidly than other breast cancers, putting women with HER2-positive breast cancer at a much higher risk of death.

Successful completion of multi-centric clinical trials in India led to the approval and subsequent launch in 2014 of the biosimilar under the brand name CANMAb™ in India for treatment of HER-2 positive breast cancer.

2017

The U.S. FDA approval of Ogivri®, our biosimilar Trastuzumab, in 2017 was an endorsement of Biocon and Mylan's combined strength of cutting-edge science, clinical development and manufacturing capabilities.

Putting India on the Global Biosimilars Map

We had started a global study in 2013 to evaluate the comparative efficacy and safety of our biosimilar Trastuzumab versus the reference product. This HERITAGE study was the last major step of a multi-phased program to demonstrate that our biosimilar Trastuzumab met the criteria for equivalence in comparison to the reference product. Results of the landmark study allowed our partner Mylan to submit a robust data package to the U.S. FDA as part of its Biologics License Application for biosimilar Trastuzumab in November 2016.

In mid-2017, the U.S. FDA's Oncologic Drugs Advisory Committee (ODAC), which provides independent expert advice to the agency on issues including product approvals, unanimously concluded that no clinically meaningful differences existed between our biosimilar and the innovator product in terms of safety, purity and potency.

The 16-0 recommendation by ODAC culminated in the final approval for Ogivri® in December 2017, making us the first globally to win U.S. approval for biosimilar Trastuzumab indicated for certain HER2-positive early stage and metastatic breast cancers, as well as, metastatic gastric cancer. It was a historic achievement, as we were the first company from India to get U.S. FDA approval for a biosimilar.

We followed up with regulatory approvals for Ogivri® in the developed markets of EU and Australia in 2018. Breast and gastric cancer patients in several countries in Europe are now benefiting from our biosimilar Trastuzumab after Mylan commercialized it in early 2019.

We have also made this key cancer therapy affordable and thus accessible for cancer patients in several emerging markets in the Latin America, AFMET and APAC regions.

1st to Launch Key Biosimilar Cancer Therapy in U.S.

Biocon and Mylan achieved another first in the form of U.S. FDA approval for the jointly developed biosimilar Pegfilgrastim, Fulphila®, in June 2018, crossing the finishing line ahead of a pack of strong competitors.

The approval for Fulphila® was based on a comprehensive package of analytical, non-clinical and clinical data, which confirmed that the product is highly similar to the innovator brand. The drug reduces the duration of febrile neutropenia (fever or other signs of infection with a low count of neutrophils, a type of white blood cells) in patients treated with chemotherapy in certain types of cancer.

Fulphila® became the first biosimilar from our joint portfolio and the first biosimilar Pegfilgrastim commercialized in the U.S. Since its introduction in July 2018, Fulphila® has captured a 21% share of Pegfilgrastim syringes market volume in the U.S. *(Bloomberg Symphony data in Goldman Sachs report May 2019)*.

60+

Our biosimilar Insulin Glargine has been approved in over 60 countries and has been commercialized in several countries globally.

Fulphila® has also won approvals in the developed markets of EU, Australia and Canada. These approvals have expanded our oncology portfolio for the benefit of cancer patients and supported our global mission to improve access to high quality, affordable biologic therapies to treat cancer.

Expanding our Oncology Portfolio In India

We launched KRABEVA®, our biosimilar Bevacizumab, in India in November 2017. Our second oncology biosimilar in India after Trastuzumab, KRABEVA® is prescribed for metastatic colorectal cancer (mCRC) and several other types of lung, kidney, cervical, ovarian and brain cancers. We obtained approval to market this biosimilar in India on the basis of a Phase III clinical study conducted on mCRC patients.

To take the drug to a global patient pool we are conducting global Phase III clinical trials for biosimilar Bevacizumab, which are making good progress.

Working on Next-Gen Biosimilars

In 2018, we signed another global partnership for biosimilars with Sandoz, a Novartis division to co-develop a set of immunology and oncology biosimilars.

The collaboration with Sandoz will give us the opportunity to participate in end-to-end development and manufacturing of partnered products, as well as obtaining regulatory approvals and commercializing them in chosen geographies.

Work on the biosimilars partnered with Sandoz, though at an early stage, prepares us for the next wave of biosimilar opportunities scheduled to emerge by the middle of next decade.

Promising Opportunities Ahead

Given their potential to deliver enhanced patient care, the medical and pharmaceutical world is very optimistic about the biosimilars opportunity. More than 400 million patient days of clinical experience worldwide have been generated between and 2006 and 2016, providing enough evidence to suggest that biosimilars can be used as safely and effectively as their reference medicines.

At the same time, biosimilars have increased patient access to latest treatments. The availability of biosimilar Filgrastim ensured 44% more patients in the five largest EU markets gained earlier access to gold standard medicines between 2006 and 2014 *(Medicines for Europe report)*.

Thus, biosimilars are an exciting space to be in, promising long-term growth for early movers like Biocon.

Over a span of a decade, we have developed a rich pipeline of approved and in-development biosimilars that have concurrently built high end R&D and regulatory expertise. Along with Mylan, we have successfully commercialized three biosimilars in the developed markets, viz. Pegfilgrastim in U.S., Trastuzumab and Insulin Glargine in Europe. Biocon-supplied products also hold dominant shares for Trastuzumab, rh-Insulin and Insulin Glargine biosimilars in several key emerging markets.

Our biosimilars addressed the needs of nearly 2 million* patients in FY19, and we aim to touch 2.6 million patient lives in FY20 in line with our commitment to make a difference to patients globally in managing diseases that are chronic, and where medical needs are largely unmet and therapy costs are high.

**Note: The estimated patient reach numbers have been calculated indirectly based on volume supplied and certain assumptions related to dosage per patient, duration of treatment, units sold, internal data and market research reports.*

Status of Biocon's Global Biosimilars Portfolio

	Therapeutic Area	Molecule	Status
MYLAN & LOCAL PARTNERS	Oncology	TRASTUZUMAB	Launched in EU & Emerging Markets. Approved in U.S., Canada & Australia.
	Oncology	PEGFILGRASTIM	Launched in the U.S. Approved in EU, Australia & Canada.
	Oncology	BEVACIZUMAB	Launched in India. Global Phase III.
	Oncology	FILGRASTIM	Preclinical
	Oncology	PERTUZUMAB	Early development
	Diabetes	INSULIN GLARGINE 100 IU/ML	Launched in the EU, Japan# & Emerging Markets. Approved in Australia & New Zealand. Under review in U.S.
	Diabetes	INSULIN GLARGINE 300 IU/ML	Early development
	Diabetes	INSULIN ASPART	Global Phase III
	Diabetes	INSULIN LISPRO	Preclinical
	Diabetes	RECOMBINANT HUMAN INSULIN	Launched in Emerging Markets. In active development for U.S. (partnered with Lab PiSA)
	Autoimmune	ADALIMUMAB	Partner Mylan has launched in-licensed product Hulio® in EU. Biocon benefits from economic interest
	Autoimmune	ETANERCEPT	Partner Mylan's in-licensed product filed for approval in EU. Biocon retains economic interest
SANDOZ	Oncology & Immunology	VARIOUS ASSETS	Early stage development

#Japan launch is outside of the Mylan partnership

As on May 2019

BIOLOGICS: FY19 at a Glance

Revenue

15,169

₹ Million

Growth 97%

FY19 has been a landmark year for the Biosimilars business, with revenues of the Biologics segment doubling over last year, to cross the USD 200 million milestone. Our biosimilars strategy has begun to deliver results with the launch of our key biosimilars in the U.S. and Europe and other global markets. The launch of biosimilar Pegfilgrastim in the U.S. and increasing sales of biosimilar Trastuzumab in the emerging markets were the main contributors to this growth.

Other notable highlights include launch of biosimilar Insulin Glargine, biosimilar Trastuzumab and in-licensed biosimilar Adalimumab, by our partner Mylan in Europe.

Higher revenues, including impact of profit share in both developed and emerging markets, offset higher R&D and fixed costs, leading to significant improvement in margins not only in the Biologics segment, but also at the consolidated level. Segment PBIT improved from negative 2% last year to 26% in FY19, reflecting a very strong performance over last year.

+ Read more on Biologics Business : Page 136

Sources:
1. *Biosimilars: An emerging market opportunities in India (P Rushvi, K Charmy, C Nirav, C Narendra - Pharmaceut. Reg. Affairs, 2016)*
2. *U.S. FDA website*
3. *Cell factories for insulin production (Baeshen NA, Baeshen MN, Sheikh A, et al. - Microb Cell Fact, 2014)*
4. *Pichia Power: India's biotech industry puts unconventional yeast to work (Chandra Shekhar - Chemistry & Biology, 2008)*