White Paper

Advancing Biosimilars in the Czech Republic

Challenges and Opportunities

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Executive summary

Since their introduction more than 100 years ago, biologics have seen a steep rise in R&D as well as commercialization and a substantial increase across a wide spectrum of therapeutic areas, where they help improve patients' lives. The combination of high R&D costs, uncertain results, and difficult manufacturing processes is often a barrier for the introduction of new biologics, driving the price up and keeping innovative therapy out of reach for many patients. Biosimilar drugs, consisting of a similar molecular structure to the original biologic reference drug, bring additional competition to therapeutic areas where the patent has expired. The potential of biosimilar competition is immense – in the top 10-selling biologics alone, four products are threatened by biosimilars, which present a combined competitive threat of $58.6 billion worth of biologics sales.

At ex manufacturer's prices, excluding VAT, the biologics market in the Czech Republic is valued at CZK 30 billion as of MAT 06/2021, showing a year-on-year growth of 17.4%. The six-year CAGR of 11% shows steady growth of sales and biologics uptake, even though the market still has a long way to go to reach levels seen in the the EU4 and the UK. In the Czech Republic, original biologics account for 94%[1] of the entire market or CZK 28.5 billion – that can be split into patented biologics with sales of CZK 23.5 billion (78% market share) and biologics with expired patents with sales of CZK 4.9 billion (17% market share)[2].

Meanwhile biosimilars sales reached CZK 1.7 billion as of MAT 06/2021, representing a four-year CAGR of 26%. 86% of all biosimilars sales are within the ATC1 L category – antineoplastic and immunomodulating agents, while the other categories account for 3-4% each.

Currently, there are several areas which present both opportunities and challenges for further advancement of biosimilars in the Czech Republic, including a multi-faceted tendering system, which is good for competition but also presents increased operational complexity and lower transparency. Overall, the competitive environment for biosimilars in the Czech Republic is very fragmented with many direct and indirect influences in place. However, the Czech Republic has a strict pricing policy embedded in its legal framework, firmly regulating drug prices.

To make drug prices affordable, the Czech Republic employs a policy which requires generic medicine to be at least 40% cheaper than the originator; for biosimilars, the requirement has been raised from 15% to 30%. With the already stringent pricing policies in place requiring drug prices in the Czech Republic to be the equivalent of the three lowest prices in the EU reference basket, such pricing requirements put additional pressure on manufacturers who may prefer delayed or no entry to the Czech market.

Biosimilars' uptake remains generally slower than in Western Europe. The current environment in the Czech Republic has both risks and benefits for biosimilars – while individual tenders support the competitive environment and desired long-term innovation and prescribing freedom helps healthcare professionals gain experience with multiple biosimilar alternatives, the complexity of the entire system and strong emphasis on pushing prices as low as possible makes the market a difficult one. The introduction of a unified European pharmaceutical strategy may bring some more clarity to the system and help drive the uptake of biosimilars in the Czech Republic. We maintain a positive outlook and expect the environment to develop in favor of greater biosimilar adoption in the Czech Republic.

1 Percentage shares may not add up to 100% due to rounding.
2 Percentage shares may not add up to 100% due to rounding.

The role of biosimilar drugs from a global point of view

Biologics are drugs derived from living organisms that have been used in medicine for over 100 years. Unlike synthesized, non-biological medicines, which are traditionally produced using well-defined molecular structures and chemical processes, biologic drugs are produced differently. According European Medicines Agency, "biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast) and are often produced by cutting-edge technology."[3]

Certainly, the largest downside of innovative biologic medicines is their very high cost, which is due to large capital expenditure in research and development, clinical trials, and expensive manufacturing processes. The cost of biologics is a significant expense driver for healthcare systems. Patient access to some innovative biologics may therefore be limited due to their high prices, both in countries with private healthcare systems and in countries with publicly funded healthcare systems.

When biologic drugs lose their patent protection, new competitors may enter the market by launching biosimilar medicines. According to the European Medicines Agency, "A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."[4] However, unlike conventional prescription drugs and their generic competition, biosimilar drugs do not contain an identical copy of the molecule. This means that scientific evidence still needs to be gathered to prove positive treatment effects in patients. It is important to point out a very unique aspect of biosimilars and the approval process – "if the total evidence supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer."[5] With sufficient scientific evidence, biosimilarity can be then extrapolated to all other indications of the original reference product. This allows biosimilar medicines to possibly serve multiple indications of the reference product at once with much less research effort than the reference drug underwent, usually in multiple stages for individual indications. For example, the Norwegian government-funded NOR-SWITCH trial showed that switching from originator infliximab to a cheaper biosimilar alternative, CT-P13, produced satisfactory results with minimal differences in patients given the biosimilar alternative compared to patients continuing on their original infliximab treatment.[6] Since the very first biosimilar – Omnitrope – was approved in 2006[7], numerous new biosimilars have been approved.

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3 European Medicines Agency. *Biosimilar medicines: Overview*. December 2021. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview.

4 European Medicines Agency. *Guideline on similar biological medicinal products*. October 2014. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-Biological-medicinal-products-rev1_en.pdf.

5 IQVIA Institute for Human Data Science. *The Prospects for Biosimilars of Orphan Drugs in Europe*. July 2020. Available from: https://www.iqvia.com/es-ar/insights/the-iqvia-institute/reports/the-prospects-for-Biosimilars-of-orphan-drugs-in-europe.

6 G. L. Goll, et al. *Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial*. April 2019. Available from: https://pubmed.ncbi.nlm.nih.gov/30762274/.

7 Martin Schiestl, Markus Zabransky and Fritz Sörgel. *Ten years of biosimilars in Europe: development and evolution of the regulatory pathways*. May 2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440034/#:~:text=The%20first%20Biosimilar%20medicine%2C%20Omnitrope,by%20the%20EMA%20in%202006.

When new biosimilar competition enters the biologics market, the price of treatment is likely to be driven lower, and innovative treatment may therefore become available to more patients. As outlined in the example below, evidence clearly shows that biosimilar alternatives can achieve a lower price in comparison to the originators' pre-biosimilar price. While the price discount ranges differ significantly for individual biosimilars, from a global perspective, a 30% price discount expectation on average appears to be reasonable, even though higher discounts may occur in the future.

For example, in the United States, the presence of biosimilars in the market is projected to generate over $100 billion in savings between 2020 and 2024. Another important example from the United States is the 2–4% increase in incremental demand for a molecule, showing that biosimilars bring lower-cost treatment options to more patients.[8]

[PLEASE NOTE THAT ALL FOLLOWING VALUES ARE SHOWN AT EX-MANUFACTURERS' PRICES, EXCLUDING VAT.]

The global biologics market is valued at $421.7 billion (as of MAT 6/2021) and biosimilars sales reached $22.4 billion or ~5.3% of all biologics sales.[9] In terms of overall biologics sales from the financial perspective, the United States is the clear world leader with 59% of global sales, followed by the EU4 and the UK with 14% and Japan with 5%; the rest of the world accounts for 22% of all other sales combined. Global biosimilars sales are also led by the United States – 37%, followed by the EU4 and the UK – 34%, Japan 4%, and the rest of the world combined accounts for the remaining 25% of sales.[10] From a global point of view, biosimilars have grown enormously in recent years. The 6-year CAGR of 51% highlights the immense interest in producing and providing more affordable biologic treatments to patients across the world.[11]

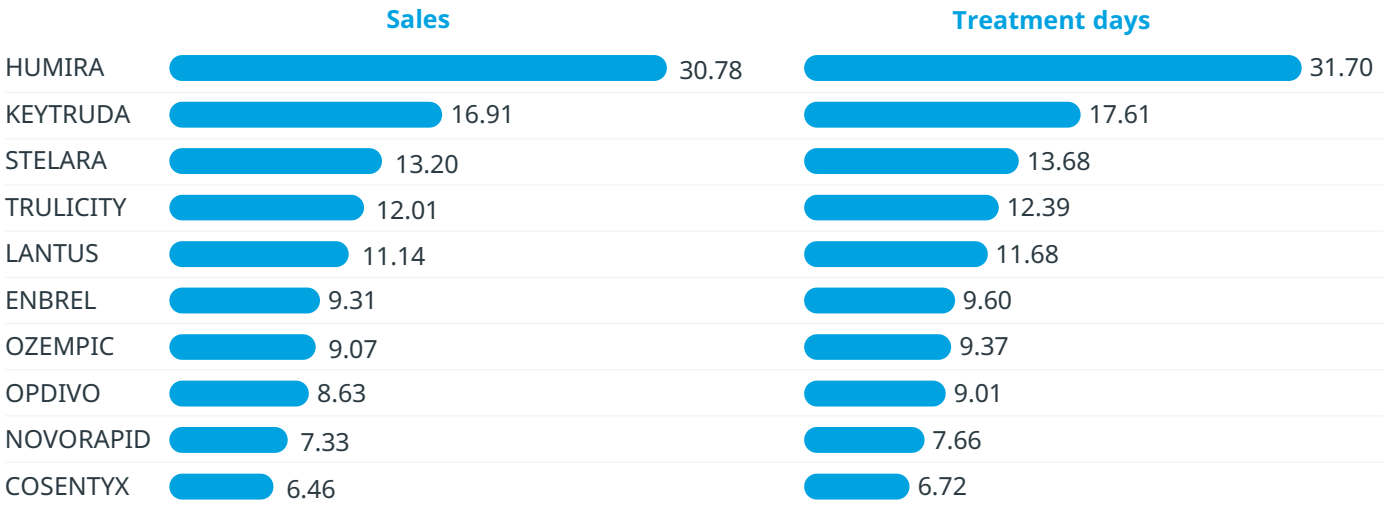
With sales over $9.5 billion in MAT 6/2021, Europe accounted for ~50% of all global biosimilars sales, making it the largest biosimilars market in the world.[12] However, the majority of sales is driven by the EU4 countries and the UK.

In terms of key players in the global biologics market, Humira remains the number one product with sales of $30.78 billion. In comparison, its best-performing biosimilar competitor, Amgevita, reached sales of $921 million in MAT 6/2021. However, Amgevita is yet to be launched on the US market in 2023.[13]

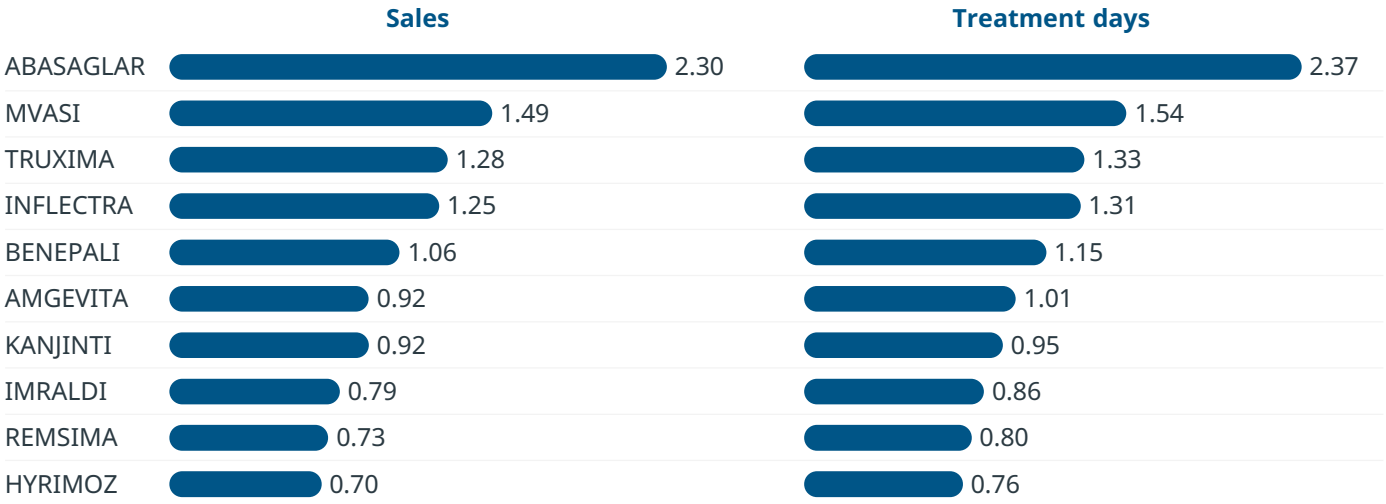
8 Murray Aitken, Michael Kleinrock and Elyse Muñoz. *Biosimilars in the United States 2020–2024*. October 2020. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/Biosimilars-in-the-united-states-2020-2024.
9 IQVIA MIDAS MTH, June 2021
10 IQVIA MIDAS MTH, June 2021
11 IQVIA MIDAS MTH, June 2021
12 IQVIA MIDAS MTH, June 2021
13 IQVIA MIDAS MTH, June 2021

Exhibit 1: Top 10 products in biologics and biosimilars[14]

Global TOP 10 biologics
[USD bn; treatment days bn MAT 06/2021]



Global TOP 10 biosimilars
[USD bn; treatment days bn MAT 06/2021]



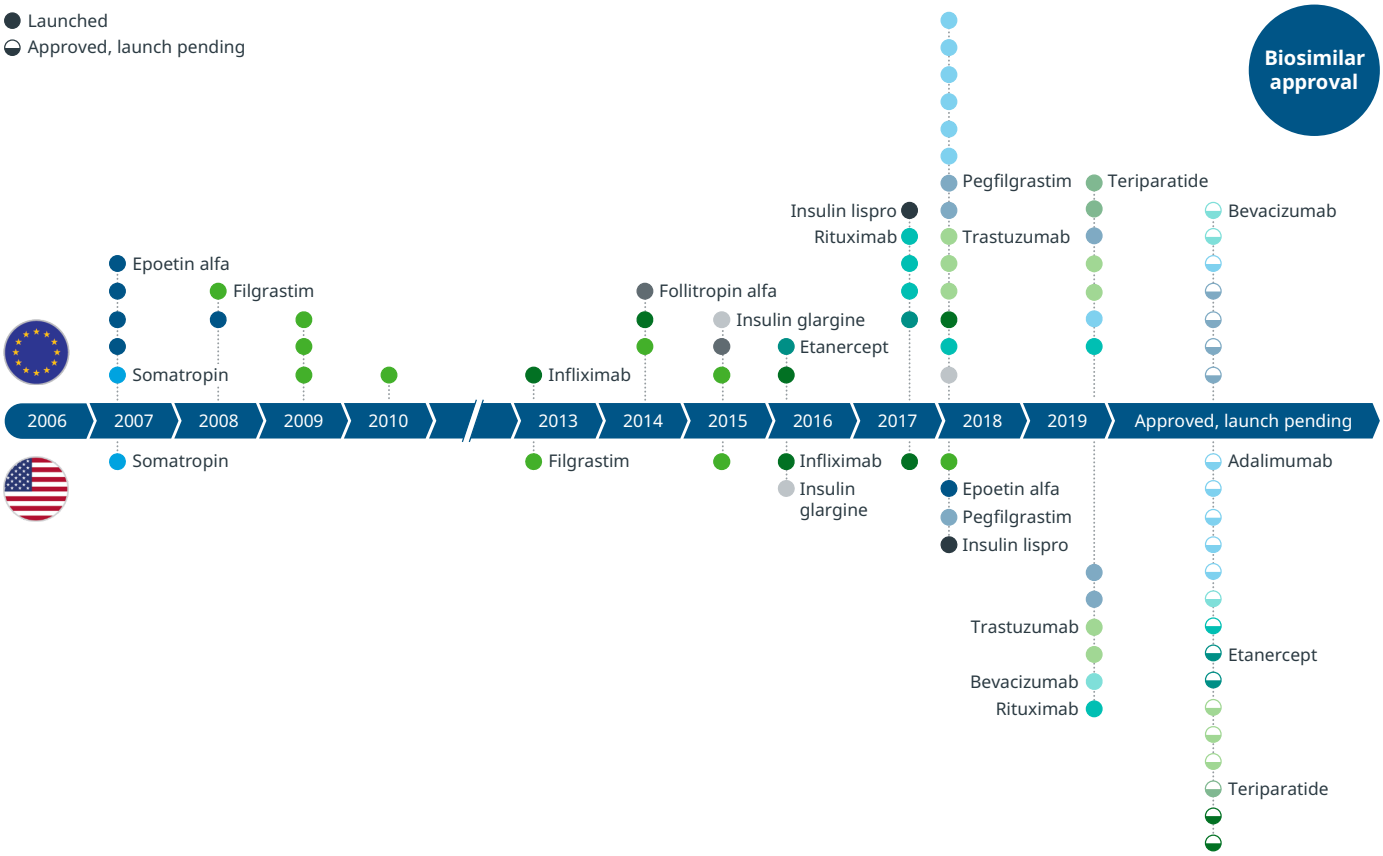
With more biologic patents expiring, the market is set to grow further in future years. In the top 10-selling biologics alone, four products are threatened by biosimilars – they present a combined competitive threat of $58.6 billion worth of biologics sales, representing 14% of all global biologics sales[15]. This illustrates how much potential growth for biosimilars there is, making it an attractive field for both pharmaceutical companies and especially medical professionals seeking more affordable biologic treatments for patients.

14 IQVIA MIDAS MTH, June 2021
15 IQVIA MIDAS MTH, June 2021

Biosimilars in the European Union

As of July 2021, 65 biosimilars for 18 molecules have been approved in the European Union[16], making it the most progressive biosimilars market in the world. Biologics continue to increase their share of the European prescription drug market. IQVIA's findings from 2018 data show that "in Europe over 30% of all drug spending is on biological medicines of which 1.5% are biosimilars".[17]

Exhibit 2: Historical overview of biosimilars approval progress until 2019[18, 19]



Since its first biosimilar approval in 2006 in the EU, the European Medicines Agency has collected evidence suggesting that biosimilars "can be used as safely and effectively in all their approved indications as other biological medicines."[20] Overall, the approach to biosimilars at both the European and country level generally supports the facilitation of safe biosimilar medication to provide better treatments at lower costs to patients

16 European Medicines Agency. *Medicines*. July 2021. Available from: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised-36/ema_medicine_types/field_ema_med_Biosimilar/search_api_aggregation_ema_medicine_types/field_ema_med_Biosimilar/ema_group_types/ema_medicine/field_ema_med_status/authorised-36.

17 Per Troein, Max Newton, Jyoti Patel and Kirstie Scott. *The Impact of Biosimilar Competition in Europe*. October 2019.

18 IQVIA Global Biosimilar database; IQVIA Institute, December 2019

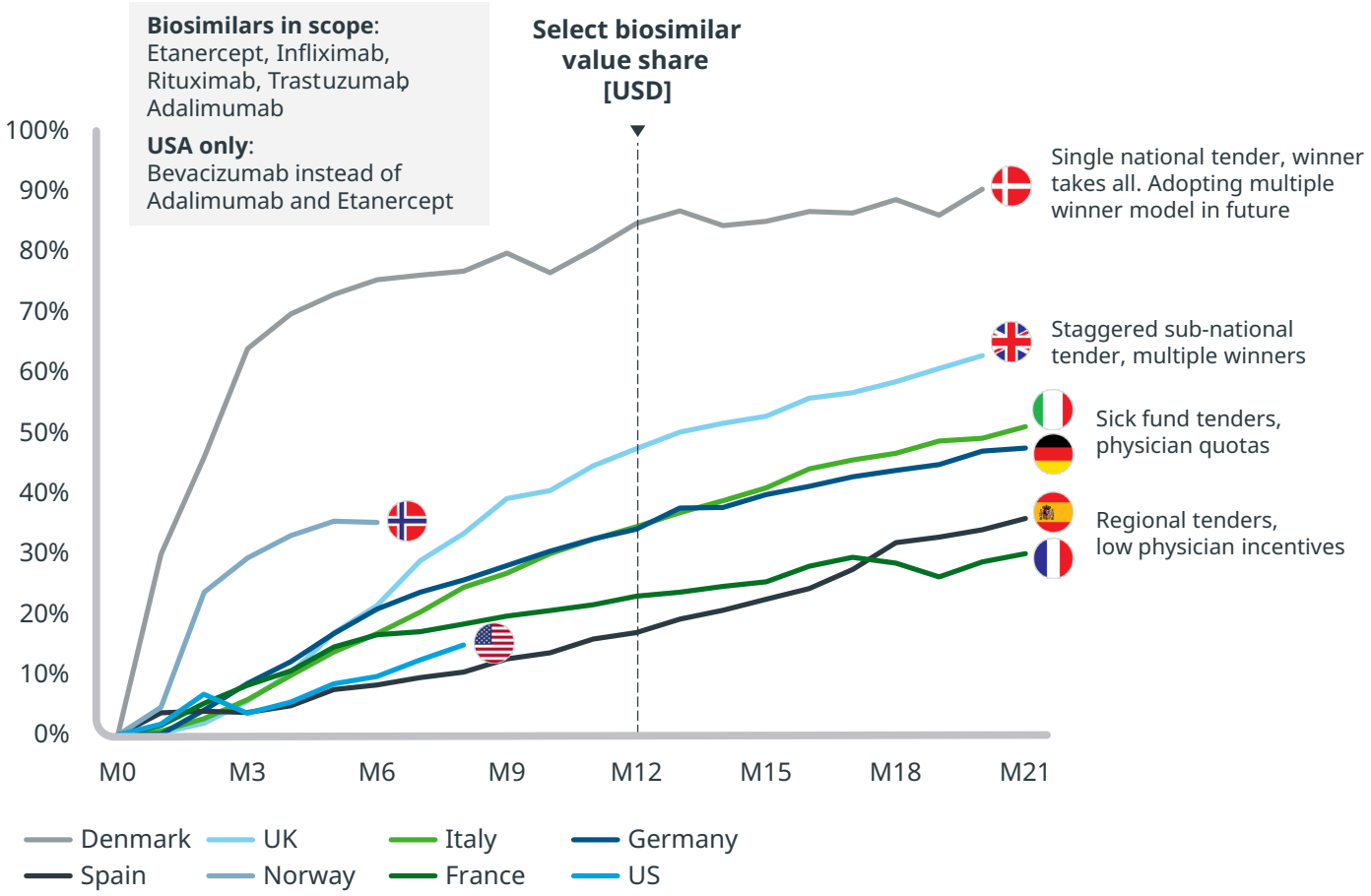
19 Chart notes: IQVIA Institute defines biosimilars as non-original versions of biologic products where a reference product is part of an abbreviated approval. In the US, this definition includes approvals through the 351(a), 351(k), and 505(b)(2) pathways. Biosimilars that have not been approved as of December 2019 have not been included. Biosimilar molecule entry date determined by launch anywhere in the EU. EMA considers inhixa and thorinane as biosimilars of enoxaparin sodium, however they do not meet the IQVIA Institute definition, and therefore are excluded. FDA approved M-Enoxaparin via the standard generic pathway as an ANDA and also does not consider it a biosimilar.

20 European Medicines Agency. *Biosimilar medicines: Overview*. July 2021. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/Biosimilar-medicines-overview.

in the European Union.[21] This supportive approach directly translates into clear savings for payers and relief for the often-stretched healthcare budgets in countries across the European Union.

Across a representative section of biosimilars, the EU4 countries + the UK achieved 20-40% uptake in market share (measured in values, USD) in the first year, showing that there is still room for improvement even in more developed markets in terms of biosimilars adoption time. The UK is a clear leader within the EU4 countries + the UK, with biosimilar market average reaching 40% after 12 months and poised to reach 60% after 24 months.

Exhibit 3: Biosimilar market share [selected molecules, USD][22]



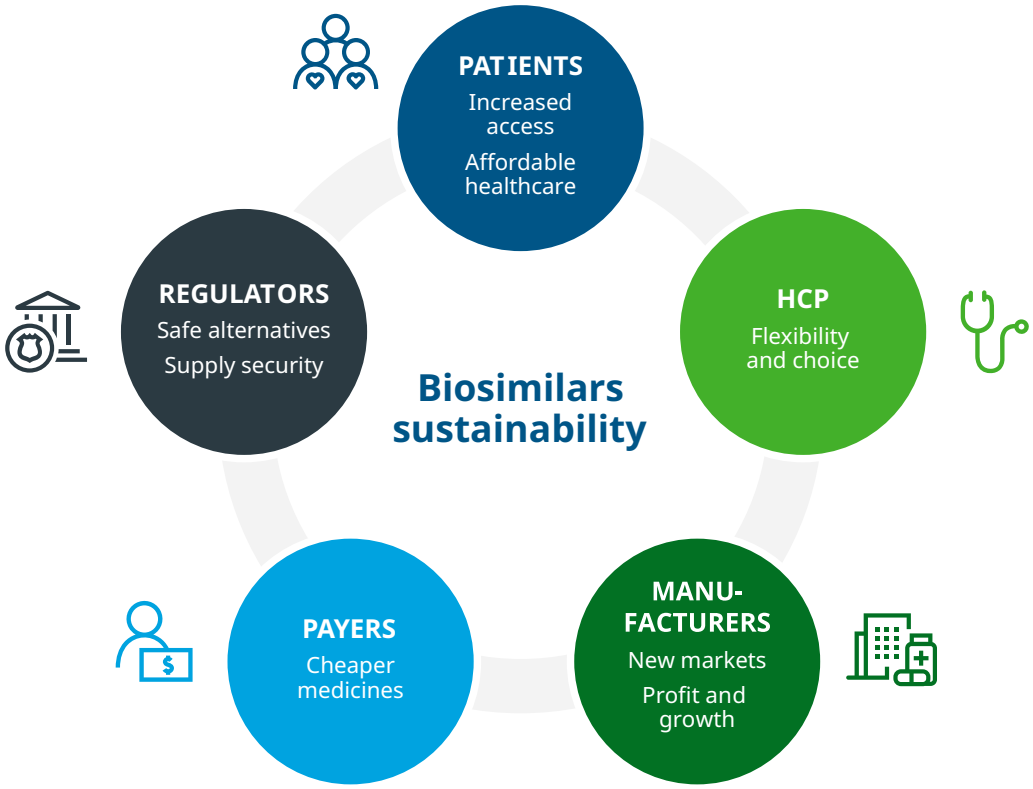
The first to market biosimilars encounter a favourable pricing environment and generally achieve much higher sales, although they still need to compete when it comes to the physicians' perception. Later entries, on the contrary, must be significantly more competitive and differentiated to avoid simply competing by lowering prices. The high importance of a properly timed market entry can be seen in the charts below, showing that the first entrant usually outperforms their competitive counterparts that entered later.

However, the concept of introducing biosimilars to European markets is not straightforward, and all stakeholders' positions need to be carefully considered to achieve biosimilars' sustainability.

21 Murray Aitken, Isabel Rodríguez, Joanna Diamantara and Manuel Vázquez. *Advancing Biosimilar. Sustainability in Europe*. September 2018. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-Biosimilar-sustainability-in-europe

22 IQVIA European Thought Leadership; IQVIA MIDAS MTH, June 2020

Exhibit 4: Cross-collaboration of all stakeholders is needed to ensure a healthy biosimilars ecosystem[23]



Patients primarily seek access to safe, affordable, and innovative biologic treatments – as such, biosimilars certainly lead to increased access to biologic treatments, both due to broader availability of products and competitive forces which drive prices lower. On the contrary, for example, patients with orphan diseases as well as their doctors may be reluctant to switch to a biosimilar alternative because they develop strong positive feelings towards the original drug which initially helped their condition.[24] The same applies to patients using self-administered biologics; they may be attached to the original biologic drug, thus they could be opposed to switching to a biosimilar product. Incentives in terms of lower co-pays or even the elimination of co-pays can help promote biosimilars among patients. In addition, adequate communication from health care professionals about the safety and benefits of biosimilars to patients is key.

European regulators aim to provide secure and reliable supply of biologics to the European Union while ensuring that safe alternatives are being provided to European patients to drive treatment costs lower. The centralized European approach to evaluation and regulation helps nurture the competitive environment, as it allows biologic manufacturers to access a large market with unified rules and requirements, making Europe attractive – thus providing patients access to a broad selection of biosimilar alternatives. The European market's regulation is unified except for interchangeability – switching and substitution, as individual EU member states are responsible for the regulation of prescribing practices and advice to prescribers, these areas fall under each state's own legal framework.[25]

23 IQVIA European Thought Leadership, June 2021

24 IQVIA Institute for Human Data Science. *The Prospects for Biosimilars of Orphan Drugs in Europe*. July 2020. Available from: https://www.iqvia.com/es-ar/insights/the-iqvia-institute/reports/the-prospects-for-Biosimilars-of-orphan-drugs-in-europe.

25 European Medicines Agency and European Commission. *Biosimilars in the EU*. October 2019. Available from: https://www.ema.europa.eu/en/documents/leaflet/Biosimilars-eu-information-guide-healthcare-professionals_en.pdf.

Healthcare professionals value flexibility and prescribing freedom – switching generally falls under the physician's prescribing freedom, as automatic substitution by the pharmacy is generally not allowed in the EU. In hospital settings, management and hospital pharmacists can enter the discussion and promote switching within the institution. When it comes to doctors, proper communication of biosimilars' safety and benefits for the healthcare system by pharmaceutical companies, regulators, and payers is key for increased uptake and confidence in biosimilars among doctors and patients. One of the European Medicines Agency's steps to increase public and healthcare professionals' trust in biosimilars is the transparency of the approval process as well as providing reliable information to health care professionals.[26] Faster biosimilar uptake and penetration is more common in specialties where health care professionals have been exposed to biosimilars before and are familiar with them.[27]

From the perspective of biosimilar manufacturers, apart from providing affordable treatment to patients, biosimilars represent an immense growth opportunity. Biosimilar manufacturers seek new markets, growth, and opportunities to maximize profits. As outlined above, the European market is generally unified in terms of regulation, thus quite attractive to operate in. Biosimilar manufacturers need to focus on communicating all benefits clearly and comprehensively to all stakeholders involved.

Finally, from the payers and policymakers' perspective, the goal with biosimilars is to provide safe and financially affordable biologic treatment while maintaining continuity of supply, sustainability of medicines, respecting prescribers' freedom, and patients' best interests. With healthcare budgets often being stretched, any savings on expensive biologic treatments are of great interest to payers. Simply put, a balance needs to be found between achieving maximum savings and maintaining the competitive forces of the market which lead to innovation, healthy competition, and sufficient, diversified supply. It is important to note that there are various approaches to biosimilars across Europe.[28] One of the key areas payers and country policymakers need to consider is the purchasing mechanism – some approaches include direct contracts between insurers and manufacturers, contracts between hospitals and manufacturers as well as bidding tenders, both with a single contract winner or multiple contract winners. Other bidding tender methods and their combinations are used across the EU, including single national tenders, multiple tenders, and various other combinations. In the case of a single contract, biosimilar manufacturers compete simply based on their product's price, which limits prescribers' freedom of choice and the competitive nature of the market. However, clinical rationale should be prioritized over economic benefits and physicians can still opt for other biologics as an exception. Most multi-winner tenders look at criteria beyond price and expect market forces to figure out the price, while providing a wider variety of biologics to patients and maintaining a competitive environment. According to a study conducted by the IQVIA Institute in 2018, countries with national tenders achieve the best price reduction on biologic molecules and have faster and higher biosimilar uptake, especially where a single-winner tender is conducted. Meanwhile, countries where national tenders are not used see moderate biosimilar uptake as physicians need more time to become familiar with individual biosimilar alternatives. However, markets with multiple-winner tenders may achieve lower average costs per defined daily dose for a region overall in some instances.[29]

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26 European Medicines Agency and European Commission. ***Biosimilars in the EU***. October 2019. Available from: *https://www.ema.europa.eu/en/documents/leaflet/Biosimilars-eu-information-guide-healthcare-professionals_en.pdf*.

27 IQVIA Biosimilar Sustainability Primary Market Research Program, expert interviews conducted. Jun-Jul 2018 in Murray Aitken, Isabel Rodríguez, Joanna Diamantara and Manuel Vázquez. ***Advancing Biosimilar Sustainability in Europe.*** September 2018. Available from: *https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-Biosimilar-sustainability-in-europe*.

28 Murray Aitken, Isabel Rodríguez, Joanna Diamantara and Manuel Vázquez. ***Advancing Biosimilar Sustainability in Europe***. September 2018. Available from: *https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-Biosimilar-sustainability-in-europe*.

29 Murray Aitken, Isabel Rodríguez, Joanna Diamantara and Manuel Vázquez. ***Advancing Biosimilar Sustainability in Europe***. September 2018. Available from: *https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-Biosimilar-sustainability-in-europe*.

Therefore, the selection process of biosimilars is not straightforward, especially when considering all sustainability factors as well as the continuity of supply, stocking issues, manufacturing issues, and the incentive to produce new biosimilars.[30]

It is also important to note that countries with already high usage of biologics see smaller absolute increase in biologic use upon biosimilar entry. On the contrary, countries with lower biologic use see a more significant uptake of biologic treatments when biosimilars enter their respective markets, such as in the Central Eastern European region.[31]

Exhibit 5: Biosimilar penetration [June 2021, treatment days][32]

		Hospital									Mixed	Insulin	
		Infliximab	Etanercept	Rituximab	Rituximab IV	Trastuzumab	Trastuzumab IV	Pegflagrastim	Bevacizumab	Teriparatide	Adalimumab	Insulin Glargine	Insulin Lispro
The EU4 and the UK	UK	95%	85%	93%	97%	45%	89%	77%	5%	67%	81%	13%	1%
	Germany	69%	79%	87%	90%	78%	87%	43%	80%	36%	72%	14%	5%
	France	76%	40%	80%	94%	47%	96%	73%	91%	20%	33%	25%	0%
	Italy	92%	71%	83%	96%	76%	97%	79%	57%	43%	72%	18%	11%
	Spain	79%	55%	82%	95%	65%	90%	90%	65%	45%	54%	15%	0%
	Netherlands	93%	32%	95%	96%	83%	100%	85%	94%	22%	43%	33%	14%
	Denmark	99%	93%	90%	100%	96%	99%	99%	95%	29%	96%	4%	0%
	Finland	98%	41%	90%	99%	73%	100%	45%	60%	4%	49%	4%	47%
	Norway	99%	3%	93%	99%	87%	99%	99%	92%	86%	90%	4%	1%
	Poland	100%	71%	90%	90%	38%	100%	100%	40%		95%	29%	27%
	Canada	26%	40%	51%	77%	88%	88%	98%	84%	9%	5%	28%	2%
	Japan	24%	47%	75%	75%	55%	55%	0%	12%	56%	3%	46%	17%
	US	26%	0%	55%	55%	69%	69%	36%	69%	0%	0%	23%	8%

High uptake — *Low uptake*

From the European point of view, there are significant differences in the uptake rates between both the retail and hospital channels as well as geographies. The uptake of biosimilars is generally quicker in hospital settings where contracts and hospital pharmacies may influence the prescribing decisions of physicians. In addition, any payer-driven incentives as well as specific contracts directly affect the financial results of a given medical institution. In the retail sector, biosimilars take longer to gain market share since HCPs outside hospitals have no direct connection to the national healthcare budget in addition to both HCPs' and patients' understanding of biosimilars. Various kinds of positive and negative payer-driven incentives have been implemented in Europe, including prescribing targets with financial and non-financial incentives and federal or national prescribing targets. Indirect incentives to patients, as discussed earlier, usually come in the form of lowering or eliminating co-pays.

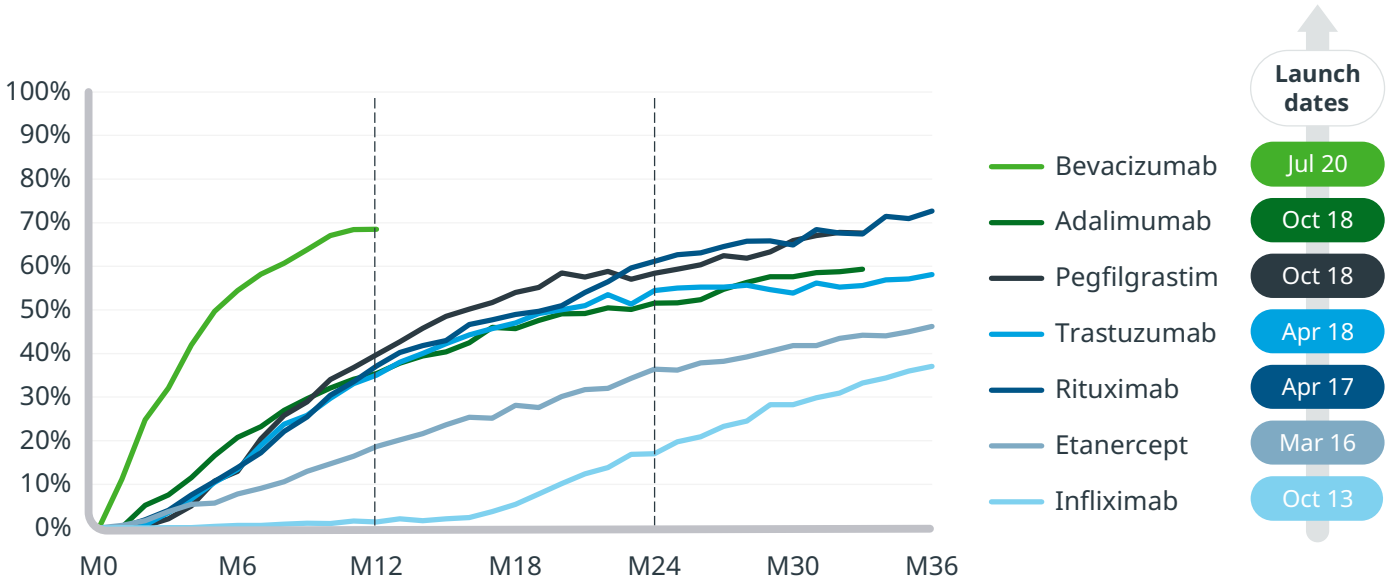
30 For detailed explanation tender analysis, see: Murray Aitken, Isabel Rodríguez, Joanna Diamantara and Manuel Vázquez. *Advancing Biosimilar Sustainability in Europe*. September 2018. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-Biosimilar-sustainability-in-europe.

31 Per Troein, Max Newton, Jyoti Patel and Kirstie Scott. *The Impact of Biosimilar Competition in Europe*. October 2019.

32 IQVIA MIDAS MTH, June 2021

For hospitals, the incentives are less direct and formal but translate directly into uptake of biosimilars. However, any payer-driven incentives reduce prescription freedom to some extent and may influence HCPs to value economic judgement over clinical judgment.

Exhibit 6: Representative example of European biosimilar uptake rate, months since launch in treatment days[33, 34]



In terms of achieving maximum biosimilar penetration and uptake, the single-winner tender approach and utilization of payer-driven incentives happen to be the most effective as they increase patients' access to biologic medicines relatively quickly. However, from the long-term perspective, payer-driven incentives negatively impact the competitive environment and may exclude certain manufacturers from being able to compete in a given country. The utilization of single-winner tenders directly excludes competition from the marketplace but it theoretically provides increased access to biologics for more patients. However, such an approach may limit a healthy level of competition and innovation in the long run. Selecting a single provider of a given medicine also poses a risk to medicine supply in case of any disruption in the manufacturer's supply chains or factories. Therefore, finding the right balance between achieving maximum savings and nurturing a healthy market competition that stimulates innovation is key for a long-term, sustainable strategy for biosimilars in Europe.

33 IQVIA European Thought Leadership; IQVIA MIDAS MTH, June 2021
34 Includes subcutaneous formulations for rituximab, trastuzumab and infliximab

Opportunities and challenges for advancing biosimilars in the Czech Republic[35]

[PLEASE NOTE THAT ALL FOLLOWING VALUES ARE SHOWN AT EX-MANUFACTURERS' PRICES, EXCLUDING VAT.]

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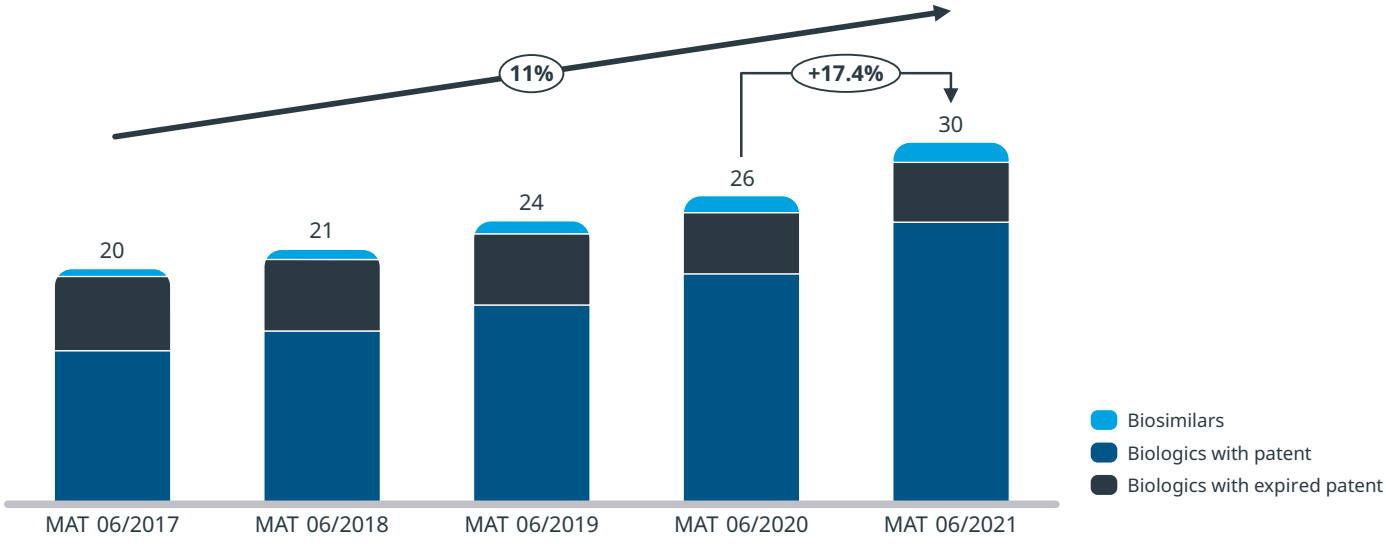
Exhibit 7: Total biologics sales in the Czech Republic [CZK bn][37]



According to IQVIA sell-in data, as of MAT/06/2021, biosimilars sales reached CZK 1.68 billion, representing a four- ear CAGR of 26%.

35 All financial figures presented in this chapter are at EX-MNF level, excluding VAT
36 Percentage shares may not add up to 100% due to rounding
37 IQVIA MIDAS MTH, June 2021

Exhibit 8: Czech Republic biosimilars market value [CZK m][38]

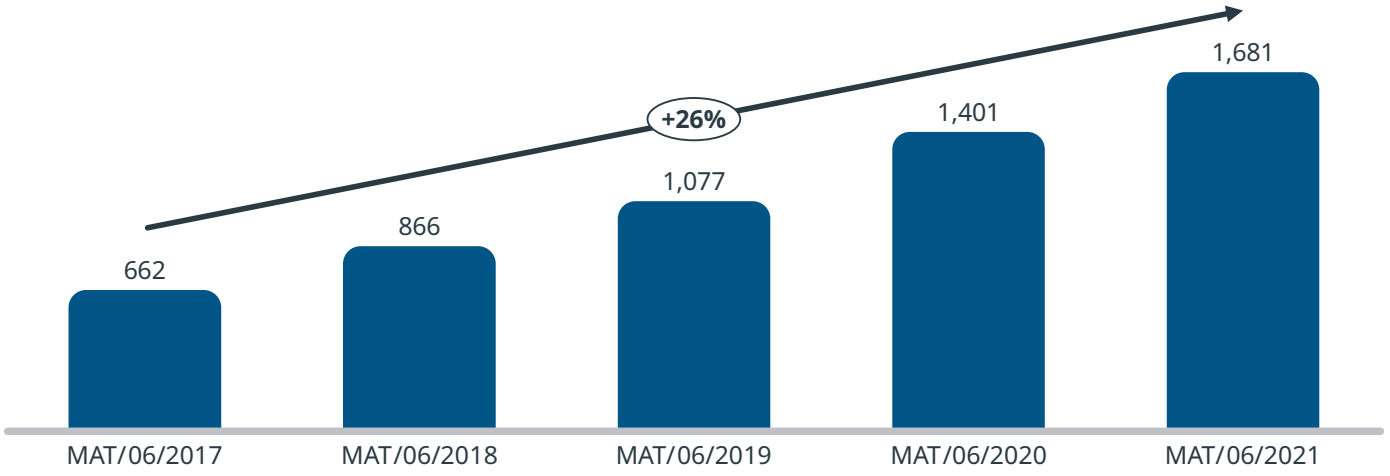
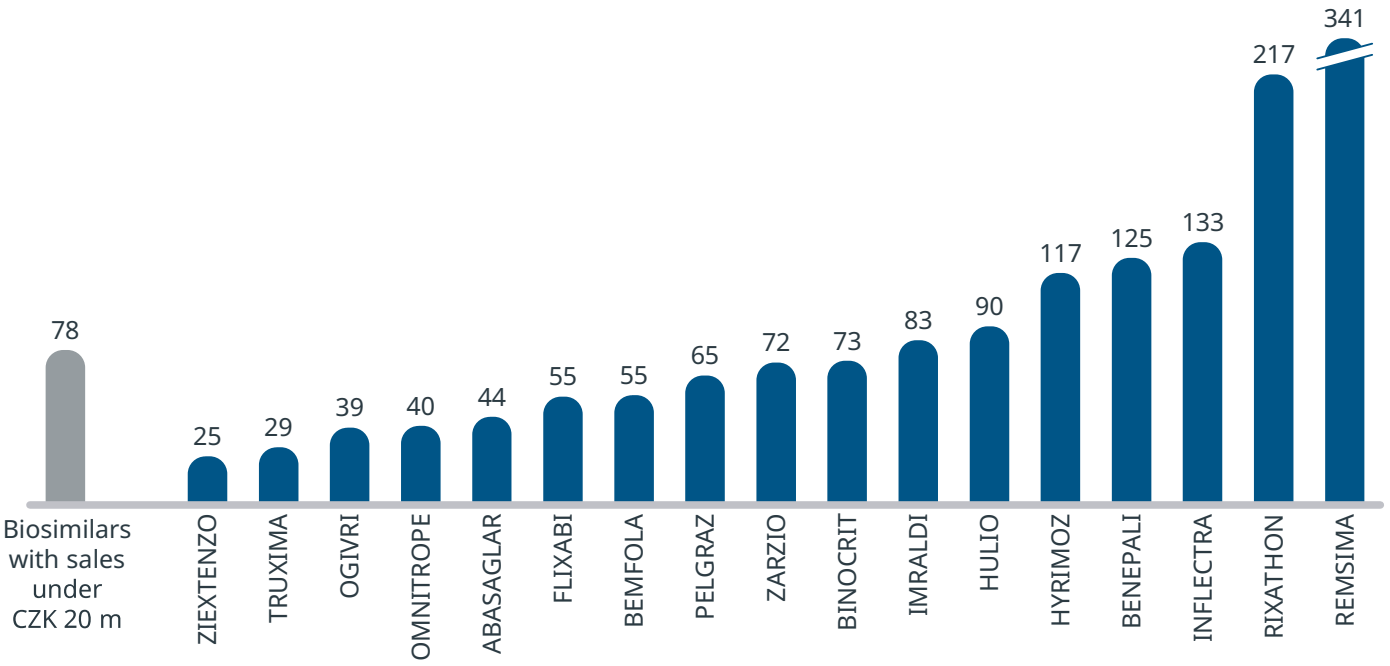


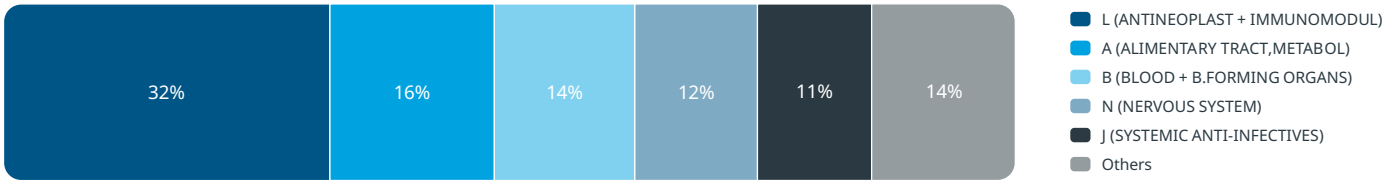
Exhibit 9: Share of biosimilar sales in the Czech market [MAT 06/2021 in CZK m][39]



The sales of biologics in the Czech Republic are led by the ATC1 L biologics (antineoplastic and immunomodulating agents), accounting for 32% of sales. Followed by the ATC1 A biologics (alimentary tract and metabolism) at 16%, ATC1 B (blood and blood forming organs) at 14%, ATC1 N (nervous system) at 12%, ATC1 J (anti-infectives for systemic use) at 11%, and other groups accounting for 14% combined.[40]

38 IQVIA CZ Sell-in, MAT June 2021
39 IQVIA CZ Sell-in, MAT June 2021
40 Percentage shares may not add up to 100% due to rounding.

Exhibit 10: Breakdown of biologics sales in the Czech Republic by ATC1 [MAT 06/2021][41]



However, with biosimilars, the situation is quite different – 86% of all biosimilars sales are within the ATC1 L category – antineoplastic and immunomodulating agents, while the other categories account for 3-4% each.

The disparity between the original biologics' and biosimilars' share of sales shows that in the future, as patents continue to expire, the potential market for biosimilar competition will be large. However, the possible adoption rate is subject to clinical development and trials, approval processes and adoption by HCPs as well as payer approach as discussed earlier.[42]

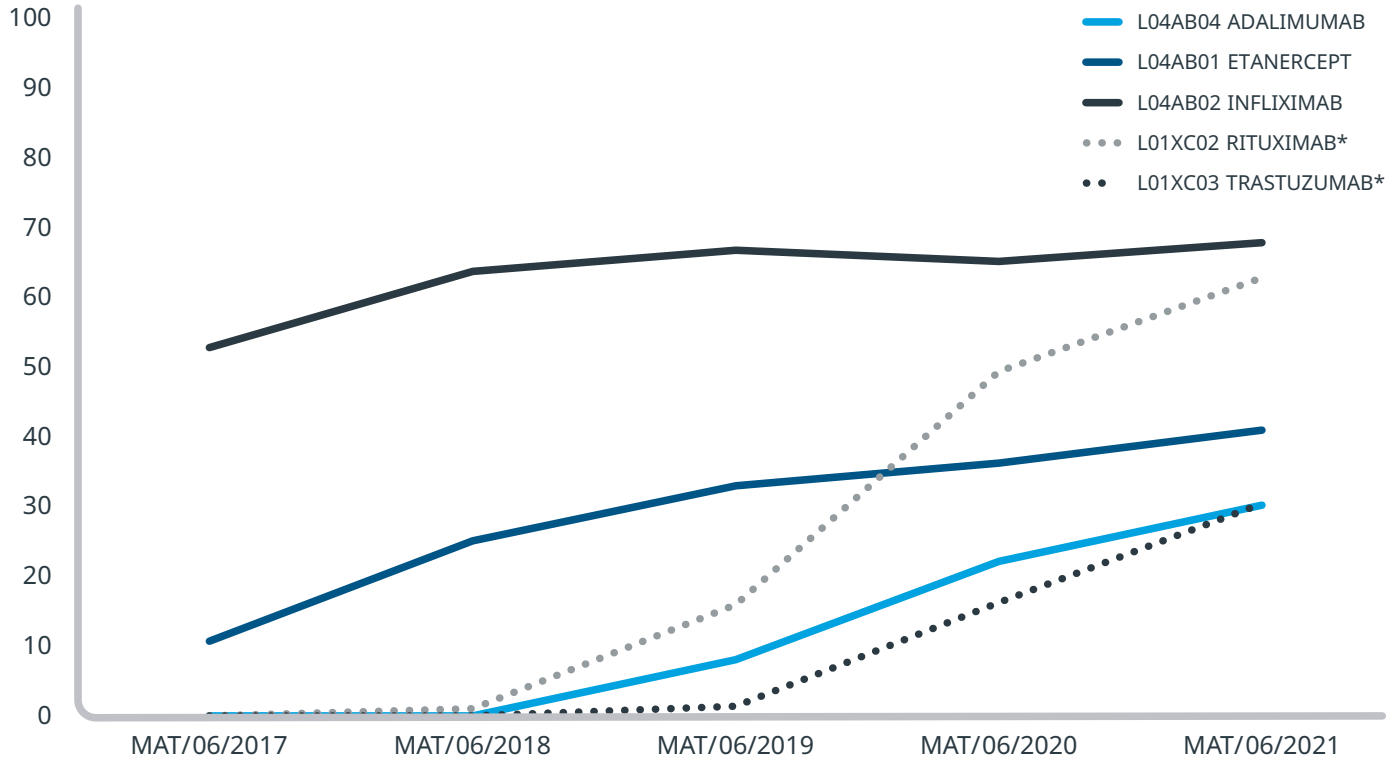
Exhibit 11: Breakdown of biosimilars sales in the Czech Republic by ATC1 [MAT 06/2021][43]

A detailed analysis of biosimilars market share and uptake in the Czech Republic was conducted using IQVIA's sell-in distributor data as of MAT 06/2021. The following findings are measured using the defined daily dose (DDD) except for L01XC02 RITUXIMAB, L01XC03 TRASTUZUMAB, and L01XC07 BEVACIZUMAB, where units were used instead due to individual dosing.[44]

Overall, the uptake of biosimilar medicines in the Czech Republic varies greatly with an average of 39% of the biosimilar share across all 16 categories.

41 IQVIA CZ Sell-in, MAT June 2021
42 Percentage shares may not add up to 100% due to rounding.
43 IQVIA CZ Sell-in, MAT June 2021
44 For Rituximab, Trastuzumab and Bevacizumab, units were used as a measure due to individual dosing and the absence of DDD.

Exhibit 12: Uptake of biosimilars in selected biologics categories in the Czech Republic[45]



**For Rituximab and Trastuzumab, units were used as a measure due to individual dosing and the absence of DDD*

Exhibit 13: Detailed overview of all biosimilar uptake across a wide range of biologic categories in the Czech Republic[46]

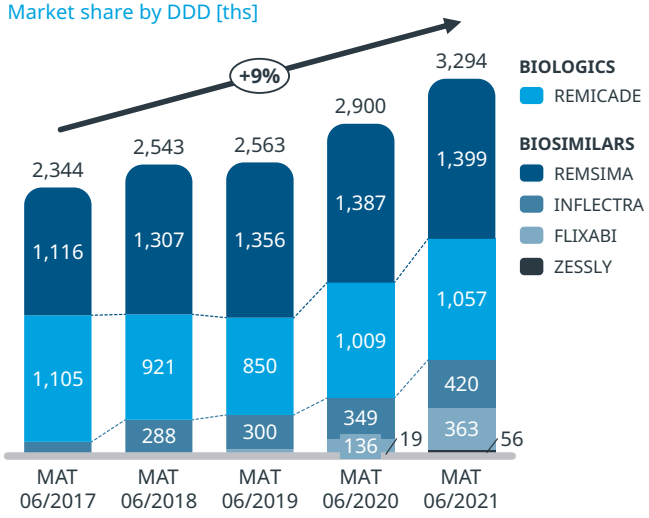
Biologic category	MAT/06/2017	MAT/06/2018	MAT/06/2019	MAT/06/2020	MAT/06/2021
L03AA02 FILGRASTIM	92%	96%	100%	100%	100%
L03AA13 PEGFILGRASTIM	0%	0%	26%	67%	96%
L04AB02 INFLIXIMAB	53%	64%	67%	65%	68%
L01XC02 RITUXIMAB*	0%	1%	16%	49%	63%
H05AA02 TERIPARATIDE	0%	0%	0%	23%	53%
B03XA01 ERYTHROPOIETIN	43%	40%	40%	48%	51%
L04AB01 ETANERCEPT	11%	25%	33%	36%	41%
G03GA05 FOLLITROPIN ALFA	8%	22%	32%	33%	39%
A10AB05 INSULIN ASPART	0%	10%	29%	35%	39%
L01XC03 TRASTUZUMAB*	0%	0%	1%	16%	30%
L04AB04 ADALIMUMAB	0%	0%	8%	22%	30%
A10AB04 INSULIN LISPRO	0%	0%	0%	0%	20%
H01AC01 SOMATROPIN	7%	8%	8%	9%	9%
A10AE04 INSULIN GLARGINE	9%	10%	10%	9%	8%
L01XC07 BEVACIZUMAB*	0%	0%	0%	0%	0%
B01AB05 ENOXAPARIN	0%	0%	0%	0%	0%

**For Rituximab, Trastuzumab and Bevacizumab, units were used as a measure due to individual dosing and the absence of DDD*

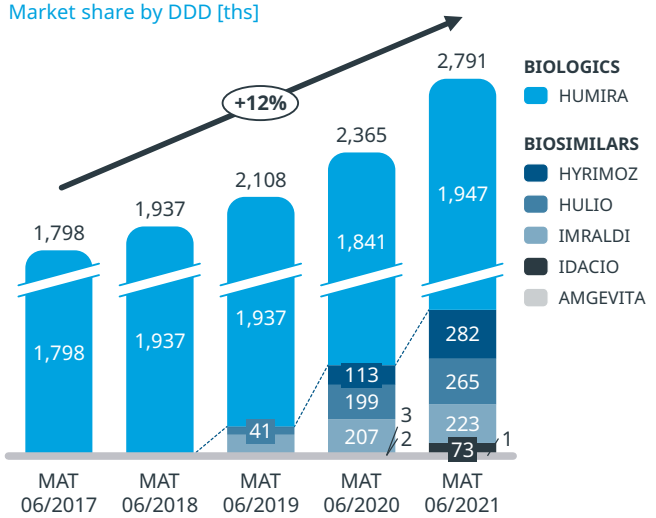
45 State Institute for Drug Control's database of Reporting Deliveries of Distributed Medicinal Products for Human Use (MAT/06/2021)
46 State Institute for Drug Control's database of Reporting Deliveries of Distributed Medicinal Products for Human Use (MAT/06/2021)

Exhibit 14: Detailed overview of biosimilar uptake across key biologic molecules in the Czech Republic[47]

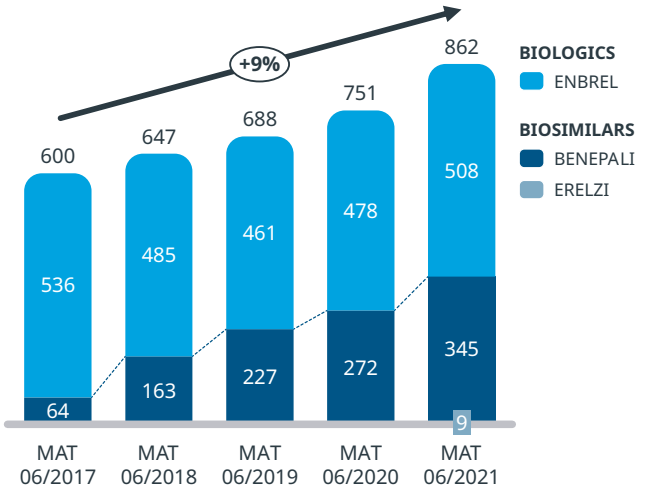
L04AB02 INFLIXIMAB
Market share by DDD [ths]



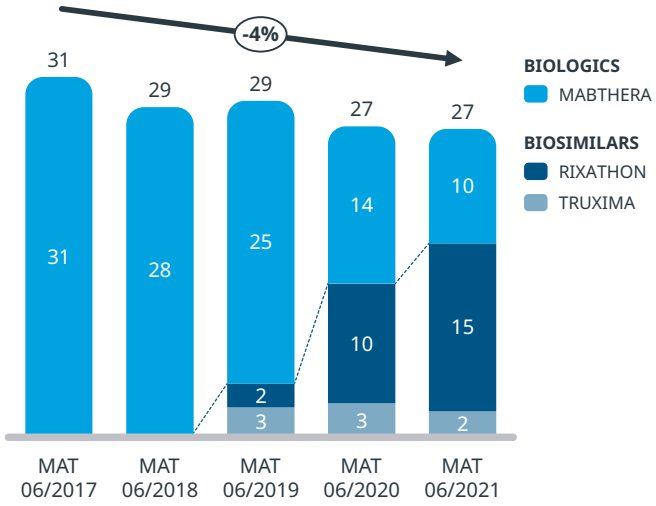
L04AB04 ADALIMUMAB
Market share by DDD [ths]



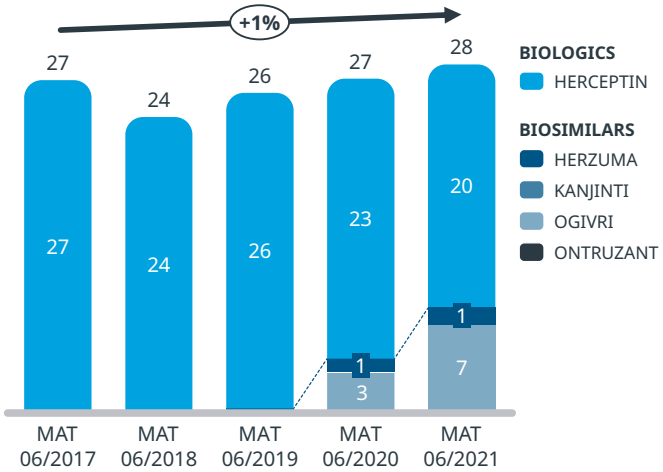
L04AB01 ETANERCEPT
Market share by DDD [ths]



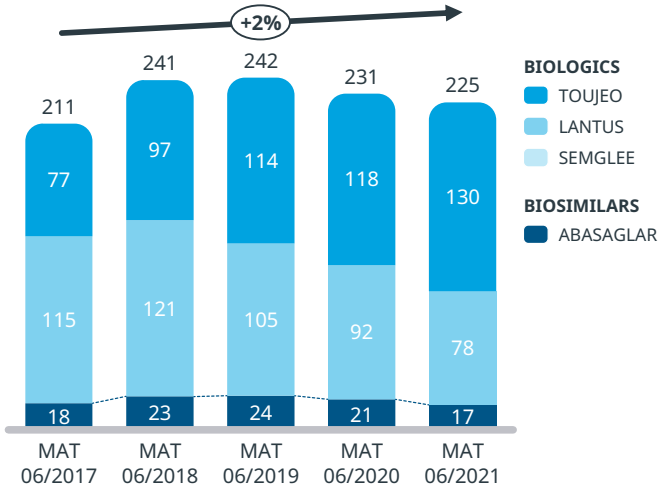
L01XC02 RITUXIMAB
Market share by units [ths]*



L01XC03 TRASTUZUMAB
Market share by units [ths]*



A10AE04 INSULIN GLARGINE
Market share by DDD [100 ths]



**For Rituximab and Trastuzumab, units were used as a measure due to individual dosing and the absence of DDD*

47 State Institute for Drug Control's database of Reporting Deliveries of Distributed Medicinal Products for Human Use (MAT/06/2021)

Boosting Czech patients' access to biologic treatment

The access of Czech patients to innovative biologic treatment can certainly be boosted through the introduction of biosimilars to the market. Currently, there are several areas which present both opportunities and challenges for further advancement of biosimilars in the Czech Republic.

The Czech Republic employs a multifaceted system of competitive tendering for both original biologics and biosimilars. Tenders are held separately at various levels for individual healthcare facilities, such an environment allows for competitive pricing and should be good for attracting competition and maintaining strong prescription freedom of HCPs. However, the complexity also brings a challenge in terms of transparency and operating difficulty, as bidding for various types of tenders at different regional levels as well as negotiations of discounts and rebates adds additional complexity to the already complicated system. Unlike Denmark with single-winner national tenders or the United Kingdom with sub-national multi-winner tenders, the competitive environment for biosimilars in the Czech Republic is very fragmented.

While tenders are often held by individual healthcare facilities, the Czech Republic has a strict pricing policy embedded in its legal framework, firmly regulating drug prices. To make drug prices affordable, the Czech Republic employs a policy that requires generic medicine to be at least 40% cheaper than the originator; for biosimilars, the requirement has been raised from 15% to 30%. As such, biosimilars must now be priced 30% or lower than the original biologic drug (Act No. 378/2007).[48] Such an approach benefits the healthcare system by making biologic treatment more affordable and accessible to more patients. For payers, the presence of biosimilars means a broader portfolio of biologic treatments and lower prices, relieving the often-stretched healthcare system's budget.

However, the uptake of biosimilars in the Czech Republic has generally been slower than in Western Europe, especially for newly launched biosimilar competitors. With the already stringent pricing policies in place, requiring drug prices in the Czech Republic to be the equivalent of the three lowest prices in the EU reference basket, such pricing requirements put additional pressure on manufacturers who may prefer delayed or no entry to the Czech market. By contrast, from the short-term point of view, the strict emphasis on low biosimilar prices theoretically allows more patients to access biologic treatments. Nevertheless, the question of whether further price reductions mean savings for payers and/or potentially increased co-pays for patients remains unanswered.

Another often-discussed argument among professionals in the Czech pharmaceutical market is the possibility of re-exports of biosimilars caused by ultra-low prices. When drugs are re-exported to be sold at higher prices in other countries, there may be insufficient drug supply at times. Further pressure on lowering biosimilar prices in the Czech Republic may also prevent Czech patients from accessing new innovative treatments.

For healthcare facilities in the Czech Republic, biosimilars certainly represent a good way to provide biologic treatments to more patients, as professor Milan Lukáš stated in a commentary on the introduction of infliximab biosimilars: "The situation changed significantly in 2015. At our facility, we currently use the biosimilar infliximab for nearly 400 patients with bowel inflammation. By implementing it, the costs associated with biologic therapies were reduced by almost 50 to 60%. The budgets of individual payers remained the same or were slightly higher, therefore we could treat more patients."[49]

48 Poslanecká sněmovna Parlamentu České republiky. *Předpis 378/2007 Sb*. November 2020. Available from: https://www.psp.cz/sqw/sbirka.sqw?cz=378&r=2007.

49 Zdravotnický deník. *Proléčenost biologickou terapií u pacientů s idiopatickými střevními záněty roste. Díky biosimilars*. January 2017. Available from: https://www.zdravotnickydenik.cz/2017/01/prolecenost-biologickou-terapii-u-pacientu-s-idiopatickymi-strevnimi-zanety-roste-diky-biosimilars/.

In 2017, a scientific study was published with the support from the Ministry of Health in the Czech Republic, finding that there was "no consistent trend of change in disease activity measures and PROMs that would suggest a decrease in efficacy in the limited time frame of our study,"[50] showing that the infliximab biosimilar alternative was a reliable alternative and lending further credibility to biosimilars in the country.

The Chairwoman of the Patient Organization Revma Liga Czech Republic, Edita Müllerová, expressed her opinion on biosimilars in 2020: "There is a steady flow of more modern medicines entering the market which can significantly help relieve patients' conditions and change their lives. The roadblock in their implementation is usually the price. The price, however, has been decreasing gradually due to biosimilar medicines – a copy of original drugs with the same effect."[51]

Outlook for biosimilars in the Czech Republic

The current environment in the Czech Republic has both risks and benefits for biosimilars – while individual tenders support the competitive environment and desired long-term innovation and prescribing freedom helps healthcare professionals gain experience with multiple biosimilar alternatives, the complexity of the entire system and emphasis on pushing prices as low as possible makes the market a difficult one. The introduction of a unified European pharmaceutical strategy may bring some more clarity to the system and help drive the uptake of biosimilars in the Czech Republic.

Despite its challenges in the Czech Republic, biosimilars continue to find their way to the market for now. The discussion should focus on increasing uptake levels in critical innovative treatment areas as well as establishing an environment that is sustainable in the long term, considering both savings for the healthcare system as well as increasing patient access to innovative biologic treatment through biosimilars. Lessons from Europe show that a decentralized, competitive environment is good for maintaining pharmaceutical innovation and competitive market forces which lower overall treatment costs across different areas. Transparency helps the biologics market attract a wide portfolio of players which is beneficial both for the competitive pressure of the natural market on prices, prescription freedom of HCPs, and access to multiple manufacturers in times of crisis and unpredictable events impacting steady supplies of biologic medicines to the country. The proposed, centralized Pharmaceutical strategy for Europe[52], as introduced by the European Commission in November 2020, may help drive more biosimilar uptake in the Czech Republic among many other critical areas and be the next impulse for advancement of biosimilars in the Czech Republic.

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50 Šárka Forejtová et al. *A Non-Medical Switch from Originator Infliximab to Biosimilar CT-P13 in 36 Patients with Ankylosing Spondylitis: 6 – Months Clinical Outcomes from the Czech Biologic Registry Attra*. September 2017. Available from: https://acrabstracts.org/abstract/a-non-medical-switch-from-originator-infliximab-to-biosimilar-ct-p13-in-36-patients-with-ankylosing-spondylitis-6-months-clinical-outcomes-from-the-czech-biologic-registry-attra/.

51 Deník.cz. *Pozor na bolest a otékání kloubů*. Revmatoidní artritida může končit invaliditou May 2020. Available from: https://www.denik.cz/zdravi/artritida-bolest-kloubu-lecba-20210324.html.

52 European Commission. *A pharmaceutical strategy for Europe*. November 2020. Available from: https://ec.europa.eu/health/human-use/strategy_en.

Appendices

List of approved biosimilars in the European Union[53]

Medicine name	Active substance	ATC code	Marketing authorization holder/ company name	Marketing authorisation date
Abasaglar (previously Abasria)	insulin glargine	A10AE04	Eli Lilly Nederland B.V.	09-09-2014
Abseamed	epoetin alfa	B03XA01	Medice Arzneimittel Pütter GmbH Co. KG	27-08-2007
Accofil	filgrastim	L03AA02	Accord Healthcare S.L.U.	17-09-2014
Alymsys	bevacizumab	L01XC07	Mabxience Research SL	26-03-2021
Amgevita	adalimumab	L04AB04	Amgen Europe B.V.	21-03-2017
Amsparity	adalimumab	L04AB04	Pfizer Europe MA EEIG	13-02-2020
Aybintio	bevacizumab	L01XC07	Samsung Bioepis NL B.V.	19-08-2020
Bemfola	follitropin alfa	G03GA05	Gedeon Richter Plc.	26-03-2014
Benepali	etanercept	L04AB01	Samsung Bioepis NL B.V.	13-01-2016
Binocrit	epoetin alfa	B03XA01	Sandoz GmbH	28-08-2007
Blitzima	rituximab	L01XC02	Celltrion Healthcare Hungary Kft.	13-07-2017
Cegfila (previously Pegfilgrastim Mundipharma)	pegfilgrastim	L03AA13	Mundipharma Corporation (Ireland) Limited	19-12-2019
Epoetin Alfa Hexal	epoetin alfa	B03XA01	Hexal AG	27-08-2007
Equidacent	bevacizumab	L01XC07	Centus Biotherapeutics Europe Limited	24-09-2020
Erelzi	etanercept	L04AB01	Sandoz GmbH	23-06-2017
Filgrastim Hexal	filgrastim	L03AA02	Hexal AG	06-02-2009
Flixabi	infliximab	L04AB02	Samsung Bioepis NL B.V.	26-05-2016
Fulphila	pegfilgrastim	L03AA13	Mylan S.A.S	20-11-2018
Grastofil	filgrastim	L03AA02	Accord Healthcare, SLU	17-10-2013
Grasustek	pegfilgrastim	L03AA13	Juta Pharma GmbH	20-06-2019
Hefiya	adalimumab	L04AB04	Sandoz GmbH	26-07-2018
Herzuma	trastuzumab	L01XC03	Celltrion Healthcare Hungary Kft.	08-02-2018
Hulio	adalimumab	L04AB04	Mylan S.A.S.	17-09-2018
Hyrimoz	adalimumab	L04AB04	Sandoz GmbH	26-07-2018
Idacio	adalimumab	L04AB04	Fresenius Kabi Deutschland GmbH	02-04-2019
Imraldi	adalimumab	L04AB04	Samsung Bioepis NL B.V.	24-08-2017
Inflectra	infliximab	L04AB02	Pfizer Europe MA EEIG	10-09-2013
Inhixa	enoxaparin sodium	B01AB05	Techdow Pharma Netherlands B.V.	15-09-2016
Insulin aspart Sanofi	insulin aspart	A10AB05	sanofi-aventis groupe	25-06-2020
Insulin lispro Sanofi	insulin lispro	A10AB04	sanofi-aventis groupe	18-07-2017
Kanjinti	trastuzumab	L01XC03	Amgen Europe B.V.	16-05-2018
Kixelle	insulin aspart	A10AB05	Mylan IRE Healthcare Limited	05-02-2021

53 European Medicines Agency. *Medicines*. July 2021. Available from: *https://www.ema.europa.eu/en/medicines/field_ema_web_categories% 253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised-36/ema_medicine_types/field_ema_med_Biosimilar/search_api_aggregation_ema_medicine_types/field_ema_med_Biosimilar/ema_group_types/ema_medicine/field_ema_med_status/authorised-36*.

Medicine name	Active substance	ATC code	Marketing authorization holder/ company name	Marketing authorisation date
Livogiva	teriparatide	H05AA02	Theramex Ireland Limited	27-08-2020
Movymia	teriparatide	H05AA02	STADA Arzneimittel AG	11-01-2017
Mvasi	bevacizumab	L01XC07	Amgen Technology (Ireland) UC	15-01-2018
Nepexto	etanercept	L04AB01	Mylan IRE Healthcare Limited	20-05-2020
Nivestim	filgrastim	L03AA02	Pfizer Europe MA EEIG	07-06-2010
Nyvepria	pegfilgrastim	L03AA13	Pfizer Europe MA EEIG	18-11-2020
Ogivri	trastuzumab	L01XC03	Mylan S.A.S	12-12-2018
Omnitrope	somatropin	H01AC01	Sandoz GmbH	12-04-2006
Onbevzi	bevacizumab	L01XC07	Samsung Bioepis NL B.V.	11-01-2021
Ontruzant	trastuzumab	L01XC03	Samsung Bioepis NL B.V.	15-11-2017
Ovaleap	follitropin alfa	G03GA05	Theramex Ireland Limited	27-09-2013
Oyavas	bevacizumab	L01XC07	STADA Arzneimittel AG	26-03-2021
Pelgraz	pegfilgrastim	L03AA13	Accord Healthcare S.L.U.	21-09-2018
Pelmeg	pegfilgrastim	L03AA13	Mundipharma Corporation (Ireland) Limited	20-11-2018
Ratiograstim	filgrastim	L03AA02	Ratiopharm GmbH	15-09-2008
Remsima	infliximab	L04AB02	Celltrion Healthcare Hungary Kft.	10-09-2013
Retacrit	epoetin zeta	B03XA01	Pfizer Europe MA EEIG	18-12-2007
Ritemvia	rituximab	L01XC02	Celltrion Healthcare Hungary Kft.	13-07-2017
Rixathon	rituximab	L01XC02	Sandoz GmbH	15-06-2017
Riximyo	rituximab	L01XC02	Sandoz GmbH	15-06-2017
Ruxience	rituximab	L01XC02	Pfizer Europe MA EEIG	01-04-2020
Semglee	insulin glargine	A10AE04	Mylan S.A.S	23-03-2018
Silapo	epoetin zeta	B03XA01	Stada Arzneimittel AG	18-12-2007
Terrosa	teriparatide	H05AA02	Gedeon Richter Plc.	04-01-2017
Tevagrastim	filgrastim	L03AA02	Teva GmbH	15-09-2008
Trazimera	trastuzumab	L01XC03	Pfizer Europe MA EEIG	26-07-2018
Truxima	rituximab	L01XC02	Celltrion Healthcare Hungary Kft.	17-02-2017
Yuflyma	adalimumab	L04AB04	Celltrion Healthcare Hungary Kft.	11-02-2021
Zarzio	filgrastim	L03AA02	Sandoz GmbH	06-02-2009
Zercepac	trastuzumab	L01XC03	Accord Healthcare S.L.U.	27-07-2020
Zessly	infliximab	L04AB02	Sandoz GmbH	18-05-2018
Ziextenzo	pegfilgrastim	L03AA13	Sandoz GmbH	22-11-2018
Zirabev	bevacizumab	L01XC07	Pfizer Europe MA EEIG	14-02-2019
Zirabev	bevacizumab	L01XC07	Pfizer Europe MA EEIG	14/02/2019

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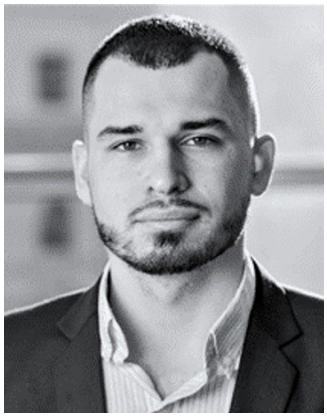

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