GENERICS AND BIOSIMILARS INITIATIVE JOURNAL
Building trust in cost-effective treatments

Patent expiry dates for biologicals: 2017 update

Abstract:
Although small molecule drugs still dominate the global pharmaceutical market in terms of numbers, biologicals are making a significant dent. However, the high cost of biologicals is putting increasing pressure on healthcare budgets, thus opening the door to biosimilars. With patents on originator biologicals expiring, biosimilars are expected to take an increasing share of the biologicals market. In light of these facts, this paper gives estimated patent expiry dates for some of the best-selling biologicals.

Submitted: *12 December 2017;* ***Revised:*** *25 January 2018;* ***Accepted:*** *26 January 2018;* ***Published online first:*** *7 February 2018*

Biologicals are making up an ever-increasing share of the pharmaceutical market. Biologicals dominate the top 10 list of best-selling medicines in Europe, with seven of the top 10 best-selling drugs being biologicals in 2017. This compares to only three biologicals that made the top 10 list back in 2008 [1]. Although biologicals represent many of the most promising new therapies for previously intractable diseases, they are extremely expensive [2], putting pressure on healthcare budgets. One way to offset these costs is to introduce biosimilars for biologicals where the patents and exclusivity periods have expired.

The European Medicines Agency (EMA) approved its first biosimilar Omnitrope (somatropin) back in 2006 [3]. Since then, EMA has approved 38 biosimilars within the product classes of human growth hormone (HGH), granulocyte colony-stimulating factor (G-CSF), erythropoiesis-stimulating agent (ESA), insulin, follicle-stimulating hormone (FSH), parathyroid hormone, tumour necrosis factor (TNF)-inhibitor and monoclonal antibody, for use in the European Union (EU) [3].

The price of new biologicals is increasing fast. For example, eight cancer medicines approved by the US Food and Drug Administration (FDA) in 2015 had six-figure price tags [4]. One way to combat these increasing costs is to introduce biosimilars. By 2018, biologicals worth more than US$68 billion in current annual sales will lose patent protection, making the case for using biosimilars clear. Even with only a 20% discount, this could give the world a US$14 billion health innovation fund. Whereas, a 30% discount could save US$20 billion and a 40% discount could save US$27 billion [4].

There has been significant harmonization across the globe with respect to patents, mainly as a result of the World Trade Organization's TRIPS agreement (agreement on Trade-Related Aspects of Intellectual Property Rights). This has resulted in most patent laws nowadays, giving the term of a patent as 20 years from the filing date of the application. This is the case both in Europe and the US, where patents have a term of 20 years from the date of filing [5].

For both Europe and the US exclusivity periods should also be considered, see footnote of Tables 1, 2 and 3.

Table 1: Estimated patent and exclusivity expiry dates for best-selling biologicals: not humanized antibodies

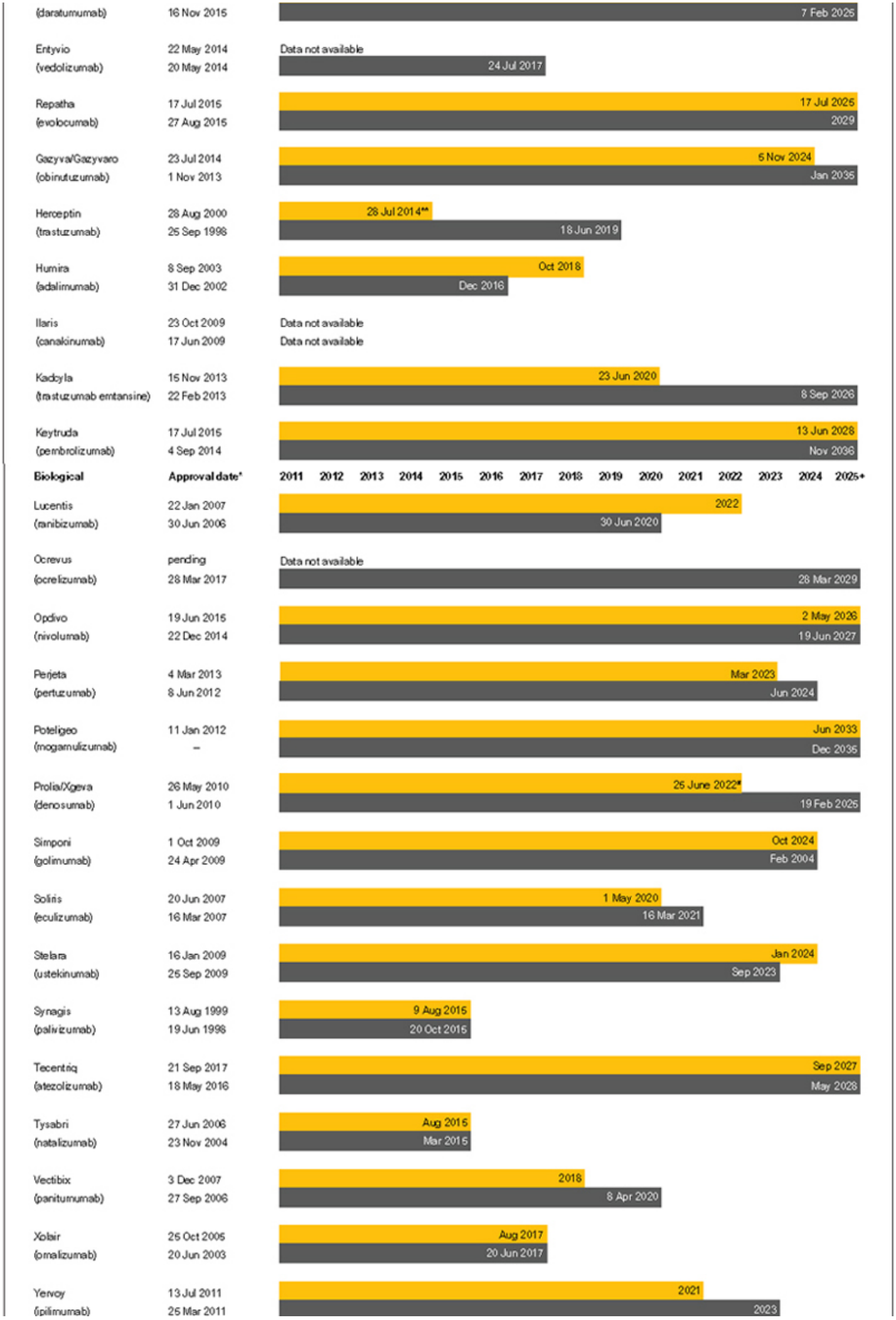
Biological	Approval date*	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025+
Adcetris (brentuximab vedotin)	26 Oct 2012 19 Aug 2011													1 Aug 2023		
														2016–2031		
Bexxar (tositumomab)	Withdrawn 27 Jun 2003	Data not available														
														Jan 2029		
Prostascint (capromab)	– 28 Oct 1996	Data not available														
														Nov 2096		
Erbitux (cetuximab)	29 Jun 2004 12 Feb 2004				29 Jun 2014											
							13 Feb 2016									
Orthoclone OKT3 (muromonab-CD3)	– 14 Sep 1992	Data not available														
												2021				
Remicade (infliximab)	13 Aug 1999 24 Aug 1998					13 Feb 2015										
									4 Sep 2018							
Removab (catumaxomab)	20 Apr 2009 –	Data not available										May 2020				
Reopro (abciximab)	– 16 Dec 1993	Data not available														
									Jun 2015							
Rituxan/MabThera (rituximab)	2 Jun 1998 26 Nov 1997				12 Nov 2013											
							22 Sep 2016									
Simulect (basiliximab)	9 Oct 1998 12 May 1998				Apr 2013											
		Data not available														
Sylvant (siltuximab)	22 May 2014 23 Apr 2014															Jul 2034
																1 Aug 2027
Zevalin (ibritumomab)	16 Jan 2004 19 Feb 2002				2013											
									19 Feb 2016							

European Union (EU) US

*EU provides 10 years of exclusivity (8 years data exclusivity and 2 years market exclusivity + 1-year possible extension), US BPCI Act provides 12 years exclusivity (4 years data exclusivity and 8 years market exclusivity).

Table 2: Estimated patent and exclusivity expiry dates for best-selling biologicals: humanized antibodies

Biological	Approval date*	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025+
Abthrax (raxibacumab)	15 Oct 2014 14 Dec 2012	Data not available														
																2026
Actemra/RoActemra (tocilizumab)	16 Jan 2009 8 Jan 2010							23 Apr 2017#								
							22 Dec 2015									
Avastin (bevacizumab)	12 Jan 2005 26 Feb 2004												22 Jan 2022			
									4 Jul 2019							
Arzerra (ofatumumab)	19 Apr 2010 26 Oct 2009	Data not available														
										Dec 2018						
Benlysta (belimumab)	13 Jul 2011 9 Mar 2011											2021				
														2023		
Campath/Lemtrada (alemtuzumab)	12 Sep 2003 7 May 2001											7 May 2021				
												6 Jul 2021				
Cimzia (certolizumab pegol)	1 Oct 2009 22 Apr 2008											6 Jul 2021				
														13 Feb 2024		
Cyramza (ramucirumab)	19 Dec 2014 21 Apr 2014													May 2023		
																Nov 2025
Cosentyx (secukinumab)	15 Jan 2015 21 Jan 2015	Data not available														
											8 Oct 2020					
Darzalex	25 May 2016															25 May 2026


(daratumumab) 16 Nov 2015 7 Feb 2025
Entyvio 22 May 2014 Data not available
(vedolizumab) 20 May 2014 24 Jul 2017
Repatha 17 Jul 2015 17 Jul 2025
(evolocumab) 27 Aug 2015 2029
Gazyva/Gazyvaro 23 Jul 2014 6 Nov 2024
(obinutuzumab) 1 Nov 2013 Jan 2035
Herceptin 28 Aug 2000 28 Jul 2014**
(trastuzumab) 25 Sep 1998 18 Jun 2019
Humira 8 Sep 2003 Oct 2018
(adalimumab) 31 Dec 2002 Dec 2016
Ilaris 23 Oct 2009 Data not available
(canakinumab) 17 Jun 2009 Data not available
Kadcyla 15 Nov 2013 23 Jun 2020
(trastuzumab emtansine) 22 Feb 2013 8 Sep 2026
Keytruda 17 Jul 2015 13 Jun 2028
(pembrolizumab) 4 Sep 2014 Nov 2036
Biological Approval date* 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025+
Lucentis 22 Jan 2007 2022
(ranibizumab) 30 Jun 2006 30 Jun 2020
Ocrevus pending Data not available
(ocrelizumab) 28 Mar 2017 28 Mar 2029
Opdivo 19 Jun 2015 2 May 2026
(nivolumab) 22 Dec 2014 19 Jun 2027
Perjeta 4 Mar 2013 Mar 2023
(pertuzumab) 8 Jun 2012 Jun 2024
Poteligeo 11 Jan 2012 Jun 2033
(mogamulizumab) – Dec 2035
Prolia/Xgeva 26 May 2010 25 June 2022*
(denosumab) 1 Jun 2010 19 Feb 2025
Simponi 1 Oct 2009 Oct 2024
(golimumab) 24 Apr 2009 Feb 2004
Soliris 20 Jun 2007 1 May 2020
(eculizumab) 16 Mar 2007 16 Mar 2021
Stelara 16 Jan 2009 Jan 2024
(ustekinumab) 25 Sep 2009 Sep 2023
Synagis 13 Aug 1999 9 Aug 2015
(palivizumab) 19 Jun 1998 20 Oct 2015
Tecentriq 21 Sep 2017 Sep 2027
(atezolizumab) 18 May 2016 May 2028
Tysabri 27 Jun 2006 Aug 2015
(natalizumab) 23 Nov 2004 Mar 2015
Vectibix 3 Dec 2007 2018
(panitumumab) 27 Sep 2006 8 Apr 2020
Xolair 25 Oct 2005 Aug 2017
(omalizumab) 20 Jun 2003 20 Jun 2017
Yervoy 13 Jul 2011 2021
(ipilimumab) 25 Mar 2011 2023

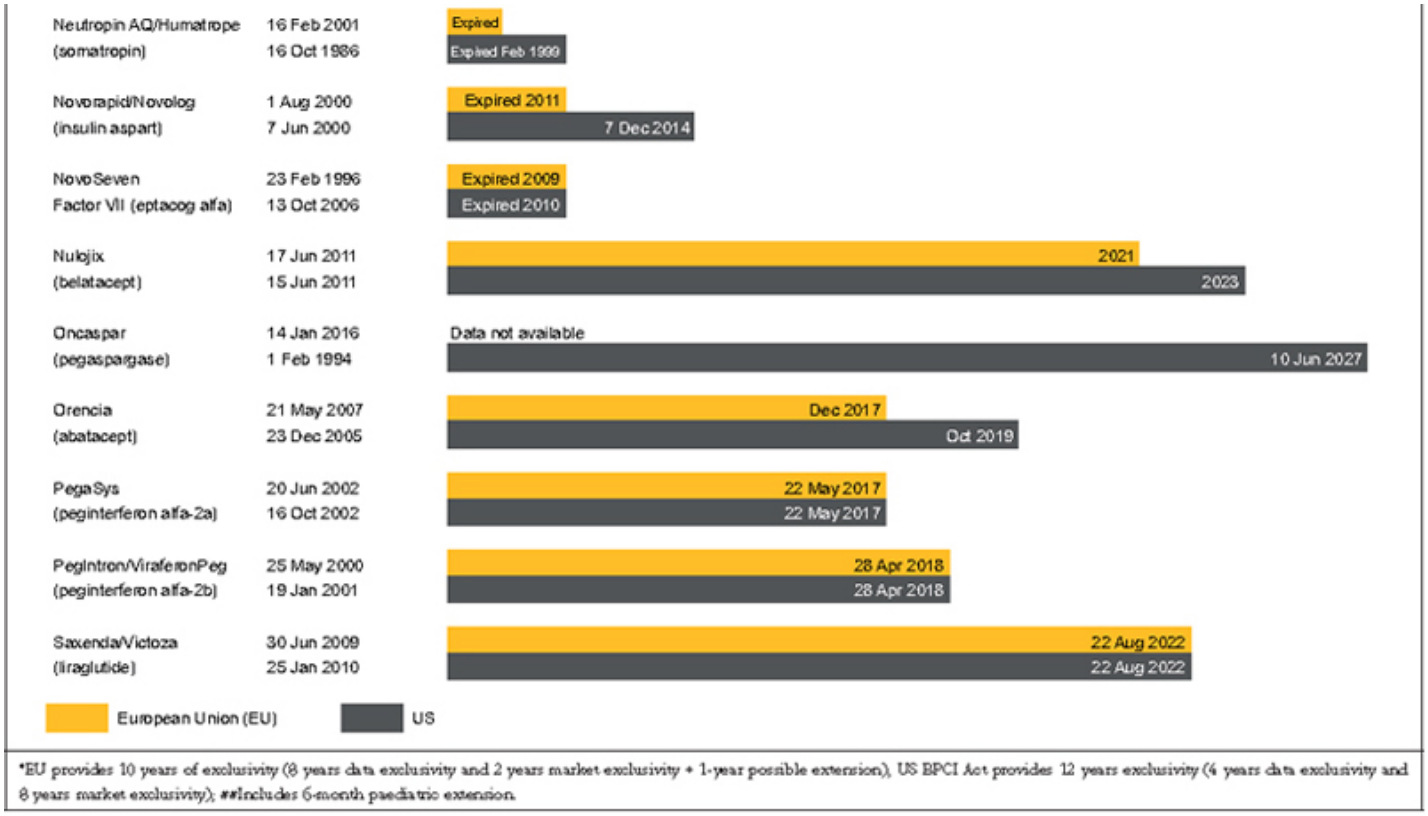
Zenapax	26 Feb 1999	Mar 2013
(daclizumab)	10 Dec 1997	Data not available

European Union (EU) US

*EU provides 10 years of exclusivity (8 years data exclusivity and 2 years market exclusivity + 1-year possible extension), US BPCI Act provides 12 years exclusivity (4 years data exclusivity and 8 years market exclusivity); #Based on Supplementary Protection Certificate; **In the UK. Other EU markets follow on 28 August 2015: patent protecting the cells that make certain levels of erythropoietin lasts until 25 May 2015.
#Except for France, Italy, Spain and the UK.

Table 3: Estimated patent and exclusivity expiry dates for best-selling biologicals: not antibodies

Biological	Approval date*	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025+
Actrapid/Novolin (rhu insulin)	7 Oct 2002 25 Jun 1991	No patent No patent														
Advate Factor VIII (optacog alfa)	2 Mar 2004	Expired Jan 2010														
Aranesp (darbepoetin alfa)	6 Aug 2001 17 Sep 2001			6 Jul 2016												
				15 May 2024												
Avonex/Rebif (interferon beta-1a)	19 Mar 2009 7 Feb 2003					2015 2015										
Betaferon/Betaseron (interferon beta-1b)	30 Nov 1995 23 Jul 1993														6 Jul 2024	
				7 May 2013												
Botox (onabotulinum toxin A)	9 Dec 1991	No patent No patent														
Enbrel (etanercept)	3 Feb 2000 2 Nov 1998					1 Aug 2015 ##										
																22 Nov 2028
Epogen/Eprex/Procrit (epoetin alfa)	10 Jun 1989 1 Jun 1989	Expired Jun 2004														
				20 Aug 2013												
Eylea (aflibercept)	22 Nov 2012 18 Nov 2011															14 Jun 2027
																21 Jun 2027
Forteo/Forsteo (teriparatide)	10 Jun 2003 26 Nov 2002									Aug 2019						
										19 Aug 2019						
Gonal-f (follitropin alfa)	20 Oct 1995 25 Mar 2004	Expired 2009														
										23 Aug 2019						
Humalog (insulin lispro)	30 Apr 1996 14 Jun 1996			May 2013												
				7 May 2013												
Humulin/Insuman (human insulin)	21 Feb 1997 29 Apr 1992	Expired														
		Expired 2000														
Kineret (anakinra)	8 Mar 2002 14 Nov 2001	Expired May 2009														
											24 Nov 2020					
Lantus (insulin glargine)	9 Jun 2000 24 Apr 2000					2014										
						2014										
Lovenox (enoxaparin/sodium)	29 Mar 1993			2012												
		Expired														
Levemir (insulin detemir)	1 Jun 2004 19 Oct 2005									9 Nov 2018						
										16 Jun 2019						
Mircera (Methoxy polyethylene glycol/epoetin beta)	20 Jul 2007 14 Nov 2007	Data not available														
											28 Jun 2020					
NeoRecormon/Recormon (epoetin beta)	16 Jul 1997	Expired 2005														
Neulasta (pegfilgrastim)	22 Aug 2002 31 Jan 2002								21 Aug 2017							
									20 Oct 2015							
Neupogen (filgrastim)	20 Feb 1991	Expired														
				3 Dec 2013												
Biological	Approval date*	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025+



Estimated patent and exclusivity period expiry dates for some of the best-selling biological molecules are shown in Tables 1, 2 and 3 for not humanized antibodies, humanized antibodies and biologicals that are not antibodies.

Although the EU previously defined a period of 10 years data exclusivity, this was revised at the latest review of pharmaceutical EU legislation to the following:

> Ten years if the reference product is centrally approved or application to the centralized procedure has been made before 20 November 2005. Or eight years data exclusivity + 2 years market exclusivity + 1 year possible extension if a full dossier is submitted on or after 30 October 2005 via a national procedure or after 20 November 2005 via the centralized procedure [6].

The expiration of patents and other intellectual property rights for originator biologicals over the next decade opens up opportunities for biosimilars to enter the market and increase industry competition. Price reduction strategies should increase adoption among physicians and patients alike, spurring increases in the biosimilars market share.

According to a report by MarketsandMarkets the global market for biosimilars is expected to be worth US$10.9 billion by 2021. This represents a compound annual growth rate (CAGR) of 26.3%, increasing from US$3.39 billion in 2016. Geographically, the biosimilars market is dominated by Europe, followed by Asia, North America, and the Rest of the World. Growth in Europe is primarily driven by the need to curtail healthcare costs, patent expiry of biologicals and the arrival of new biosimilars, rising incidence of chronic disorders such as cancer, diabetes and rheumatoid arthritis, and the emergence of new market participants. However, the Asian market is projected to grow at the highest CAGR.

Although the US is the largest biologicals market globally, it is still playing catch up when it comes to biosimilars. EMA approved its first biosimilar back in 2006 and has now approved more than 38 biosimilars [3]. In contrast, the US Food and Drug Administration (FDA) only approved its first biosimilar in 2015 and to date (December 2017) has approved only nine biosimilars and two follow-on biologicals [6].

The EU, however, is not without its problems. Uptake of biosimilars varies significantly between the different countries of the EU, with some, such as Italy and Spain, having quite low biosimilars use compared to countries where there is high acceptance of biosimilars, e.g. Austria, Germany, The Netherlands and Sweden [7]. In fact, many countries appear to be struggling to find the most appropriate approach to encourage the use of biosimilars [8]. However, favourable clinical outcomes demonstrated through clinical trials of biosimilars are expected to increase confidence and boost uptake of biosimilars. In fact, positive data on switching has already been demonstrated in the results of several trials comparing originator and biosimilar infliximab [9–11]. In addition, results of the NOR-SWITCH study suggest that patients can safely be switched between originator and biosimilar infliximab [12].

In addition, lessons learnt from the launch of Zarxio in the US point to aggressive price discounts in markets with multiple biosimilar entrants. As the landscape evolves, biosimilars will get favoured tier coverage and/or formulary exclusivity from

payers as manufacturers increase rebates. In addition, early biosimilar market entrants need to invest in their brand to gain buy-in from key stakeholders [13].

Key players in the biosimilars market include Amgen, Apotex, Biocon, Boehringer Ingelheim, Celltrion, Dr Reddy's, Eli Lilly, Fuji Pharma, Merck, Samsung Bioepis, Pfizer, Sandoz, Teva Pharmaceuticals and more.

Competing interests: None.

Provenance and peer review: Article prepared based on extensive research; internally peer reviewed.

Michelle Derbyshire, PhD, *GaBI Online* Editor

References

1. GaBI Online &#8211 Generics and Biosimilars Initiative. Biologicals dominate Europe's best sellers [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Reports/Biologicals-dominate-Europe-s-best-sellers
2. GaBI Online &#8211 Generics and Biosimilars Initiative. Barriers to biologicals competition [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Biosimilars/Research/Barriers-to-biologicals-competition
3. GaBI Online &#8211 Generics and Biosimilars Initiative. Biosimilars approved in Europe [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe
4. Ekman N, Cornes P, Vulto AG. Reducing healthcare costs and building trust in biosimilar medicines. Generics and Biosimilars Initiative Journal (GaBI Journal). 2016;5(2):84-8. doi:10.5639/gabij.2016.0502.020
5. Derbyshire M. Patent expiry dates for best-selling biologicals. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(4):178-9. doi:10.5639/gabij.2015.0404.040
6. European Commission. Volume 2A Procedures for marketing authorisation. Chapter 1 Marketing Authorisation July 2015; [cited 2018 Jan 25]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf
7. GaBI Online &#8211 Generics and Biosimilars Initiative. Biosimilars use in Europe [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Reports/Biosimilars-use-in-Europe
8. Vogler S, Schneider P. Do pricing and usage-enhancing policies differ between biosimilars and generics? Findings from an international survey. Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(2):79-88. doi:10.5639/gabij.2017.0602.015
9. GaBI Online &#8211 Generics and Biosimilars Initiative. Switching to biosimilar infliximab in IBD patients [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Biosimilars/Research/Switching-to-biosimilar-infliximab-in-IBD-patients
10. GaBI Online &#8211 Generics and Biosimilars Initiative. Switching from reference infliximab to CT P13 in IBD patients [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Biosimilars/Research/Switching-from-reference-infliximab-to-CT-P13-in-IBD-patients
11. GaBI Online &#8211 Generics and Biosimilars Initiative. Positive phase III switching results for Celltrion's infliximab biosimilar [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2018 Jan 25]. Available from: www.gabionline.net/Biosimilars/Research/Positive-phase-III-switching-results-for-Celltrion-s-infliximab-biosimilar
12. Perks B. Randomized non-inferiority trial fails to find inferiority switching from infliximab originator to CT-P13 biosimilar. Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(4):188-9. doi:10.5639/gabij.2017.0604.042
13. Sarshad M. Major lessons learned from Zarxio's US launch: the start of a biosimilar revolution. Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(4):165-73. doi:10.5639/gabij.2017.0504.035

Disclosure of Conflict of Interest Statement is available upon request.

Source URL: http://gabi-journal.net/patent-expiry-dates-for-biologicals-2017-update.html

---

Generics and Biosimilars Initiative (GaBI)
Tel: +32 474989572 | Fax: +32 14 583 048