Biopharmaceutical benchmarks 2018

Gary Walsh

Monoclonal antibodies (mAbs) continue to reign supreme, although cellular and gene therapies are slowly starting to gather momentum. Burgeoning growth in biosimilars may threaten future brand monopolies for mAbs and other biologics.

Antibodies continue to dominate biopharmaceutical approvals, but new nucleic acid modalities and cellular therapies are also slowly launching on the market. This article provides an update on three previous surveys of biopharmaceutical approvals[1–3]. The current survey period (January 2014 to July 2018) witnessed the approval of 155 biopharmaceutical products (see **Table 1** for definition) in the United States and/or European Union, when counted by product trade name. Some products contain identical active ingredients or are sold under different trade names in the two regions. Taking this into account, 129 distinct biopharmaceutical active ingredients entered the market.

With these new approvals, the number of individual biopharmaceutical products having gained a license in these regions now totals 374, containing 285 distinct active biopharmaceutical ingredients. However, over the years, 58 products have been withdrawn from the market following approval in one or both regions, almost always for commercial reasons. When withdrawals are taken into account, the number of individual biopharmaceutical products with current active licenses stands at 316 (**Table 1**).

Annual approval numbers over the current survey period ranged from a low of 14 in Europe in 2014 to a high of 36, also in Europe, in 2017 (**Fig. 1a**). Products approved over the four and a half years include 68 mAbs, 23 hormones, 16 clotting factors, 9 enzymes, 7 vaccines, 5 nucleic acid–based products and 4 engineered cell–based products. As this study period was coming to a close, the first RNA interference (RNAi) drug was approved in the United States.

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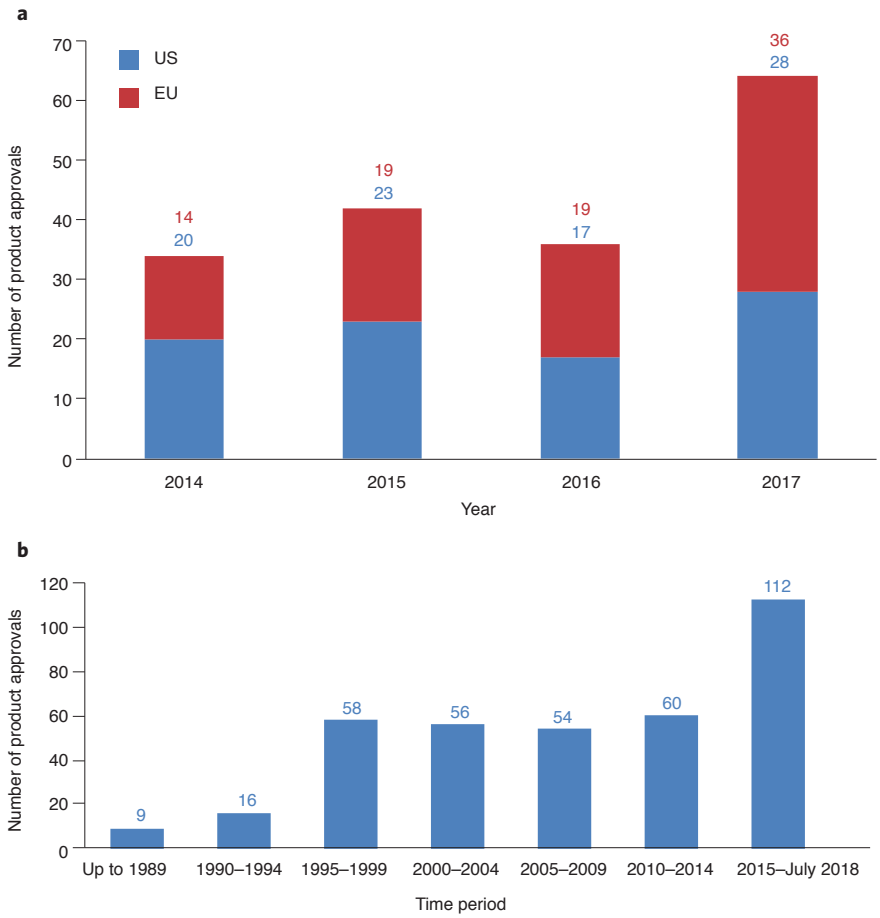

Figure 1 Product approvals profile. (**a**) Annual product approval numbers (by product trade name) by individual region. (**b**) Number of product approvals in one or both regions over the indicated periods.

Here I list all recombinant biologics approved during the past four and a half years (from January 2014 to July 2018), examining the types of biopharmaceutical drugs that have reached the US and EU markets as well as the indications for which they are registered. As in previous articles[1–3], I have not included tissue-engineering products, which the US Food and Drug Administration (FDA) classifies as pure medical devices.

In a snapshot

Overall, new approvals followed relatively predictable lines, with cancer representing the single most common indication (33 products). Other common indications included various

inflammation-related conditions (24 products), hemophilia (16 products) and diabetes (15 products). Approvals for other indications, less commonly targeted by biopharmaceuticals, included asthma, migraine, HIV and inhalational anthrax.

Of the 155 individual biopharmaceutical products approved, 81 (52%) were genuinely new to the market, with the remaining products representing biosimilars, me-too products, and products previously approved elsewhere. Those 81 new products (by trade name) contained a total of 71 distinct active biopharmaceutical ingredients (**Table 2**). Looking at each region independently, 97 products were licensed in the United States in the survey timeframe while 109 products gained marketing authorization in the European Union.

In the same period, US regulators approved a grand total of 207 products containing novel molecular (chemical or biological) entities, indicating that 47% of all genuinely new drug approvals in the US were biopharmaceuticals. This represents a substantial increase over values reported in our previous surveys in 2010 and 2014 (21% and 26%, respectively)[1,2], but tallies well with data presented in our 2006 survey[3], which estimated that some 44% of all drugs in the then developmental pipeline were biotech-based. Ambiguity in EU data reporting structures precludes calculation of an analogous figure for Europe.

Table 2 Biopharmaceuticals approved in the US and/or EU January 2014–July 2018 by category

Category	Products (by trade name)
Genuinely new biopharmaceuticals	Adynovi/Adynovate, Vonvendi, Obizur, Elocta/Eloctate, Andexxa, Rebinyn/Refixia, Alprolix, Idelvion, Suliqua/Soliqua, Xultophy, Myalepta/Myalept, Ozempic, Eperzan/Tanzeum, Trulicity, Oxervate, Plegridy, Shingrix, Trumenba, pandemic influenza vaccine H5N1, Mosquirix, Aimovig, Crysvita, Fasenra, Hemlibra, Ilumya, Trogarzo, Bavencio, Besponsa, dinutuximab beta Apeiron/Qarziba, Dupixent, Imfinzi, Kevzara, Kyntheum/Siliq, Rituxan Hycela, Tecentriq, Tremfya, Zinplava, Anthim, Cinqair/Cinqaero, Darzalex, Empliciti, Lartruvo, Taltz, Blincyto, Cosentyx, Keytruda, Nivolumab BMS[a]/Opdivo, Nucala, Praluent, Praxbind, Repatha, Unituxin[a], Cyramza, Entyvio, Sylvant, Palynziq, Lamzede, Brineura, Mepsevii, Kanuma, Strensiq, Vimizim, Tegsedi, Luxturna, Spinraza, Exondys 51, Imlygic, Alofisel, Kymriah, Yescarta, Strimvelis, Zalmoxis
Biosimilars	Semglee, insulin lispro Sanofi, Lusduna, Abasaglar/Basaglar, Bemfola, Movymia/Terrosa, Retacrit[b], Fulphila, Nivestym/Nivestim[b], Zarxio[b], Accofil, Halimatoz/Hefiya/Hyrimoz, Herzuma, Kanjinti, Mvasi, Trazimera, Zessly, Amgevita/Amjevita/Solymbic, Blitzima/Truxima/Ritemvia/Rituzena, Cyltezo, Imraldi, Ixifi, Ogivri, Ontruzant, Renflexis/Flixabi, Rixathon/Riximyo, Inflectra/Remsima[b], Erelzi, Benepali
Reformulated, me-too, different indication, and related	Afstyla, Vihuma/Nuwiq, Iblias/Kovaltry, Ixinity, Admelog, Fiasp, Toujeo, Afrezza, Rekovelle, Natpara, Natpar, Saxenda, Ristempa[a], Heplisav-b, Gardasil 9, Ocrevus, Portrazza, Zinbryta[a], Oncaspar, Lifmior, Spectrila
Previously approved elsewhere	Rixubis, Ruconest, Ryzodeg 70-30/Ryzodeg, Tresiba, Bexsero, Mylotarg, Gazyva/Gazyvaro

[a]Products were both approved and subsequently withdrawn from one or both regions within the survey timeframe.
[b]Biosimilars approved in one region since 2014, but which were approved in the other region before 2014.

Overall trends

Comparing approvals over the current survey period with those in earlier periods, or with cumulative approvals, reveals interesting, if not somewhat predictable, trends. Approval numbers in each five-year period from 1995 until 2014 have remained remarkably constant (54–60 approvals; **Fig. 1b**). However, approvals have accelerated markedly since that time. The past three and a half years alone (January 2015 to July 2018) have seen 112 (**Fig. 1b**) product approvals—essentially double the typical five-yearly historical approval pace. Although a wave of biosimilar approvals contributed to this trend, the number of genuinely novel approved products hasn't lagged far behind: such drugs represented 52% of approvals in the past four and a half years compared with 59% in the period 2010 to 2014 (ref. 1).

The era of the antibody is upon us

The data also show an increasing dominance of mAbs within the universe of biopharmaceutical approvals. Although they represented just over a quarter (27%) of all first-time approvals from 2010 to 2014, they comprise over half (53%) of first time approvals from 2015 to July 2018 (**Fig. 2a**). The relative importance of mAbs in terms of the percentage of overall biopharmaceutical product sales also continues to grow steadily (**Fig. 2b**), although not so dramatically as product approval numbers might imply. However, antibody sales, both in terms of absolute value and as a percentage of overall biopharmaceutical sales, will likely continue to increase, particularly as revenues derived from the recent glut of mAb approvals grow toward maximum market value.

Notably, approvals of gene- and other nucleic acid–based products (antisense oligonucleotides (ASOs) and gene therapies, including gene-engineered cells) increased as well during this period. The number of nucleic acid and cell-based products approved in the period totaled nine, five nucleic acid and four engineered cells (**Table 1**).

The period of this study also witnessed a pickup in approvals of some traditional product classes as compared with previous study periods, notably clotting factors (**Box 1**) and some hormones, although approvals of most traditional product classes continued to drop off. For example, no recombinant thrombolytic agent, anticoagulant, interleukin or human growth hormone has been approved since 2014, and only one interferon and one erythropoietin were approved. This continued trend likely reflects market saturation relative to demand for these products.

Another continuing trend is the increased prominence of mammalian over nonmammalian expression systems used for producing approved products (**Fig. 3**). In fact, the trend toward mammalian cell lines has accelerated dramatically in the past three to four years. Sixty-two of the 71 genuinely new biopharmaceutical active ingredients that have come on the market in the survey period (**Table 2**) are recombinant proteins. Of those, 52 (84%) are expressed in mammalian cell lines, one (Kanuma, sebelipase alfa) is expressed in a mammalian transgenic system, and the remaining nine are produced using *Escherichia coli* (five products) or yeast (four products), all in *S. cerevisiae*. The surge in mammalian-based production is unsurprising, given the many recent mAb and clotting factor product approvals, with both product classes bearing post-translational modifications and thus requiring mammalian expression systems.

Chinese hamster ovary (CHO) cell-based systems remain by far the most common mammalian cell line in use; 84% (57 of the 68 mAb products approved in the current survey period) are produced in CHO systems, with the remaining antibodies approved produced in either NS0 cells (nine products) or Sp2/0 cells (two products). Overall, recent approvals (**Tables 1** and **2**) also confirm that there is little industrial enthusiasm for exploring new expression systems.

The current survey period has also been characterized by a continual rise in the market value of biopharmaceuticals. Data from various La Merie financial reports indicate that cumulative sales over 2014–2017 reached $651 billion, whereas total sales for 2017 alone reached $188 billion (http://www.lamerie.com)[4].

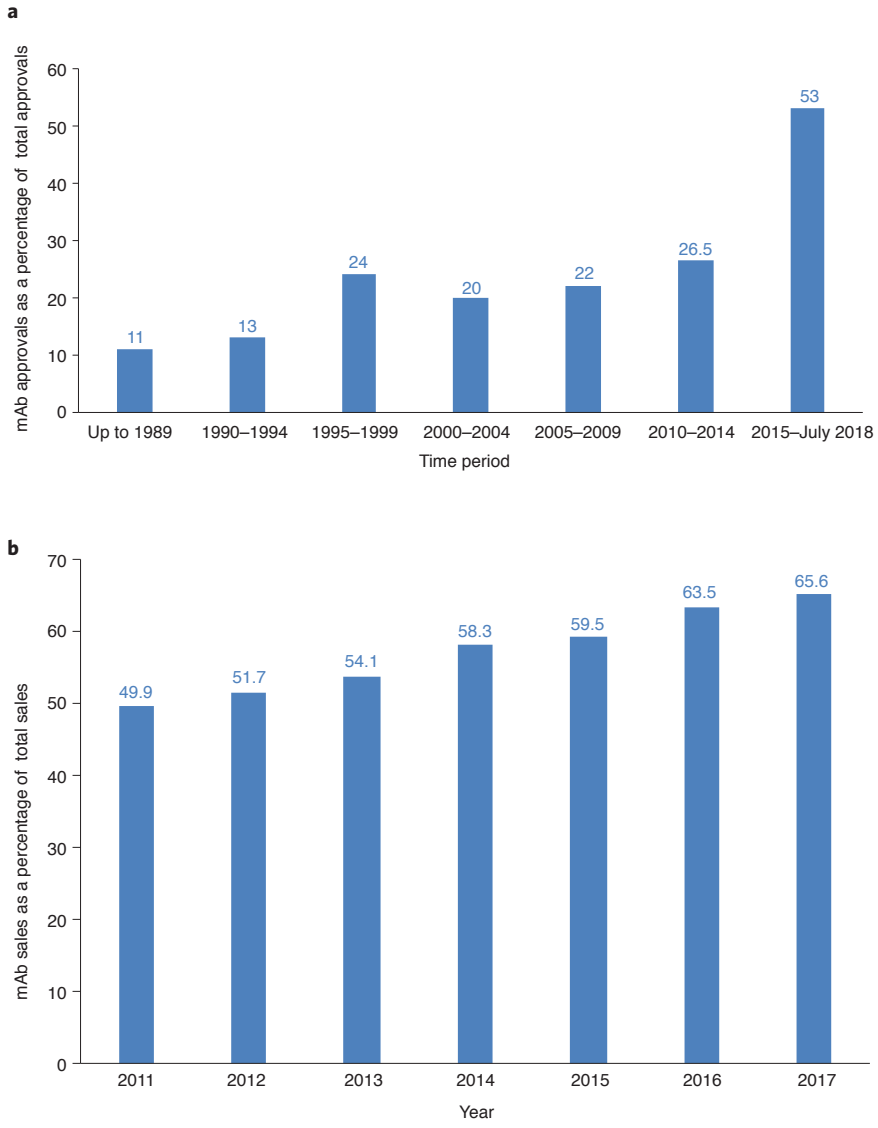

Figure 2 Overview of mAb approvals. (**a**) mAbs approved for the first time in the indicated periods, expressed as a percentage of total biopharmaceuticals approved for the first time in the same time period. (**b**) mAbs global annual sales value expressed as a percentage of total biopharmaceutical global sales for the indicated years. Financial data from La Merie Business Intelligence.

The mAb Humira (adalimumab) has been by far the single most lucrative product each year during the survey period, having generated global sales just short of $19 billion in 2017 and $62.6 billion cumulatively between 2014 and 2017 (**Table 3**). The top ten selling biopharmaceuticals together generated sales of $80.2 billion in 2017, representing almost 44% of total biopharmaceutical product revenues. Forty-five individual biopharmaceutical products recorded 'blockbuster' status sales (>$1 billion) last year.

mAbs continue to represent the most lucrative single product class. Total mAb sales (including Fc fusion protein–based antibody-like traps) reached $123 billion last year ($103.4 billion if fusion products are excluded). Moreover, mAbs represented eight of the top ten products by sales in 2017 (six of the top ten if the fusion traps are excluded). In terms of target indications, the vast majority of antibody or antibody-like trap fusion products target inflammatory, autoimmune conditions (cumulative 2017 sales of $64.6 billion, with products targeting tumor necrosis factor (TNF)-α alone generating $39.8 billion) and cancer (2017 cumulative sales of $43.1 billion). In terms of non-antibody-based products, insulins are the next most lucrative product class, collectively generating sales of $22 billion in 2017.

Biosimilars blossom

The survey period witnessed a surge in biosimilar approvals, signaling that this class of product is maturing. When considered by product trade name, 52 biosimilars have gained approval in the European Union and/or the United States since 2006 (**Table 4**), although 3 were subsequently withdrawn for commercial reasons.

By product category, the majority of biosimilar product approvals were antibody based (27 of 52), with 10 approvals of granulocyte colony stimulating factor (G-CSF) biosimilars and single-digit approvals of all others. The 52 licensed biosimilar products are actually based on 34 distinct active ingredients (**Table 4**). For example, the four rituximab-based biosimilars approved in Europe in 2017 (under the trade names Blitzima, Truxima, Ritemvia and Rituzena) all contain the same active substance: Celltrion's biosimilar rituximab, developed as CT-P10.

By region, 48 biosimilar products have received marketing authorization in the European Union, with 31 of these (65%) having gained authorization in the current survey period. In the United States, far fewer (13) biosimilars gained a license, the first being Zarzio (filgrastim-sndz) in March 2015, with the first biosimilar mAb (Inflectra; infliximab-dyyb) gaining approval in April 2016. This geographical discrepancy is unsurprising, given that the EU biosimilar regulatory framework (including the underpinning legislation and follow-on regulatory guidelines) pre-dates the US regulatory framework by almost a decade.

Of the 52 biosimilars approved thus far, two-thirds (35) are first-time approvals since 2014. This period witnessed few approvals of 'traditional' biosimilars, unlike earlier periods, in which most biosimilars approved were human growth hormone, erythropoietin or G-CSF products. Since 2014, approvals of these biosimilars have invariably been approvals in the United States of products previously approved in the EU. In recent years, the focus of approvals has shifted toward engineered insulins (4 approvals) and mAbs (25 product approvals; **Table 4**). Drivers here are market value, coupled with patent expiry and the availability of analytical methodology capable of demonstrating structural similarity in the context of proteins as large and complex as mAbs (**Box 2**). The survey period has therefore witnessed the approval of a raft of products demonstrating biosimilarity to the top-selling drugs, with biosimilar versions having come on-stream for eight of the top ten global-selling originator products (**Table 3**).

Biosimilars have achieved a widespread degree of acceptance in the European Union, where several such products have been on the market for over a decade. In that time,

Box 1 Clotting factors

Genetic defects characterized by lowered expression (or altered amino acid sequence) of any clotting factor can compromise the blood clotting process, leading to congenital hemophilia. Characterized by spontaneous and prolonged hemorrhage, hemophilia is due in over 80% of cases to a deficiency in factor VIII activity (hemophilia A), while in most of the remainder it is due to a deficiency in factor IX (hemophilia B). Global incidence of hemophilia is estimated at between 200,000 and 400,000, with hemophilia A having an average incidence of ~2 people per 10,000. Disease severity is linked to the percentage of residual active factor produced by the patient, and the disease is treated via intravenous administration of the missing clotting factor. Before the introduction of clotting factor concentrates in the 1960s, the life expectancy was of the order of 15–25 years. In the early 1980s, before the advent of screening tests of HIV in donated blood, large numbers of hemophiliacs contracted AIDS from clotting factors purified from human plasma. The introduction of recombinant clotting factors beginning in the early 1990s drastically reduced dependence on plasma-derived products, and the 2017 global market value for such recombinant products stood at $8.5 billion. Treatment costs typically vary from $30,000 to several hundred thousand dollars annually, depending on condition severity and the development of inhibitory antibodies (which 20–30% of hemophilia A patients can develop).

The current survey period witnessed a surge in clotting factor approvals, with ten factor VIII and six factor IX products coming on-stream, although several share the same active ingredient (**Table 1**). In the main, the products approved either are characterized by manufacturing process improvements over earlier-generation products or are engineered to increase serum half-life. For example, Bayer's Kovaltry/Iblias is essentially an updated Kogenate, a recombinant factor VIII. Unlike Kogenate, Kovaltry/Iblias is produced in a baby hamster kidney (BHK) cell line that also expresses heat shock protein 70, with resulting improvement in recombinant productivity. Moreover, all animal- and human-derived additives have been eliminated from the cell culture and purification processes, and a virus filtration step has been introduced for improved nonenveloped viral clearance robustness.

Clotting factor products are usually administered therapeutically (to control active bleeding) or prophylactically (to reduce frequency of future bleeding events). Administration for therapeutic purposes is tailored to individual circumstance while prophylactic administration of unmodified (first-generation) factors typically occurs three times weekly. Engineering to increase serum half-life has relied on PEGylation (Adynovi/Adynovate and Rebinyn/Refixia), Fc fusion (Elocta/Eloctate and Alprolix) or albumin fusion (Idelvion). Engineering had typically reduced prophylactic administration to twice weekly, and such products would be described by some as biobetter clotting factors.

The current survey period also witnessed the approval of a novel mAb-based product indicated for the prophylaxis of hemophilia A in patients who produce anti–factor VIII antibodies, which neutralize any exogenously administered factor VIII). Hemlibra (emicizumab) is a bispecific IgG, one arm of which binds factor IXa while the other binds factor X, effectively triggering factor VIII–independent clot formation. Market analysts predict Hemlibra may attain blockbuster status (sales above $1 billion) by 2019, reaching $4 billion by 2022 (https://clarivate.com/blog/life-sciences-connect/green-light-market-hemlibra-hemophilia-inhibitors-us/).

EU-monitoring systems for safety concerns have not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines, and a decade of clinical experience accrued with these products shows that the approved biosimilars can be used as safely and effectively in all their approved indications as other biological medicines[5]. Acceptance in the United States is not as strong, which is unsurprising given the shorter window of experience with biosimilars.

A 2016 report from consultants IMS Health on the impact of biosimilar competition in the European economic area[6] identifies EU-wide average price reductions from 8% in the case of anti-TNF biosimilar products to 33–34% savings in the context of erythropoietin and G-CSF biosimilars, relative to reference product pricing the year before biosimilar entrance. Moreover, the report found that biosimilar entry affected not only the price of the relevant reference product, but of the whole product class. Globally, 2017 sales generated cumulatively by all biosimilar reference products reached $73.3 billion. An interesting although hypothetical calculation suggests savings of up to $22 billion to global healthcare systems if biosimilar entry drove a 30% savings across the board in relation to all these products.

The development of so-called 'biobetters' represents a potential threat to biosimilar development. A biobetter describes an already approved biopharmaceutical entity altered in some way (e.g., a structural modification or an altered finished product combination or formulation) to improve some aspect of its clinical performance. The current period witnessed the approval of very few such products; mainly, they included novel insulin formulations or combinations (Suliqua/Soliqua and Xultophy; **Table 1**), as well as clotting factors with extended half-lives (**Box 2**). Biobetter development is likely tempered by the fact that such products are treated as a new product from a regulatory perspective.

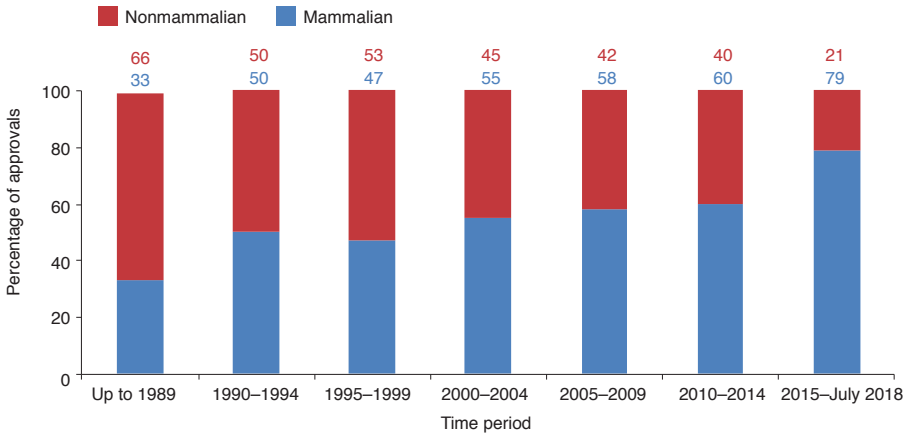

Figure 3 Relative use of mammalian- versus nonmammalian-based production cell lines in the manufacture of biopharmaceuticals approved over the indicated periods. Each dataset is expressed as a percentage of total biopharmaceutical product approvals for the period in question.

Table 3 The 20 top-selling biopharmaceutical products in 2017

Rank	Product	Sales, 2017 ($ billions)[a]	Cumulative sales, 2014–2017 ($ billions)	Year first approved	Company	Patent expiry[b]	Biosimilar version(s) approved
1	Humira (adalimumab; anti-TNF)	18.94	62.6	2002	AbbVie, Eisai	2016 (US) 2018 (EU)	Halimatoz/Hefiya/Hyrimoz, Amgevita/Amjevita/Solymbic, Cyltezo, Imraldi
2	Enbrel (etanercept; anti-TNF)	8.34	35.4	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015 (EU) 2028 (US)	Erelzi, Benepali
3	Rituxan/MabThera (rituximab; anti-CD20)	7.78	29.1	1997	Roche, Biogen Idec	2013 (EU) 2016 (US)	Blitzima/Truxima, Ritemvia, Rituzena, Rixathon/Riximyo
4	Remicade (infliximab; anti-TNF)	7.77	35.6	1998	Johnson & Johnson, Merck, Mitsubishi Tanabe Pharma	2015 (EU) 2018 (US)	Zessly, Ixifi, Renflexis/Flixabi, Inflectra/Remsima
5	Herceptin (trastuzumab; anti-HER2)	7.39	27.1	1998	Roche	2014 (EU) 2019 (US)	Herzuma, Kanjinti, Trazimera, Ogivri, Ontruzant
6	Avastin (bevacizumab; anti-VEGF)	7.04	27.0	2004	Roche	2017 (US) 2019 (EU)	Mvasi
7	Lantus (insulin glargine)	6.72	27.4	2000	Sanofi	2014 (EU & US)	Semglee, Lusduna, Abasaglar/Basaglar
8	Eylea (aflibercept; anti-VEGF)	5.93	18.0	2011	Regeneron, Bayer	2020 (EU) 2021 (US)	
9	Opdivo (nivolumab; anti-PD-1 receptor)	5.79	11.4	2014	Bristol-Myers Squibb, Ono Pharmaceutical	2027 (US) 2026 (EU)	
10	Neulasta (pegfilgrastim)	4.53	20.1	2002	Amgen, Kyowa Hakko Kirin	2014 (US) 2015 (EU)	Fulphila
11	Stelara (ustekinumab; anti-IL-12 & IL-23)	4.01	12.2	2009	Janssen Cilag (Johnson & Johnson)	2023 (US) 2024 (EU)	
12	Keytruda (pembrolizumab, anti-PD-1)	3.81	5.7	2014	Merck	2036 (US) 2028 (EU)	
13	Prolia/Xgeva (denosumab, anti-RANKL)	3.54	11.6	2010	Amgen	2025 (US) 2022 (EU)	
14	Lucentis (ranibizumab; anti-VEGF)	3.38	14.3	2006	Roche, Novartis	2016 (EU & US)	
15	Novolog/Novorapid (insulin aspart)	3.31	11.7	1999	Novo Nordisk	2015 (EU & US)	
16	Soliris (eculizumab; anti–C5 complement protein)	3.14	10.7	2007	Alexion Pharmaceuticals	2021 (US) 2020 (EU)	
17	Simponi (golimumab; anti-TNF)	2.94	9.7	2009	Merck, Janssen, Mitsubishi Tanabe	2024 (EU & US)	
18	Humalog mix 50:50 (insulin lispro)	2.86	11.3	1996	Eli Lilly	2014 (US) 2015 (EU)	Insulin lispro Sanofi
19	Xolair (omalizumab) anti-IgE	2.75	8.7	2003	Roche, Novartis	2017 (EU & US)	
20	Aranesp/Nesp (darbepoetin alfa)	2.62	10	2001	Amgen, Kyowa Hakko Kirin	2016 (EU) 2024 (US)	

[a]Financial data from La Merie Business intelligence. [b]Patent data from various sources, including http://www.gabionline.net/Biosimilars/General/Biologicals-patent-expiries.
HER2, human epidermal growth factor receptor 2; IgE, immunoglobulin E; IL, interleukin; PD-1, programmed cell death receptor 1; RANKL, receptor activator of nuclear factor-κB ligand; VEGF, vascular endothelial growth factor.

mAb approvals

The data in our survey underscore the current and increasing dominance of mAbs in the biopharma sector, in terms of overall product approvals, biosimilar approvals and market value. Whereas cancer remains the most common target indication, during the period several products aimed at nontraditional mAb target conditions were approved. These include Aimovig (erenumab), indicated for migraine; Fasenra (benralizumab) and Cinqair/Cinqaero (reslizumab) for asthma; Trogarzo (ibalizumab) for HIV infection; and Anthim (obiltoxaximab) for inhalation anthrax. Also notable was the approval of several anti-interleukin mAbs to treat psoriasis, as opposed to the more traditional anti-TNF products for this indication. The new products include Cosentyx (secukinumab), Ilumya (tildrakizumab-asmn), Kyntheum/Siliq (brodalumab), Tremfya (guselkumab) and Taltz (ixekizumab). Taltz is also unusual in that it is a humanized immunoglobulin G4 (IgG4). It was consequently engineered to contain a serine-to-proline substitution (S228P), which reduces the frequency of half-antibody formation or other heterologous antibody combinations sometimes observed with IgG4 antibodies.

It is also notable that all the mAbs approved in the survey period were engineered in some way: virtually all novel antibodies approved are either humanized or fully human. One new antibody–drug conjugate (Besponsa, inotuzumab ozogamicin) made it to market, along with two new bispecific products (Hemlibra, emicizumab/emicizumab-kxwh; Blincyto, blinatumomab; **Boxes 1** and **3**). Tecenetriq (atezolizumab), a mAb against programmed cell death receptor ligand 1 (PD-L1), is unusual in that it contains an amino acid substitution (asparagine to alanine) at position 298, in the CH2 domain of each heavy chain. This substitution prevents antibody glycosylation and thus blocks glycan-dependent Fc-effector functions, which is in turn important in the context

Table 4 Biosimilar products that had gained marketing authorization within the European Union and/or the United States by July 2018

Product type	Biosimilar (trade name)	Year (and region) approved	Reference product	Drug (active ingredient) manufacturer
Somatropin-based				
Human growth hormone–based	Omnitrope	2006 (EU)	Genotropin	Sandoz (Kundl, Austria)
	Valtropin	2006 (EU) Withdrawn 2012	Humatrope	LG Life Sciences (Jeonbuk-do, Republic of Korea)
Epoetin-based				
Epoetin-based	Binocrit	2007 (EU)	Eprex/Erypo	Rentschler (Laupheim, Germany) & Lek (Menges, Slovenia)
	Epoetin alfa hexal	2007 (EU)	Eprex/Erypo	Rentschler & Lek
	Abseamed	2007 (EU)	Eprex/Erypo	Rentschler & Lek
	Retacrit	2018 (US) 2007 (EU)	Eprex/Erypo (EU) Epogen/Procrit (US)	Norbitec (Uetersen, Germany) Norbitec (Uetersen, Germany)
	Silapo	2007 (EU)	Eprex/Erypo	Norbitec
Filgrastim-based				
G-CSF-based	Ratiograstim	2008 (EU)	Neupogen	Sicor (Vilnius, Lithuania)
	Filgrastim ratiopharm	2008 (EU) Withdrawn 2011	Neupogen	Sicor
	Biograstim	2008 (EU) Withdrawn 2015	Neupogen	Sicor
	Tevagrastim	2008 (EU)	Neupogen	Sicor
	Zarxio (US) Zarzio (EU)	2015 (US) 2009 (EU)	Neupogen	Sandoz (Kundl, Austria)
	Filgrastim hexal	2009 (EU)	Neupogen	Sandoz (Kundl, Austria)
	Nivestym (US) Nivestim (EU)	2018 (US) 2010 (EU)	Neupogen	Hospira (Pfizer) (Zagreb, Croatia)
	Grastofil	2013 (EU)	Neupogen	Intas Biopharmaceuticals (Gujarat, India)
	Accofil	2014 (EU)	Neupogen	Intas Biopharmaceuticals
Pegfilgrastim-based	Fulphila	2018 (US)	Neulasta	Mylan (Zurich)
Follicle-stimulating hormone–based				
Follicle-stimulating hormone–based	Ovaleap	2013 (EU)	Gonal F	Merckle Biotec (Ulm, Germany)
	Bemfola	2014 (EU)	Gonal F	Polymun Scientific Immunbiologische Forschung (Klosterneuburg, Austria)
Insulin-based				
Insulin glargine–based	Abasaglar	2014 (EU)	Lantus	Lilly del Caribe (Carolina, Puerto Rico, USA) Eli Lilly (Indianapolis)
	Lusduna	2017 (EU) 2017 (US), tentative	Lantus	Merck Sharp & Dohme (Elkton, VA, USA)
	Semglee	2018 (EU)	Lantus	Biocon Nusajaya (Johor, Malaysia)
Insulin lispro–based	Insulin lispro Sanofi	2017 (EU)	Humalog	Sanofi-Aventis (Frankfurt)
mAb-based and related				
Infliximab-based	Inflectra	2016 (US) 2013 (EU)	Remicade	Celltrion (Incheon, Republic of Korea)
	Remsima	2013 (EU)	Remicade	Celltrion
	Flixabi	2016 (EU)	Remicade	Biogen (Hillerod, Denmark) Samsung Bioepis (Incheon, Republic of Korea)
	Renflexis	2017 (US)	Remicade	Biogen (Hillerod, Denmark) Samsung Bioepis
	Ixifi	2017 (US)	Remicade	Pfizer
	Zessly	2018 (EU)	Remicade	Boehringer Ingelheim (Biberach an der Riss, Germany)
Adalimumab-based	Amgevita (EU) Amjevita (US)	2017 (EU) 2016 (US)	Humira	Amgen (Thousand Oaks, CA, USA)
	Solymbic	2017 (EU)	Humira	Amgen
	Cyltezo	2017 (EU & US)	Humira	Boehringer Ingelheim (Fremont, CA, USA)
	Halimatoz	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Hefiya	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Hyrimoz	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Imraldi	2017 (EU)	Humira	Biogen (Research Triangle Park, NC, USA) Biogen (Hillerød, Denmark)

Table 4 Continued

Product type	Biosimilar (trade name)	Year (and region) approved	Reference product	Drug (active ingredient) manufacturer
Rituximab-based	Blitzima	2017 (EU)	MabThera	Celltrion
	Truxima	2017 (EU)	MabThera	Celltrion
	Ritemvia	2017 (EU)	MabThera	Celltrion
	Rituzena	2017 (EU)	MabThera	Celltrion
	Rixathon	2017 (EU)	MabThera	Sandoz (Langkampfen, Austria)
	Riximyo	2017 (EU)	MabThera	Sandoz (Langkampfen, Austria)
Trastuzumab-based	Ontruzant	2017 (EU)	Herceptin	Biogen (Hillerød, Denmark)
	Ogivri	2017 (US)	Herceptin	Mylan
	Herzuma	2018 (EU)	Herceptin	Celltrion
	Kanjinti	2018 (EU)	Herceptin	Patheon Biologics (Groningen, the Netherlands)
	Trazimera	2018 (EU)	Herceptin	Boehringer Ingelheim (Biberach an der Riss, Germany)
Bevacizumab-based	Mvasi	2018 (EU) 2017 (US)	Avastin	Amgen
Etanercept-based	Benepali	2016 (EU)	Enbrel	Biogen (Hillerød, Denmark)
	Erelzi	2017 (EU) 2016 (US)	Enbrel	Sandoz (Novartis) (Langkampfen, Austria) (EU) Novartis Pharma (Stein, Switzerland) (US)
Teriparatide-based				
Teriparatide-based	Movymia	2017 (EU)	Forsteo	Richter-Helm BioLogics (Bovenau, Germany)
	Terrosa	2017 (EU)	Forsteo	Richter-Helm BioLogics

of the product's mode of action and safety profile. Fasenra, by contrast, is engineered such that its glycocomponent is afucosylated (like that of Gazyva/Gazyvaro (obinutuzumab), approved initially in 2013), which increases the antibody-dependent cell-mediated cytotoxicity activity important for its mode of action. The period also witnessed the approval of one Fab antibody fragment (Praxbind; idarucizumab), designed to bind and thus neutralize the anticoagulant drug dabigatran.

Although technically outside the timeframe of this survey, the approval of Cablivi (caplacizumab) in Europe at the end of August represents a major milestone in mAb therapeutics, as it is the first nanobody to gain regulatory approval. It is indicated to treat acquired thrombotic thrombocytopenic purpura, which is a rare, life-threatening, autoimmune blood clotting disorder. Cablivi is a humanized, 259 amino acid, 2.78 kDa bivalent nanobody produced in *E. coli* that binds to von Willebrand factor, a key protein in hemostasis. This in turn inhibits the interaction of von Willebrand factor with blood platelets, preventing platelet adhesion and hence the clotting characteristic of the condition.

Although often considered the poster child of biopharma, antibody-based products are just as susceptible to commercial influence and pharmacovigilance as any other therapeutic product. Three mAbs approved in the current survey period have been withdrawn within this period. European marketing authorizations for Unituxin (dinutuximab, approved for neuroblastoma) from United Therapeutics and nivolumab BMS (nivolumab, approved for non-small-cell lung cancer) from Bristol-Myers Squibb were withdrawn, due to drug supply difficulties in the case of Unituxin and for commercial reasons in the case of nivolumab BMS. Biogen and AbbVie's Zinbryta (daclizumab), which was approved in 2016 for multiple sclerosis, was withdrawn globally in 2018 after serious adverse events, such as liver damage and immune reactions, became apparent.

Recombinant enzymes and transgenic production

The survey period also witnessed the approval of nine recombinant enzymes for the treatment of various genetic conditions. From a technological perspective, Alexion Pharmaceuticals' Kanuma (sebelipase alfa; recombinant human lysosomal acid lipase) is interesting in that it is produced in the eggs of transgenic chickens, with enzyme purification directly from transgenic egg white. The transgenic chicken line was developed via injection of a retroviral vector carrying the human coding sequence into chick embryos.

However, transgenic-based platforms for biopharmaceutical production have failed to gain widespread use in the biopharmaceutical sector. Technical challenges arising from random integration of transgenes into host chromosomes and the difficulty of controlling transgene copy number in production animals has limited the appetite for commercial investment in transgenic animal platforms capable of generating economically viable levels of recombinant proteins. It will be interesting to follow whether recent developments in CRISPR-based gene editing, which overcome some of these technical difficulties[7], change the industry outlook. Ovalbumin, for example, is expressed at two grams per hen egg, with one hen capable of laying more than 300 eggs a year. CRISPR-targeted insertion of a therapeutic-protein-encoding sequence into the ovalbumin gene could therefore afford high-level protein production[8].

Nucleic acid–based approvals

Nucleic acid–based products (gene therapies, DNA or RNA vaccines, ASOs, small interfering RNAs (siRNA), aptamers and modified RNA molecules) have yet to exert a profound influence on the biopharma product landscape, although the period witnessed the approval of five such products (three ASOs and two gene therapies). This brings the total tally of approvals in this category to nine, although the gene therapy Glybera (alipogene tiparvovec) was withdrawn from the market last year.

Glybera was approved as a single-administration gene therapy for adults suffering from familial lipoprotein lipase deficiency with a treatment price tag on the order of $1 million. The developer and manufacturer opted not to renew its European marketing authorization in 2017 due to lack of demand for the product. Luxturna (voretigene neparvovec-rzyl), approved last year in the United States, appears set to be almost as costly; the one-time treatment will cost $850,000. Luxturna contains a live, nonreplicating adeno-associated virus serotype 2 genetically modified to express the human retinal pigment epithelium-specific 65-kDa (*RPE65*) gene. Delivered directly via

subretinal injection, it is indicated for patients with inherited retinal disease due to mutations in both copies of this gene. The headline costs of either of these products likely reflect the rarity of the target conditions and thus potential market size, as opposed to a fundamental cost basis for gene therapy products *per se*. The third gene therapy approval, Imlygic (talimogene laherparepvec), for example, is projected to cost an average of $65,000 per patient. Indicated for the treatment of melanoma recurrent after initial surgery, Imlygic is a live, attenuated herpes simplex virus type 1 carrying the human GM-CSF coding sequence. Viral replication subsequent to injection directly into the tumor is believed to trigger cell lysis, and it is believed that the release of tumor-derived antigens along with the GM-CSF may also promote an antitumor effect.

Three approved ASO products hold orphan status for the treatment of rare conditions with limited therapeutic options. It is notable that one of these ASO products, Ionis Pharmaceuticals' Spinraza (nusinersen) for spinal muscular atrophy, was the main source of sales growth for Biogen in 2017, generating $188 million in sales in the first quarter of 2018. Spinraza targets splicing defects that lead to this disorder, and rare conditions arising due to mRNA mis-splicing are likely to be an increasing area of focus for this modality.

In terms of downregulation of misregulated mRNA expression, ASOs now have to compete with siRNAs. Although technically outside the timeframe of this current survey, the recent approval of Alnylam's Onpattro (patisiran) represents the most notable recent approval of an oligonucleotide-based therapeutic. Approved in both US and EU in August 2018, Onpattro is the first RNAi-based gene expression silencing product to gain approval in either region.

Traditional biotech product approvals

The current survey period also witnessed the approval of 46 traditional biotech products classified as new by regulatory authorities in terms of active substance—just one more than recorded in our previous survey. Traditional products refer to those produced naturally or via nonrecombinant means in or by a biological source.

The profile of approvals (**Supplementary Table 1**) by and large mirrors product types approved in previous surveys and include a range of blood-derived products (for example, plasma-purified human albumin, clotting factors and immunoglobulins), as well as traditional (nonrecombinant) vaccines and nonengineered cells.

Box 2 Analytical approaches to validating biosimilar mAb quality

Biosimilar guidelines require the generation of comparative data between a proposed new biosimilar product and the reference product to which it claims similarity, at the levels of both the active substance and finished product. The marketing application, relative to a standard product application, must contain a full quality module, incorporating comparative quality analysis, as well as reduced comparative clinical and nonclinical data modules. Comparative quality studies largely rely on analytical techniques and instrumentation, now capable of fully characterizing biopharmaceuticals as large and complex as mAbs, with mass spectrometry (MS)-based techniques coming to the fore. Any comparative differences identified (for example, differences in glycocomposition) are then considered in terms of effect on biosimilarity, with further investigation via biological assay or preclinical or clinical evaluation, as appropriate.

An analysis of the comparative quality information presented in the European public assessment reports of approved biosimilar mAbs provide insight into the broad range of state-of-the-art analytical techniques used in practice (similar techniques are used as appropriate in the context of other protein-based biosimilars). The commonly applied analytical approaches discernible in these documents include the following:

- Determination of intact molecular mass by electrospray MS. Other size analysis modalities cited included size exclusion high performance liquid chromatography (SE-HPLC) and capillary electrophoresis in the presence of sodium dodecyl sulfate.
- Primary structural analysis by methods including classic C- and N-terminal sequencing (partial sequence determination), with full sequence determination invariably relying on initial protein fragmentation, peptide mapping and MS techniques such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS or liquid chromatography/tandem MS (LC-MS/MS). This includes the detection of C-terminal lysine variability (common in IgGs, but without anticipated clinical impact as C-terminal lysines are rapidly removed in serum).
- Sulfhydryl analysis via ultraviolet (UV)/visible light spectrophotometry and SE-HPLC, with disulfide linkage assignment via LC-MS-based peptide mapping under reducing and nonreducing conditions.
- Higher order structural analysis: secondary structural analysis via far-UV circular dichroism spectroscopy and/or Fourier transform infrared spectroscopy; tertiary analysis via near-UV circular dichroism spectroscopy or intrinsic fluorescence spectroscopy; thermal stability of higher order structure via differential scanning calorimetry; X-ray crystallography of the Fc domain.
- Glycosylation analysis: composition or structural determination, including levels of fucosylation and terminal galactosylation (which can influence antibody effector functions), by exoglucanase digestion and hydrophobic interaction chromatography analysis, high-performance anion-exchange chromatography with pulsed amperometric detection (HPAE-PAD).
- Analysis of additional modifications (for example, site specific deamidation, oxidation) by MS-based methods, peptide mapping with LC-MS).
- Charge heterogeneity profile by ion exchange-based HPLC, isoelectric focusing.
- Purity analysis: HPLC-based separation modalities based on size, charge and hydrophobicity, capillary gel electrophoresis, western blot analysis.

Engineered cell–based approvals

Traditional cell-based therapeutics containing cells extracted from human tissue or blood continue to come on the market. Examples include hematopoietic progenitor cells derived from cord blood, as well as autologous cultured chondrocytes used to treat cartilage defects (**Supplementary Table 1**).

A notable recent milestone in cell-based therapeutics is the approval of genetically engineered cell–based therapies, four of which have been approved since 2016: Kymriah (tisagenlecleucel), Yescarta (axicabtagene ciloleucel), Zalmoxis and Strimvelis. These products may be viewed as both cell and gene therapies, given that the cells carry a therapeutic gene into the patient's body. All four products have orphan status or target niche conditions and either are under additional monitoring or require further postauthorization safety studies. Three of the four (Kymriah, Yescarta and Strimvelis) use autologous cells, whereas the fourth (Zalmoxis) uses allogeneic cells as a starting point. One is a hematopoietic stem cell therapy (Strimvelis) and the other

Box 3 BiTE technology

Pioneered by Micromet, a biotechnology company acquired by Amgen, the first bispecific T-cell engager (BiTE) product, Blincyto (blinatumomab), gained approval in the United States and European Union for the treatment of B-cell precursor acute lymphoblastic leukemia during the current survey period. The BiTE platform consists of a bispecific antigen-binding antibody fragment, one arm of which is designed to bind the CD3 cell surface receptor complex, invariably found on cytotoxic T cells, while the other arm is designed to bind a surface tumor antigen associated with a target cancer cell type[17,18]. The BiTE construct therefore acts as a bridge, bringing cytotoxic T cells into close proximity to the target cancer cells and triggering lysis of the latter by the former.

The Blincyto construct consists of two single-chain variable fragments (scFv domains) joined by a short, flexible linker sequence consisting of glycine and serine residues. The 55 kDa, 504 amino acid construct includes a C-terminal hexahistidine sequence, which facilitates purification using zinc-immobilized metal affinity chromatography. One scFv domain targets the T-cell CD3 receptor, while the other binds the pan-B-cell antigen CD19, facilitating T-cell-mediated lysis of B cells. Because of its relatively low molecular mass, the construct has a short serum half-life (2–3 h). This requires continuous infusion over a four-week period, representing a limitation in terms of patient convenience. Approaches to the development of next-generation constructs with extended serum half-lives include fusion to human albumin and Fc-based constructs, with an aim of facilitating a once-weekly dosage schedule.

The Amgen pipeline contains several more BiTE constructs undergoing phase 1 clinical trials for the treatment of various cancers, including multiple myeloma and acute myeloid leukemia. BiTE constructs targeting solid tumors have thus far yielded limited success. Limitations may include the degree of tumor penetration (by the construct and T cells), as well as the relatively broad expression of target antigen, which may limit dose escalation.

three are T-cell therapies. In all cases, genetic modification is undertaken *ex vivo* using a viral vector to achieve transduction, followed by infusion of the genetically modified cells into the patient.

Two of the products (Kymriah and Yescarta) fall into the new wave of cellular immunotherapies for oncology. They are notable in that they are the first chimeric antigen receptor (CAR)-T cell-based products[9,10] to gain regulatory approval, effectively validating this technology from a regulatory standpoint. In addition to US approval in 2017, both gained marketing authorization in Europe in August 2018. In the case of both approved products, the CAR-T cells target the CD19 antigen, found on the surface of B lymphocytes, facilitating efficient T-cell-mediated destruction of B cells—thus their indication for the treatment of B-cell-based cancers, against which they have shown striking clinical results.

Future directions

Although published estimates vary somewhat, some 40% of the 6,000 or more products currently in clinical development globally are biopharmaceuticals. This suggests that the substantial increase in the proportion of approved pharmaceutical products that are biopharmaceuticals seen in this survey period is not a blip, but will be sustained into the future.

The profile of products in advanced-stage clinical trials suggests that biopharmaceutical approvals over the next few years will continue to be predominantly protein-based (rather than nucleic acid- or cell-based), that they will be produced largely using conventional mammalian cell expression systems, that mAb-based products will continue to dominate the approvals, that a steady stream of biosimilars will continue to gain approval (particularly in indications with large, lucrative markets), and that cancer will remain the primary target indication.

Fifty-four genuinely new mAbs in late-stage clinical trials are under regulatory review in the United States and European Union[11], framing nearer-term putative approvals in these regions. Of these, 28 (52%) target cancer, 7 for liquid malignancies and 21 for solid tumors. Most are fully human or humanized IgGs, along with a smaller number (5) of antibody fragment (Fab or single-chain variable fragment (scFv)) products. Of the 28 anticancer products, 9 are conjugated to an effector molecule (radiolabel, chemical or toxin).

The antibody market, although highly successful, is also becoming very crowded. In some cases, multiple mAbs target the same therapeutic target (for example, CD20, TNF and vascular endothelial growth factor) and have overlapping indications. The mainstreaming of biosimilar mAbs and, potentially, the development of competing product types, such as CAR-T cell immunotherapies, further increases the competitive pressure and incentive to innovate. Not surprisingly, a greater diversity of modalities and targets is seen further back in the developmental pipeline, reflected in various antibody formats engineered to enhance functionality in some way, the pursuit of novel disease targets and the assessment of mAbs in combination with a second therapeutic agent.

Indeed, such competitive pressures have driven, and continue to drive, innovation among categories other than mAbs. For example, incentive to innovate is illustrated by the recent approval of several clotting factors engineered to increase serum half-life and an increasing number of trials assessing both previously approved and experimental biopharmaceuticals in combination with other drugs to treat various cancers.

Biosimilars will continue to feature with increasing prominence in the global biopharmaceutical landscape, but their greatest impact will continue to be in regions outside the more developed markets, such as the United States and European Union. Thus far, an estimated 260 biosimilar products have been approved in at least one global market—of which only a relatively small minority (52) have been approved in the European Union and/or the US. That being said, many of the additional products approved would likely find it challenging to meet EU and US regulatory expectations in the context of biosimilarity.

Globally, some 188 biosimilars are in development, 61 of which are in phase 3 trials[12]. Specifically within Europe and the United States there are an estimated 50 biosimilars in development (https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf). Despite recent headline approvals, penetration in the US market in particular is likely to occur relatively slowly, underscored by regulatory and legal uncertainties, complex pricing and contracting mechanisms and, of course, patient and clinician acceptance. Overall, however, biosimilar market growth is anticipated to be strong, with market reports (e.g., https://www.marketsandmarkets.com/Market-Reports/biosimilars-40.html) typically forecasting a $23 billion global market value within the next five to six years, up substantially from an estimated 2017 value of the order of $4.5 billion.

The predominance of protein-based approved biopharmaceuticals is likely to remain an industry reality for the foreseeable future. Nucleic acid–based products have yet

to make a substantial and sustained impact on the list of biopharmaceutical products that are registered in Europe and the United States. A study[13] from the *Journal of Gene Medicine* estimates that 2,597 gene therapy–based clinical trials have been approved globally since 1989. Despite this large body of data, gene-therapy-based approvals in Europe and the United States remain in the single digits. Advances in adeno-associated virus (AAV) and lentiviral gene therapy modalities (particularly in *ex vivo* cellular therapy contexts)—together with increasing interest in CRISPR endonuclease-based gene editing, with several companies now poised to take such approaches into human testing—are likely to provide further impetus to the development of nucleic acid–based treatments.

The rapid advances and clinical adoption of T-cell-based adoptive therapies (including CAR-T cells) is a particularly notable development in the period of this study. The success of this cellular gene therapy is built on the exceptional responses obtained in some trials for some cancers, particularly liquid malignancies. However, scientific, technological and manufacturing hurdles may all complicate its more widespread adoption, certainly in the nearer term[14–16].

Overall, the past four and a half years have witnessed continued and accelerated growth in the biopharma sector. Antibodies continue to reign supreme and look to dominate for several years to come. Elsewhere, two developments in biopharmaceutical products have been particularly notable over the past five years. First, the massive proliferative capacity of cellular therapy has been effectively harnessed in the form of immunotherapy for late-stage cancers. It is this ability to identify, expand, attack and destroy malignant cells that has made CAR-T cell therapies so successful and overshadowed the longer term goal of cellular therapy: regeneration. Regenerative cell therapy was for many years seen as the main opportunity for modalities based on living cells and, in particular, stem cells; that is no longer the case. Second, increasing evidence of safety and growing familiarity of physicians and insurers with biosimilars means the economic advantages of these products are no longer being ignored. It seems likely that the rapid growth of biosimilar products will continue over the years to come.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.4305).

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▪ BIOPHARMACEUTICAL ▪ Benchmarks

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Biopharmaceuticals are defined here as recombinant proteins, including recombinant antibody-based products, and nucleic acid–based and genetically engineered cell–based products. They are listed consecutively from most recent approval in each class, with registrations since 2014 in bold and withdrawals in red. Eight categories are shown: recombinant clotting factors; recombinant thrombolytics, anticoagulants and other blood-related products; recombinant hormones; recombinant growth factors; recombinant interferons, interleukins and tumor necrosis factor; recombinant vaccines; monoclonal antibody–based products; and other recombinant products. Where more than one drug in the same category was approved in a single year, they are listed alphabetically by trade name. Several products have been approved for multiple indications, but only the first indication for which it was approved is listed here. Some product entries describe the product as being the same as another listed product. In such instances differences invariably exist in terms of approved indication range or the company holding the marketing authorizations, usually as a result of commercial agreements.

Table 1 Biopharmaceuticals approved in the United States and European Union through end of July 2018

Product	Company (location)	Therapeutic indication	Date approved
Recombinant clotting factors			
Factor VIII			
Adynovi (rurioctocog alfa pegol), extended half-life PEGylated form of full-length r factor VIII product Advate (see below). Same product as Adynovate (see below)	**Baxalta Innovations (Vienna)**	**Hemophilia A**	**2018 (EU)**
Afstyla (lonoctocog alfa), B-domain-truncated rh coagulation factor VIII, produced in CHO cells	**CSL Behring (Marburg, Germany, & Kankakee, IL, USA)**	**Hemophilia A**	**2017 (EU 2016 (US)**
Vihuma (simoctocog alfa), rh B-domain-deleted factor VIII, produced in HEK cells. Same product as Nuwiq (see below)	**Octapharma (Stockholm)**	**Hemophilia A**	**2017 (EU)**
Iblias (octocog alfa), rh coagulation factor VIII, produced in BHK cells using the same expression construct as Bayer's Kogenate and Helixate. Same product as Kovaltry (see below)	**Bayer Pharma (Berlin)**	**Hemophilia A**	**2016 (EU)**
Kovaltry (octocog alfa), rh coagulation factor VIII, produced in BHK cells using the same expression construct as Bayer's Kogenate and Helixate. Same product as Iblias (see above)	**Bayer Pharma Bayer HealthCare (Whippany, NJ, USA)**	**Hemophilia A**	**2016 (EU & US)**
Vonvendi (von Willebrand factor (recombinant)), produced in CHO cells	**Baxalta (Westlake Village, CA, USA)**	**von Willebrand disease**	**2015 (US)**
Nuwiq (simoctocog alfa), B-domain-deleted rh factor VIII, produced in HEK cells. Same product as Vihuma (see above)	**Octapharma USA (Hoboken, NJ, USA) Octapharma**	**Hemophilia A**	**2015 (US) 2014 (EU)**
Obizur (susoctocog alfa), r B-domain-deleted porcine factor VIII, produced in BHK cells	**Baxalta Innovations Baxter Healthcare (Westlake Village, CA, USA)**	**Acquired hemophilia due to development of autoantibodies against factor VIII**	**2015 (EU) 2014 (US)**
Adynovate (recombinant, PEGylated antihemophilic factor), extended half-life PEGylated form of full-length r factor VIII product Advate (see below). Same product as Adynovi (see above)	**Baxalta**	**Hemophilia A**	**2015 (US)**
Elocta (efmoroctocog alfa) in EU, Eloctate (antihemophilic factor recombinant, Fc fusion protein) in US: rh coagulation factor VIII–Fc fusion protein comprising B-domain-deleted human factor VIII covalently linked to the Fc domain of a human IgG, produced in HEK cells	**Swedish Orphan Biovitrum (Stockholm) Biogen Idec (Cambridge, MA, USA)**	**Hemophilia A**	**2015 (EU) 2014 (US)**
NovoEight (turoctocog alfa), rh factor VIII analog that, when activated, is structurally comparable to endogenous human factor VIIIa, produced in CHO cells	Novo Nordisk (Bagsvaerd, Denmark, & Plainsboro, NJ, USA)	Hemophilia A	2013 (EU & US)
Xyntha (antihemophilic factor), rh coagulation factor VIII, produced in CHO cells	Pfizer/Wyeth (Philadelphia)	Hemophilia A	2008 (US)
Advate (octocog alfa), rh factor VIII, produced in CHO cells	Baxter Healthcare (Vienna & Deerfield, IL, USA)	Hemophilia A	2004 (EU) 2003 (US)
Helixate NexGen (octocog alfa), rh factor VIII, produced in BHK cells	Bayer (Berlin)	Hemophilia A	2000 (EU)
ReFacto (moroctocog alfa), B-domain-deleted rh factor VIII, produced in CHO cells	Pfizer/Wyeth (Sandwich, UK) Genetics Institute (Cambridge, MA, USA)	Hemophilia A	2000 (US) 1999 (EU)
Kogenate, Helixate (antihemophilic factor), rh factor VIII, produced in BHK cells. Sold as Helixate by Aventis Behring through a license agreement	Bayer (Leverkusen, Germany, & Berkeley, CA, USA)	Hemophilia A	2000 (EU) 1993 (US)
Bioclate (antihemophilic factor), rh factor VIII, produced in CHO cells	Aventis Behring (King of Prussia, PA, USA)	Hemophilia A	1993 (US)
Recombinate (antihemophilic factor), rh factor VIII, produced in CHO cells	Baxter Healthcare (Deerfield, IL, USA), Genetics Institute	Hemophilia A	1992 (US)
Other blood factors			
Andexxa (coagulation factor Xa recombinant inactivated-zhzo), r modified human factor Xa, produced in CHO cells	**Portola Pharmaceuticals (South San Francisco, CA, USA)**	**For patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding**	**2018 (US)**
Rebinyn (rh coagulation factor IX) in US, Refixia (nonacog beta pegol) in EU: rh coagulation factor IX, produced in CHO cells and PEGylated	**Novo Nordisk**	**Hemophilia B**	**2017 (EU & US)**
Alprolix (eftrenonacog alfa), rh coagulation factor IX fused to a human IgG1 Fc domain, produced in HEK cells	**Biogen Idec (Maidenhead, UK, & Cambridge, MA, USA)**	**Hemophilia B**	**2016 (EU) 2014 (US)**
Idelvion (albutrepenonacog alfa), rh factor IX–albumin fusion protein, produced in CHO cells	**CSL Behring**	**Hemophilia B**	**2016 (EU & US)**
Ixinity (coagulation factor IX (recombinant)), rh coagulation factor IX, produced in CHO cells	**Aptevo BioTherapeutics (Berwyn, PA, USA)**	**Hemophilia B**	**2015 (US)**
Rixubis (nonacog gamma), rh factor IX, produced in CHO cells	**Baxalta Innovations (Vienna) Baxter Healthcare (Westlake Village, CA, USA)**	**Hemophilia B**	**2014 (EU) 2013 (US)**
Tretten in US, Novothirteen in EU (catridecog), rh factor XIII A-subunit, produced in *S. cerevisiae*	Novo Nordisk	Congenital factor XIII A-subunit deficiency	2013 (US) 2012 (EU)
Recothrom (thrombin), rh factor IIa, produced in CHO cells	ZymoGenetics (Seattle)	Control of minor bleeding during surgery	2008 (US)
NovoSeven (eptacog alfa, activated), rh factor VIIa, produced in BHK cells	Novo Nordisk	Some forms of hemophilia	1996 (EU) 1999 (US)
Benefix (nonacog alfa), rh factor IX, produced in CHO cells	Pfizer/Wyeth	Hemophilia B	1997 (EU & US)
Recombinant thrombolytics, anticoagulants and other blood-related products			
Tissue plasminogen activator			
Metalyse (tenecteplase), modified rh tPA, produced in CHO cells	Boehringer Ingelheim (Ingelheim, Germany)	Myocardial infarction	2001 (EU) Withdrawn 2005
TNKase (tenecteplase), modified rh tPA, produced in CHO cells	Roche/Genentech (South San Francisco, CA, USA)	Myocardial infarction	2000 (US)
Ecokinase (reteplase), r tPA, produced in *Escherichia coli*; differs from human tPA in that 3 of its 5 domains have been deleted	Roche (Welwyn Garden City, UK)	Acute myocardial infarction	1996 (EU) Withdrawn 2000
Rapilysin (reteplase), r tPA (see Ecokinase above)	Actavis Group PTC (Hafnarfjordur, Iceland), Roche	Acute myocardial infarction	1996 (EU)
Retavase (reteplase), r tPA (see Ecokinase above)	Chiesi USA (Cary, NC, USA)	Acute myocardial infarction	1996 (US)
Activase (alteplase), rh tPA, produced in CHO cells	Roche/Genentech	Acute myocardial infarction	1987 (US)
Hirudin			
Refludan (lepirudin), r hirudin, produced in *S. cerevisiae*	Celgene Europe (Windsor, UK) Bayer HealthCare	Anticoagulation therapy for heparin-associated thrombocytopenia	1997 (EU) 1998 (US) Withdrawn 2012 (EU)
Revasc (desirudin), r hirudin, produced in *S. cerevisiae*	Canyon Pharmaceuticals (London)	Prevention of venous thrombosis	1997 (EU) Withdrawn 2014
Other			
Ruconest (conestat alfa), rh C1 esterase inhibitor, produced in the milk of transgenic rabbits	**Santarus (Raleigh, NC, USA) Pharming Group (Leiden, the Netherlands)**	**Acute angioedema**	**2014 (US) 2010 (EU)**
Jetrea (ocriplasmin), r truncated form of human plasmin, produced in *Pichia pastoris*	ThromboGenics (Leuven, Belgium)	Symptomatic vitreomacular adhesion, vitreomacular traction	2013 (EU) 2012 (US)
Atryn (rh antithrombin), produced in milk of transgenic goats	Laboratoire français du fractionnement et des biotechnologies (Les Ulis, France), rEVO Biologics (Framingham, MA, USA)	Hereditary antithrombin deficiency	2009 (US) 2006 (EU)
Kalbitor (ecallantide), plasma kallikrein inhibitor, produced in *P. pastoris*	Dyax (Cambridge, MA, USA)	Hereditory angioedema	2009 (US)
Xigris (drotrecogin alfa), rh activated protein C, produced in a human cell line	Eli Lilly (Houten, the Netherlands)	Severe sepsis	2001 (US) 2002 (EU) Withdrawn 2012 (EU)
Recombinant hormones			
Insulins			
Semglee (insulin glargine), r insulin glargine, produced in *P. pastoris*, biosimilar to Lantus	**Mylan (Saint-Priest, France)**	**Diabetes mellitus**	**2018 (EU)**
Admelog (insulin lispro injection), rapid-acting human insulin analog, produced in *E. coli*	**Sanofi (Bridgewater, NJ, USA)**	**Diabetes mellitus**	**2017 (US)**
Fiasp (insulin aspart injection), rapid-acting insulin analog, produced in *S. cerevisiae*	**Novo Nordisk**	**Diabetes mellitus**	**2017 (US)**
Insulin lispro Sanofi, produced in *E. coli*, biosimilar to Humalog	**Sanofi-Aventis (Paris)**	**Diabetes mellitus**	**2017 (EU)**
Lusduna (insulin glargine), engineered insulin, produced in *E. coli*, biosimilar to Lantus	**Merck Sharp & Dohme (Hoddesdon, UK)**	**Diabetes mellitus**	**2017 (EU) 2017 (US, tentative)**
Suliqua in EU, Soliqua in US (insulin glargine/lixisenatide), combination of long-acting insulin glargine, produced in *E. coli*, and a synthetically produced human GLP-1 analog	**Sanofi-Aventis (Paris) Sanofi (Bridgewater, NJ, USA)**	**Diabetes mellitus type 2**	**2017 (EU) 2016 (US)**
Xultophy (insulin degludec/liraglutide), a combination of 2 previously approved products, Victoza and Tresiba	**Novo Nordisk**	**Diabetes mellitus type 2**	**2016 (US) 2014 (EU)**
Abasaglar (previously Abasria) in EU, Basaglar in US (insulin glargine), produced in *E. coli*, biosimilar (in EU) to Lantus	**Eli Lilly (Indianapolis), Boehringer Ingelheim (Ridgefield, CT, USA) Eli Lilly (Vienna)**	**Diabetes mellitus**	**2015 (US) 2014 (EU)**
Ryzodeg 70/30 in US, Ryzodeg in EU (insulin degludec/insulin aspart), combination of two engineered insulins, produced in *S. cerevesiae*	**Novo Nordisk**	**Diabetes mellitus type 1 and 2**	**2015 (US) 2013 (EU)**
Toujeo (insulin glargine), produced in *E. coli*	**Sanofi (Bridgewater, NJ, USA)**	**Diabetes mellitus**	**2015 (US)**
Tresiba (insulin degludec), engineered long-acting human insulin analog, produced in *S. cerevisiae* (see also Ryzodeg above)	**Novo Nordisk**	**Diabetes mellitus type 1 and 2**	**2015 (US) 2013 (EU)**
Afrezza (rh insulin), produced in *E. coli*	**MannKind (Danbury, CT, USA)**	**Diabetes mellitus**	**2014 (US)**
Novolog mix (insulin aspart mix), a 50:50 mixture of engineered rh insulin, produced in *S. cerevisiae* in soluble and protamine suspension forms	Novo Nordisk	Diabetes mellitus	2008 (US)
Insulin Human Winthrop (rh insulin), produced in *E. coli*	Sanofi (Frankfurt)	Diabetes mellitus	2007 (EU) Withdrawn 2018
Exubera (inhalable rh insulin), produced in *E. coli*	Pfizer (Sandwich, UK)	Diabetes mellitus	2006 (EU & US) Withdrawn 2008 (EU)
Levemir (insulin detemir), long-acting rh insulin, produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus	2005 (US) 2004 (EU)
Apidra (insulin glulisine), rapid-acting insulin analog, produced in *E. coli*	Sanofi (Frankfurt)	Diabetes mellitus	2004 (EU & US)
Actrapid, Velosulin, Monotard, Insulatard, Protaphane, Mixtard, Actraphane, Ultratard: rh insulin formulated as short-, intermediate- or long-acting product, produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus	2002 (EU) Monotard and Ultratard withdrawn 2006 Velosulin withdrawn 2009
Novolog (insulin aspart), short-acting rh insulin analog, produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus	2001 (US)
Novolog mix 70/30 (contains insulin aspart, a short-acting rh insulin analog, in both soluble and crystalline form) (see also Novomix 30 below)	Novo Nordisk	Diabetes mellitus	2001 (US)
Novomix 30 (contains a mixture of insulin aspart, a short-acting rh insulin analog, in both soluble and crystalline form, produced in *S. cerevisiae*)	Novo Nordisk	Diabetes mellitus	2000 (EU)
Lantus (insulin glargine), long-acting rh insulin analog, produced in *E. coli*	Sanofi (Frankfurt)	Diabetes mellitus	2000 (EU & US)
Optisulin (insulin glargine), long-acting rh insulin analog, produced in *E. coli* (see also Lantus above)	Sanofi (Frankfurt)	Diabetes mellitus	2000 (EU)
NovoRapid (insulin aspart), rh insulin analog), produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus	1999 (EU)
Liprolog (insulin lispro), insulin analog, produced in *E. coli*	Eli Lilly (Houten, the Netherlands)	Diabetes mellitus	1997 (EU) Withdrawn 2001
Insuman (rh insulin), produced in *E. coli*	Sanofi (Frankfurt)	Diabetes mellitus	1997 (EU)
Humalog (insulin lispro), insulin analog, produced in *E. coli*	Eli Lilly (Houten, the Netherlands)	Diabetes mellitus	1996 (EU & US)
Novolin (rh insulin), produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus	1991 (US) Withdrawn 2010
Humulin (rh insulin), produced in *E. coli*	Eli Lilly (Indianapolis)	Diabetes mellitus	1982 (US)
Human growth hormone			
Somatropin Biopartners (somatropin), r hGH, produced in *S. cerevisiae*	Biopartners (Reutlingen, Germany)	Growth failure, growth hormone deficiency	2013 (EU) Withdrawn 2017
Accretropin (somatropin), r hGH, produced in *E. coli*	Emergent Biosolutions (Rockville, MD, USA) Cangene (Winnipeg, MB, Canada)	Growth failure or short stature associated with Turner syndrome in children	2008 (US)
Valtropin (somatropin), r hGH, produced in *S. cerevisiae*, biosimilar to Humatrope	Biopartners LG Life Sciences (Reutlingen, Germany)	Certain forms of growth disturbance in children and adults	2007 (US) 2006 (EU) Withdrawn 2012 (EU)
Omnitrope (somatropin), r hGH, produced in *E. coli*, biosimilar (in EU) to Genotropin	Sandoz (Kundl, Austria) Novartis (Princeton, NJ, USA)	Certain forms of growth disturbance in children and adults	2006 (EU & US)
Somavert (pegvisomant), PEGylated r hGH analog (antagonist), produced in *E. coli*	Pfizer (Brussels & New York) Nektar Therapeutics (San Francisco)	Acromegaly	2003 (US) 2002 (EU)
Nutropin AQ (somatropin), r hGH, produced in *E. coli*, different formulation of Nutropin (see below)	Ipsen Pharma (Boulogne-Billancourt, France)	Growth failure, Turner syndrome	2001 (EU) 1994 (US) Withdrawn 2008 (EU)
Serostim (somatropin), r hGH, produced in mouse C127 cells	EMD Serono (Geneva)	AIDS-associated catabolism and wasting	1996 (US)
Saizen (somatropin), r hGH, produced in mouse C127 cells	EMD Serono (Rockland, MA, USA)	hGH deficiency in children	1996 (US)
Genotropin (somatropin), r hGH, produced in *E. coli*	Pfizer (New York)	hGH deficiency in children	1995 (US)
Norditropin (somatropin), r hGH, produced in *E. coli*	Novo Nordisk	Growth failure in children due to inadequate growth hormone secretion	1995 (US)
Tev-Tropin, Bio-tropin (somatropin), r hGH, produced in *E. coli*	Teva Pharmaceuticals (North Wales, PA, USA)	hGH deficiency in children	1995 (US)
Nutropin (somatropin), r hGH, produced in *E. coli*	Roche/Genentech	hGH deficiency in children	1994 (US)
Humatrope (somatropin), r hGH, produced in *E. coli*	Eli Lilly (Indianapolis)	hGH deficiency in children	1987 (US)
Protropin (somatrem), r hGH differing from hGH by an extra N-terminal methionine, produced in *E. coli*	Genentech	hGH deficiency in children	1985 (US) Withdrawn 2004
Follicle-stimulating hormone			
Rekovelle (follitropin delta), rh FSH, produced in PER.C6 cells	**Ferring Pharmaceuticals (Copenhagen)**	**Anovulation**	**2016 (EU)**
Bemfola (follitropin alfa), rh FSH, produced in CHO cells, biosimilar to Gonal F	**Finox Biotech (Burgdorf, Switzerland)**	**Anovulation (women), failure of spermatogenesis (men)**	**2014 (EU)**
Ovaleap (follitropin alfa), rh FSH, produced in CHO cells, biosimilar to Gonal F	Teva Pharma (Utrect, the Netherlands)	Infertility, subfertility	2013 (EU)
Elonva (corifollitropin alfa), a modified rh FSH in which the C-terminal peptide of the β-subunit of human chorionic gonadotropin is fused to the FSH β-chain, produced in CHO cells	Merck Sharp & Dohme	Controlled ovarian stimulation	2010 (EU)
Fertavid (follitropin beta), rh FSH, produced in CHO cells. Active substance same as that in Puregon (see below)	Merck Sharp & Dohme	Infertility	2009 (EU)
Pergoveris (follitropin alfa/lutropin alfa) combination product containing rh FSH and rh luteinizing hormone, both produced in CHO cells	Merck Serono (London)	Stimulation of follicular development in women with severe luteinizing hormone and FSH deficiency	2007 (EU)
Follistim (follitropin beta), rh FSH, produced in CHO cells	Merck (Whitehouse Station, NJ, USA)	Infertility	1997 (US)
Puregon (follitropin beta), rh FSH, produced in CHO cells	Merck Sharp & Dohme (Haarlem, the Netherlands)	Anovulation and superovulation	1996 (EU)
Gonal F (follitropin alfa), rh FSH, produced in CHO cells	Merck Serono EMD Serono (Rockland, MD, USA)	Anovulation and superovulation	1997 (US) 1995 (EU)
Other hormones			
Myalepta in EU, Myalept in US (metreleptin), rh leptin analog, produced in *E. coli*	**Aegerion Pharmaceuticals (Amsterdam & Cambridge, MA, USA)**	**Some forms of lipodystrophy**	**2018 (EU) 2014 (US)**
Ozempic (semaglutide), human GLP-1 receptor agonist, produced in yeast and covalently modified by attachment of a C18 fatty acid	**Novo Nordisk**	**Diabetes mellitus type 2**	**2018 (EU) 2017 (US)**
Movymia (teriparatide), rh parathyroid hormone fragment, produced in *E. coli*, biosimilar to Fortseo. Same product as Terrosa (see below)	**STADA Arzneimittel (Bad Vilbel, Germany)**	**Osteoporosis**	**2017 (EU)**
Natpar (parathyroid hormone), rh parathyroid hormone, full length, produced in *E. coli*. Same product as Preotact (see below).	**Shire Pharmaceuticals Ireland (Dublin)**	**Hypoparathyroidism**	**2017 (EU)**
Terrosa (teriparatide), rh parathyroid hormone fragment, produced in *E. coli*, biosimilar to Fortseo. Same product as Movymia (see above)	**Gedeon Richter (Budapest)**	**Osteoporosis**	**2017 (EU)**
Natpara (parathyroid hormone), rh parathyroid hormone, produced in *E. coli*	**Shire-NPS Pharmaceuticals (Lexington, MA, USA)**	**Hypocalcemia**	**2015 (US)**
Saxenda (liraglutide), human GLP-1 analog, produced in *S. cerevisiae* and covalently modified by palmitic acid. Active substance same as that in Victoza (see below)	**Novo Nordisk**	**Obesity**	**2015 (EU)**
Eperzan in EU, Tanzeum in US (albiglutide), GLP-1 receptor agonist: two tandem copies of modified human GLP-1 fused to human albumin, produced in *S. cerevisiae*	**GSK (Carrigaline, Ireland, & Research Triangle Park, NC, USA)**	**Diabetes mellitus type 2**	**2014 (EU & US)**
Trulicity (dulaglutide), fusion protein consisting of a GLP-1 analog linked to a human IgG Fc domain, produced in a mammalian cell line	**Eli Lilly (Utrecht, the Netherlands, & Indianapolis)**	**Diabetes mellitus type 2**	**2014 (EU & US)**
Gattex in US, Revestive in EU (teduglutide), rh GLP-2 analog, produced in *E. coli*	NPS Pharma (Dublin)	Short bowel syndrome	2012 (EU & US)
Victoza (liraglutide), GLP-1 analog with attached fatty acid, produced in *S. cerevisiae*	Novo Nordisk	Diabetes mellitus type 2	2010 (US) 2009 (EU)
Preotact, rh parathyroid hormone, produced in *E. coli*	NPS Pharma	Osteoporosis	2006 (EU) Withdrawn 2014
Fortical, r salmon calcitonin, produced in *E. coli*	Upsher-Smith Laboratories (Minneapolis) Unigene Laboratories (Fairfield, NJ, USA)	Postmenopausal osteoporosis	2005 (US)
Luveris (lutropin alfa), rh luteinizing hormone, produced in CHO cells	EMD Serono (Rockland, MA, USA) Merck Europe (Amsterdam)	Some forms of infertility	2004 (US) 2000 (EU)
Forsteo in EU, Forteo in US (teriparatide), r shortened human parathyroid hormone, produced in *E. coli*	Eli Lilly (Houten, the Netherlands)	Established osteoporosis in some postmenopausal women	2003 (EU) 2002 (US)
Natrecor (nesiritide), rh natriuretic peptide, produced in *E. coli*	Johnson & Johnson/Scios (Titusville, NJ, USA)	Acutely decompensated congestive heart failure	2001 (US)
Ovitrelle in EU, Ovidrel in US (choriogonadotropin alfa) rh chorionic gonadotropin, produced in CHO cells	Merck Serono	Selected assisted reproductive techniques	2001 (EU) 2000 (US)
Thyrogen (thyrotropin alfa), rh thyroid-stimulating hormone, produced in CHO cells	Sanofi Genzyme (Cambridge, MA, USA)	Thyroid cancer (detection and treatment)	1998 (US) 2000 (EU)
Forcaltonin, r salmon calcitonin, produced in *E. coli*	Unigene UK (Bushey Heath, UK)	Paget disease	1999 (EU) Withdrawn 2008
Glucagen, rh glucagon, produced in *S. cerevisiae*	Novo Nordisk	Hypoglycemia	1998 (US)
Glucagon (glucagon, recombinant), rh glucagon, produced in *E. coli*	Eli Lilly (Indianapolis)	Hypoglycemia	1998 (US)
Recombinant growth factors			
Erythropoietin			
Retacrit (epoetin zeta in EU, epoetin alfa-epbx in US), rh EPO, produced in CHO cells, biosimilar to Eprex and Erypo	**Hospira (Royal Leamington Spa, UK) Pfizer (Lake Forest, IL, USA)**	**Anemia**	**2018 (US) 2007 (EU)**
Biopoin (epoetin theta), rh EPO, produced in CHO cells	Teva (Ulm, Germany)	Anemia	2009 (EU)
Eporatio (epoetin theta), rh EPO, produced in CHO cells	Teva (Ulm, Germany)	Anemia	2009 (EU)
Abseamed (epoietin alfa), produced in CHO cells, biosimilar to Eprex/Erypo	Medice Arzneimittel Pütter (Iserlon, Germany)	Anemia associated with chronic renal failure	2007 (EU)
Binocrit (epoetin alfa), produced in CHO cells, biosimilar to Eprex/Erypo	Sandoz	Anemia associated with chronic renal failure	2007 (EU)
Epoetin alfa Hexal (epoietin alfa), produced in CHO cells, biosimilar to Eprex/Erypo	Hexal (Holzkirchen, Germany)	Anemia associated with chronic renal failure	2007 (EU)
Mircera (methoxy polyethylene glycol-epoetin beta) PEGylated rh EPO, produced in CHO cells	Roche (Welwyn Garden City, UK)	Anemia associated with chronic kidney disease	2007 (EU & US)
Silapo (epoetin zeta), produced in CHO cells, biosimilar to Eprex/Erypo	STADA (Bad Vilbel, Germany) yes	Anemia associated with chronic renal failure	2007 (EU)
Dynepo (epoetin delta), rh EPO, produced in a human cell line	Shire Pharmaceuticals (Basingstoke, UK)	Anemia	2002 (EU) Withdrawn 2009
Aranesp (darbepoetin alfa), long-acting r EPO analog, produced in CHO cells (see Nespo below)	Amgen (Breda, the Netherlands)	Anemia	2001 (EU & US)
Nespo (darbepoetin alfa), long-acting r EPO analog, produced in CHO cells (see Aranesp above)	Dompé Biotec (Milan)	Anemia	2001 (EU) Withdrawn 2008
Neorecormon (epoietin beta), rh EPO, produced in CHO cells	Roche	Anemia	1997 (EU)
Procrit (epoietin alfa), rh EPO, produced in a mammalian cell line	Janssen Biotech (Horsham, PA, USA)	Anemia	1990 (US)
Epogen (epoietin alfa), rh EPO, produced in CHO cells	Amgen	Anemia	1989 (US)
Colony-stimulating factors			
Fulphila (pegfilgrastim-jmdb), PEGylated rh G-CSF, produced in *E. coli*, biosimilar to Neulasta	**Mylan (Rockford, IL USA)**	**Neutropenia**	**2018 (US)**
Nivestym (filgrastim-aafi) in US, Nivestim (filgrastim) in EU: rh G-CSF, produced in *E. coli*, biosimilar to Neupogen	**Pfizer (Lake Forest, IL, USA) Hospira (Royal Leamington Spa, UK)**	**Neutropenia**	**2018 (US) 2010 (EU)**
Ristempa (pegfilgrastim), covalent conjugate of rh G-CSF, produced in *E. coli* and conjugated to 20-kDa polyethylene glycol	**Amgen (Breda, the Netherlands)**	**Neutropenia**	**2015 (EU) Withdrawn 2017**
Zarxio in US, Zarzio in EU (filgrastim-sndz), rh G-CSF, produced in *E. coli*	**Sandoz (Princeton, NJ, USA, & Kundl, Austria)**	**Neutropenia**	**2015 (US) 2009 (EU)**
Accofil (filgrastim), G-CSF, produced in *E. coli*, biosimilar to Neupogen. Same product as Grastofil (see below)	**Accord Healthcare (Ahmedabad, India)**	**Neutropenia**	**2014 (EU)**
Grastofil (filgrastim), rh G-CSF, produced in *E. coli*, biosimilar to Neupogen. Same product as Accofil (see above)	Apotex (Leiden, the Netherlands)	Neutropenia	2013 (EU)
Lonquex (lipegfilgrastim), PEGylated rh G-CSF, produced in *E. coli*	Teva Pharma (Utrect, the Netherlands)	Neutropenia	2013 (EU)
Granix (tbo-filgrastim), rh G-CSF, produced in *E. coli*. Same product as Tevagrastim (see below)	Teva Pharmaceuticals USA (Frazer, PA, USA) Cephalon (Malvern, PA, USA)	Neutropenia	2012 (US)
Filgrastim Hexal (filgrastim), produced in *E. coli*, biosimilar to Neupogen	Hexal	Neutropenia	2009 (EU)
Biograstim (filgrastim), produced in *E. coli*, biosimilar to Neupogen	ABZ-Pharma (Ulm, Germany)	Neutropenia	2008 (EU) Withdrawn 2015
Ratiograstim (filgrastim), produced in *E. coli*, biosimilar to Neupogen	Ratiopharm (Ulm, Germany)	Neutropenia	2008 (EU)
Tevagrastim (filgrastim), produced in *E. coli*, biosimilar to Neupogen. Same product as Granix (see above)	Teva (Radebeul, Germany)	Neutropenia	2008 (EU)
Filgrastim Ratiopharm (filgrastim), produced in *E. coli*, biosimilar to Filgrastim	Ratiopharm	Neutropenia	2008 (EU) Withdrawn 2011
Neulasta in EU and US, Neupopeg in EU (pegfilgrastim), PEGylated rh G-CSF	Amgen (Breda, the Netherlands)	Chemotherapy-induced neutropenia	2002 (EU & US) Neupopeg withdrawn 2008 (EU)
Leukine (sargramostim), rh GM-CSF differing from the native protein by an R23L substitution, produced in *E. coli*	Sanofi-aventis U.S. (Bridgewater, NJ, USA)	Autologous bone marrow transplantation	1991 (US) Withdrawn 2008 and reformulated without EDTA 2008
Neupogen (filgrastim), rh G-CSF differing from native protein by an extra N-terminal methionine, produced in *E. coli*	Amgen (Thousand Oaks, CA, USA)	Chemotherapy-induced neutropenia	1991 (US)
Other growth factors			
Oxervate (cenegermin), rh nerve growth factor, produced in *E. coli*	**Dompé Farmaceutici (Milan)**	**Neurotophic keratitis**	**2017 (EU)**
Increlex (mecaserim), rh IGF-1, produced in *E. coli*	Ipsen Pharma	Growth failure in children with IGF-1 deficiency or hGH gene deletion (long-term treatment)	2007 (EU) 2005 (US)
iPlex (mecasermin rinfabate), a complex of rh IGF-1 and rh IGF binding protein-3, produced separately in *E. coli*	Insmed (Glen Allen, VA, USA)	Growth failure in children with severe primary IGF-1 deficiency or hGH gene deletion (long-term treatment	2005 (US) Withdrawn 2007 for IGF-1 deficiency
Kepivance (palifermin), rh keratinocyte growth factor, produced in *E. coli*	Swedish Orphan Biovitrum	Severe oral mucositis in selected patients with hematologic cancers	2005 (EU) 2004 (US) Withdrawn 2016 (EU)
GEM 21S: Regranex (see below) and tricalcium phosphate; growth-factor-enhanced matrix	BioMimetic Pharmaceuticals (Franklin, TN, USA)	Periodonatally related defects	2005 (US)
Regranex (becaplermin), rh platelet-derived growth factor receptor-BB, produced in *S. cerevisiae*	Johnson & Johnson (Raritan, NJ, USA) Janssen-Cilag International (Beerse, Belgium)	Lower extremity diabetic neuropathic ulcers	1997 (US) 1999 (EU) Withdrawn 2012 (EU)
Recombinant interferons, interleukins and tumor necrosis factor			
Interferon-α			
PEG-Intron/Rebetol combo pack (peginterferon alfa-2b/ribavirin) PEGylated rh IFN-α-2b, produced in *E. coli*, and ribavirin	Schering Plough (Kenilworth, NJ, USA)	Chronic hepatitis C	2008 (US)
Pegasys (peginterferon alfa-2a), PEGylated IFN-α-2b, produced in *E. coli*	Roche/Genentech (Welwyn Garden City, UK)	Hepatitis C	2002 (EU & US)
PEG-Intron (peginterferon alfa-2b), PEGylated IFN-α-2b, produced in *E. coli*.	Merck Sharp & Dohme	Chronic hepatitis C	2001 (US) 2000 (EU)
Viraferon (interferon alfa-2b), produced in *E. coli*	Schering Plough (Brussels, Belgium)	Chronic hepatitis B, C	2000 (EU) Withdrawn 2008
ViraferonPeg (peginterferon alfa-2b), PEGylated IFN-α-2b, produced in *E. coli*	Merck Sharp & Dohme	Chronic hepatitis C	2000 (EU)
Intron A, Alfatronol (interferon alfa-2b), produced in *E. coli*	Merck Sharp & Dohme	Cancer, genital warts, hepatitis B and C, HPV	2000 (EU) 1986 (US)
Rebetron (ribavirin/interferon alfa-2b), produced in *E. coli*	Schering Plough	Chronic hepatitis C	1999 (US)
Infergen (interferon alficon-1), r IFN-α, synthetic type I, produced in *E. coli*	Astellas Pharma Europe (Leiderdorp, the Netherlands) Kadmon Pharmaceuticals (Warrendale, PA, USA)	Chronic hepatitis C	1999 (EU) 1997 (US) Withdrawn 2006 (EU)
Roferon A (interferon alfa-2a), produced in *E. coli*	Roche	Hairy cell leukemia	1986 (US) Withdrawn 2007
Interferon-β and interferon-γ			
Plegridy (peginterferon beta-1a), rh PEGylated IFN- β-1a, produced in CHO cells	**Biogen Idec (Maidenhead, UK)**	**Multiple sclerosis**	**2014 (EU & US)**
Extavia (interferon beta-1b), rh IFN β-1b, produced in *E. coli*	Novartis Europharm (Camberley, UK) Novartis Pharmaceuticals (East Hanover, NJ, USA)	Multiple sclerosis	2009 (US) 2008 (EU)
Rebif (interferon beta-1a), rh IFN-β-1a, produced in CHO cells	EMD Serono (London)	Relapsing/remitting multiple sclerosis	2002 (US) 1998 (EU)
Avonex (interferon beta-1a), rh IFN-β-1a, produced in CHO cells	Biogen Idec (Maidenhead, UK)	Relapsing multiple sclerosis	1997 (EU) 1996 (US)
Betaferon (interferon beta-1b), r IFN-β-1b differing from native protein by C17S, produced in *E. coli*	Bayer Pharma	Multiple sclerosis	1995 (EU)
Betaseron (interferon beta-β-1b), differing from human protein by C17S, produced in *E. coli*	Berlex Laboratories (Richmond, CA, USA) Chiron (Emeryville, CA, USA)	Relapsing/remitting multiple sclerosis	1993 (US)
Actimmune (interferon gamma-1b), produced in *E. coli*	Vidara Therapeutics (Dublin)	Chronic granulomatous disease	1990 (US)
Others			
Kineret (anakinra), rh IL-1 receptor antagonist, produced in *E. coli*	Swedish Orphan Biovitrum	Rheumatoid arthritis	2001 (US)
Beromun (tasonermin), rh TNF-α, produced in *E. coli*	Boehringer Ingelheim (Ingelheim, Germany)	Adjunct to surgery for subsequent tumor removal to prevent or delay amputation	1999 (EU)
Neumega (oprelvekin), r IL-11 lacking N-terminal proline of native molecule, produced in *E. coli*	Pfizer (Philadelphia), Genetics Institute	Prevention of chemotherapy-induced thrombocytopenia	1997 (US)
Proleukin (aldesleukin) r IL-2, differs from native molecule in absence of N-terminal alanine and presence of C125S substitution, produced in *E. coli*	Prometheus Laboratories (San Diego)	Renal cell carcinoma	1992 (US)
Recombinant vaccines			
Hepatitis B			
HEPLISAV-B (hepatitis B vaccine (recombinant) adjuvanted), HBsAg, produced in *Hansenula polymorpha* yeast	**Dynavax Technologies (Berkeley, CA, USA)**	**Prevention of infection caused by all known subtypes of hepatitis B virus**	**2017 (US)**
Hexacima, also sold as Hexyon, multi-component vaccine containing r HBsAg, produced in *H. polymorpha* as one component	Sanofi Pasteur (Lyon, France)	Immunization against several pathogens and toxins	2013 (EU)
Ambirix, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK (Rixensart, Germany)	Immunization against hepatitis A and B	2002 (EU)
Pediarix, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization of children against various conditions inducing hepatitis B	2002 (US)
HBVAXPRO (r HBsAg), produced in *S. cerevisiae*	Sanofi Pasteur	Immunization of children and adolescents against hepatitis B	2001 (EU)
Twinrix, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization against hepatitis A and B	2001 (US) 1997 (EU pediatric form) 1996 (EU adult form)
Infanrix-hexa, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization against diphtheria, tetanus, pertussis, *Haemophilus influenzae* b, hepatitis B and polio	2000 (EU)
Infanrix-penta, combination vaccine, containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization against diphtheria, tetanus, pertussis, polio, and hepatitis B	2000 (EU) Withdrawn 2013
Hepacare (r S, pre-S & pre-S2 HBsAg), produced in a murine cell line	Evans Vaccines (Liverpool, UK)	Immunization against hepatitis B	2000 (EU) Withdrawn 2002
Hexavac, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	Sanofi Pasteur	Immunization against diphtheria, tetanus, pertussis, hepatitis B, polio and *H. influenzae* b	2000 (EU) Withdrawn 2012
Procomvax, combination vaccine containing r HBsAg as one component	Sanofi Pasteur	Immunization against *H. influenzae* b and hepatitis B	1999 (EU) Withdrawn 2009
Primavax, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	Sanofi Pasteur	Immunization against diphtheria, tetanus and hepatitis B	1998 (EU) Withdrawn 2000
Engerix B, r HBsAg, produced in *S. cerevisiae*	GSK	Immunization against hepatitis B	1998 (US)
Infanrix Hep B, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization against diphtheria, tetanus, pertussis and hepatitis B	1997 (EU) Withdrawn 2005
Comvax, combination vaccine containing HBsAg, produced in *S. cerevisiae* as one component	Merck (Whitehouse Station, NJ, USA)	Immunization of infants against *H. influenzae* b and hepatitis B	1996 (US)
Tritanrix-Hep B, combination vaccine containing r HBsAg, produced in *S. cerevisiae* as one component	GSK	Immunization against hepatitis B, diphtheria, tetanus and pertussis	1996 (EU) Withdrawn 2014
Recombivax, r HBsAg, produced in *S. cerevisiae*	Merck (Whitehouse Station, NJ, USA)	Immunization against hepatitis B	1986 (US)
Other			
Shingrix (zoster vaccine recombinant, adjuvanted), recombinant varicella zoster virus surface glycoprotein E antigen component, produced in CHO cells	**GlaxoSmithKline Biologicals (Rixensart, Belgium) GlaxoSmithKline (Research Triangle Park, NC, USA)**	**Prevention of herpes zoster (shingles)**	**2018 (EU) 2017 (US)**
Trumenba (meningococcal group B vaccine), two r *Neisseria meningitides* serogroup B proteins, independently expressed in *E. coli*	**Pfizer (Philadelphia)**	**Vaccine against *N. meningitides* serogroup B**	**2017 (EU) 2014 (US)**
Pandemic influenza vaccine H5N1, vaccine derived from engineered viral strain containing gene segments from appropriate viral influenza strains, produced in embryonated eggs	**MedImmune (Nijmegen, the Netherlands**	**Influenza vaccine**	**2016 (EU)**
Bexsero (meningococcal group B vaccine), mixture of 3 *N. meningitidis* serogroup B proteins, produced in *E. coli*	**Novartis (Cambridge, MA, USA, & Siena, Italy)**	**Active immunization against *N. meningitidis* serogroup B**	**2015 (US) 2013 (EU)**
Gardasil 9, mixture of the major capsid protein (L1) of 9 strains of HPV, each produced in *S. cerevisiae*	**MSD (Lyon, France) Merck (Whitehouse Station, NJ, USA)**	**Active immunization for those above 9 years of age against HPV-caused cancers and genital warts**	**2015 (EU) 2014 (US)**
Mosquirix (*Plasmodium falciparum* and hepatitis B vaccine), virus-like particles comprising the RTS fusion protein of a portion of the circumsporozoite protein from *P. falciparum* and the N- terminal end of HBsAg, coexpressed in *S. cerevisiae*	**GlaxoSmithKline Biologicals (Rixensart, Belgium)**	**Vaccination against malaria caused by the parasite *Plasmodium falciparum***	**2015 (EU); approved for use outside the EU**
Flublok, r hemagglutinin proteins from 3 influenza viruses, produced in an insect cell line	Protein Sciences (Meriden, CT, USA)	Immunization against influenza	2013 (US)
Provenge (sipuleucel-T), autologous peripheral blood mononuclear cells in combination with r prostatic acid phosphatase linked to GM-CSF, produced in an insect cell line	Dendreon (London)	Prostate cancer	2013 (EU) 2010 (US) Withdrawn 2015 (EU)
Cervarix, r C-terminally truncated major capsid L1 proteins from HPV types 16 and 18, produced in a baculovirus-based expression system	GSK	Prevention of cervical cancer	2009 (US) 2007 (EU)
Gardasil in EU & US, Silgard in EU, r vaccine containing major capsid proteins from four HPV types, produced in *S. cerevisiae*	Sanofi Pasteur Merck (Whitehouse Station, NJ, USA)	Vaccination against diseases caused by HPX	2006 (EU & US)
Dukoral (*Vibrio cholerae* and r cholera toxin B subunit)	Valneva Sweden (Stockholm)	Immunization against disease caused by *V. cholerae* subunit O1	2004 (EU)
Lymerix (r OspA), a lipoprotein found on the surface of *B. burgdorferi*, produced in *E. coli*	GSK	Immunization against Lyme disease	1998 (US) Withdrawn 2002
Triacelluvax, combination vaccine containing r modified pertussis toxin as one component	Chiron (Siena, Italy)	Immunization against diphtheria, tetanus and pertussis	1999 (EU) Withdrawn 2002
Monoclonal antibody–based products			
Aimovig (erenumab-aooe in USA, erenumab in EU), human IgG2 targeting the calcitonin gene-related peptide receptor, produced in CHO cells	**Amgen (Thousand Oaks, CA, USA) Novartis (East Hanover, NJ, USA) Novartis Europharm (Dublin)**	**Migraine**	**2018 (EU & US)**
Crysvita (burosumab in EU, burosumab-twza in USA), human IgG1 antibody to soluble fibroblast growth factor-23, produced in CHO cells	**Kyowa Kirin (Galashiels, UK) Ultragenyx Pharmaceutical (Novato, CA, USA)**	**X-linked hypophosphatemia**	**2018 (EU & US)**
Fasenra (benralizumab), humanized, afucosylated IgG1 targeting the α subunit of the human IL-5 receptor, produced in CHO cells	**AstraZeneca (Södartälje, Sweden, & Wilmington, DE, USA)**	**Asthma**	**2018 (EU) 2017 (US)**
Halimatoz (adalimumab), anti-TNF IgG, produced in CHO cells, biosimilar to Humira. Same product as Hefiya and Hyrimoz (see below)	**Sandoz**	**Various inflammatory conditions mediated by TNF, including rheumatoid arthritis and plaque psoriasis**	**2018 (EU)**
Hefiya (adalimumab), anti-TNF IgG, produced in CHO cells, biosimilar to Humira. Same product as Halimatoz and Hyrimoz (see above and below)	**Sandoz**	**Various inflammatory conditions mediated by TNF, including polyarticular juvenile idiopathic arthritis and plaque psoriasis**	**2018 (EU)**
Hemlibra (emicizumab in EU, emicizumab-kxwh in US), humanized, bispecific IgG4 capable of binding factor IXa and factor X, produced in CHO cells	**Roche Registration (Welwyn Garden City, UK) Roche/Genentech (South San Francisco, CA, USA)**	**Hemophilia A**	**2018 (EU) 2017 (US)**

Table 1 Continued

Product	Company (location)	Therapeutic indication	Date approved
Herzuma (trastuzumab), r humanized IgG1 against HER2, produced in CHO cells, biosimilar to Herceptin	Celltrion Healthcare (Budapest)	Breast and gastric cancers	2018 (EU)
Hyrimoz (adalimumab), anti-TNF IgG, produced in CHO cells, biosimilar to Humira. Same product as Halimatoz and Hefiya (see above)	Sandoz	Various inflammatory conditions mediated by TNF, including rheumatoid arthritis and plaque psoriasis	2018 (EU)
Ilumya (tildrakizumab-asmn), humanized IgG1 that binds the p19 subunit of IL-23, produced in CHO cells	Merck (Whitehouse Station, NJ, USA)	Plaque psoriasis	2018 (US)
Kanjinti (trastuzumab), r humanized IgG1 against HER2, produced in CHO cells, biosimilar to Herceptin	Amgen Europe (Breda, the Netherlands)	Breast and gastric cancers	2018 (EU)
Mvasi (bevacizumab in EU, bevacizumab-awwb in US), humanized IgG antibody to human VEGF-A1, produced in CHO cells, biosimilar to Avastin	Amgen Europe Amgen (Thousand Oaks, CA, USA)	Various cancers	2018 (EU) 2017 (US)
Mylotarg (gemtuzumab ozogamicin), antibody drug conjugate targeting the CD33 surface antigen, consisting of a humanized IgG4 chemically conjugated to *N*-acetyl-γ-calicheamicin, produced in NS0 mouse myeloma cells	Pfizer Europe (Brussels) Pfizer/Wyeth (Philadelphia)	Acute myeloid leukemia	2018 (EU) 2000 (US) Withdrawn 2010 (US) Reapproved 2017 (US) using modified dosage and regimen
Ocrevus (ocrelizumab), r humanized IgG1 targeting the CD20 surface antigen, produced in CHO cells	Roche Registration Genentech (South San Francisco, CA, USA)	Multiple sclerosis	2018 (EU) 2017 (US)
Trazimera (trastuzumab), humanized IgG, produced in a CHO cells, biosimilar to Herceptin	Pfizer (Brussels)	Breast cancer, gastric or gastroesophageal junction adenocarcinoma	2018 (EU)
TROGARZO (ibalizumab-uiyk), humanized IgG4 targeting the CD4 domain, produced in NS0 cells	TaiMed Biologics (Irvine, CA, USA) Theratechnologies (Montreal)	Human immunodeficiency virus type 1 infection	2018 (US)
Zessly (infliximab), chimeric anti-TNF IgG1 produced in CHO cells, biosimilar to Remicade (infliximab)	Sandoz	Rheumatoid arthritis and selected additional inflammatory diseases	2018 (EU)
Amgevita (adalimumab), anti-TNF human IgG1, produced in CHO cells, biosimilar to Humira. Same product as Solymbic and Amjevita (see below)	Amgen Europe	Rheumatoid arthritis and selected additional inflammatory diseases	2017 (EU)
Bavencio (avelumab), human IgG1 specific for programmed death ligand-1 (PD-L1), produced in CHO cells	Merck Europe (Amsterdam) Pfizer (New York)	Metastatic Merkel cell carcinoma, urothelial carcinoma	2017 (EU & US)
Besponsa (inotuzumab ozogamicin), antibody-drug conjugate consisting of a humanized IgG4 specific for human CD22, produced in CHO cells, covalently linked to the cytotoxic agent *N*-acetyl-γ-calicheamicin dimethylhydrazide	Pfizer (Sandwich, UK) Pfizer/Wyeth (Philadelphia)	Acute lymphoblastic leukemia	2017 (EU & US)
Blitzima (rituximab), chimeric IgG1 against cell surface antigen CD20, produced in CHO cells, biosimilar to MabThera Same product as Ritemvia, Truxima and Rituzena (see below)	Celltrion Healthcare Hungary (Budapest)	Non-Hodgkin lymphoma, CLL, granulomatosis	2017 (EU)
Cyltezo (adalimumab in EU, adalimumab-adbm in USA), rh IgG1 against human TNF, produced in CHO cells, biosimilar to Humira	Boehringer Ingelheim (Rhein, Germany) Boehringer Ingelheim (Ridgefield, CT, USA)	Range of inflammatory conditions, including psoriasis, rheumatoid arthritis and Crohn's disease	2017 (EU & US)
Dinutuximab beta Apeiron (dinutuximab beta), chimeric IgG1 against the disialoganglioside GD2, produced in CHO cells. Same product as Qarziba (see below)	Apeiron Biologics (Vienna)	Neuroblastoma	2017 (EU)
Dupixent (dupilumab), human IgG4 that binds the IL-4α receptor subunit, produced in CHO cells	Sanofi-Aventis (Paris & Bridgewater, NJ, USA), Regeneron Pharmaceuticals (Tarrytown, NY, USA)	Atopic dermatitis	2017 (EU & US)
Imfinzi (durvalumab), human IgG1 blocking the interaction of programmed cell death ligand-1 (PD-L1) with its receptor PD-1 and CD80, produced in CHO cells	AstraZeneca (Wilmington, DE, USA)	Urothelial carcinoma	2017 (US)
Imraldi (adalimumab), produced in CHO cells, biosimilar to Humira	Samsung Bioepis UK (Chertsey, UK)	Rheumatoid arthritis, selected additional inflammatory diseases	2017 (EU)
Ixifi (infliximab-qbtx), produced in a mammalian cell line, biosimilar to Remicade	Pfizer (New York)	Various inflammatory conditions, including rheumatoid arthritis, Crohn's disease and psoriasis	2017 (US)
Kevzara (sarilumab), human IgG1 that binds IL-6 receptors, produced in CHO cells	Sanofi-Aventis (Paris & Bridgewater, NJ, USA), Regeneron Pharmaceuticals (Tarrytown, NY, USA)	Rheumatoid arthritis	2017 (EU) 2017 (US)
Kyntheum in EU, Siliq in US (brodalumab), human IgG2 against human IL-17 receptor A, produced in CHO cells	LEO Pharma (Ballerup, Denmark) Valeant Pharmaceuticals (Bridgewater, NJ, USA)	Psoriasis	2017 (EU) 2017 (US)
Ogivri (trastuzumab-dkst), produced in CHO cells, biosimilar to Herceptin	Mylan (Morgantown, WV, USA, & Zurich)	Breast and gastric cancers	2017 (US)
Ontruzant, produced in CHO cells, biosimilar to Herceptin	Samsung Bioepis UK (Brentford, UK)	Breast and gastric cancers	2017 (EU)
Qarziba (dinutuximab beta; previously dinutuximab beta EUSA and dinutuximab beta Apeiron), chimeric IgG1 against carbohydrate disialoganglioside GD2, which is overexpressed by cells of neuroectodermal origin such as neuroblastoma cells, produced in CHO cells	EUSA Pharma (Hemel Hempstead, UK)	Neuroblastoma	2017 (EU)
Renflexis (infliximab-abda), chimeric IgG1 that binds TNF-α, produced in CHO cells, biosimilar to Remicade. Same product as Flixabi (see below)	Merck (Kenilworth, NJ, USA)	Crohn's disease and various other inflammatory conditions	2017 (US)
Ritemvia (rituximab), produced in CHO cells, biosimilar to MabThera. Same product as Blitzima, Rituzena and Truxima (see above and below)	Celltrion Healthcare Hungary	Non-Hodgkin lymphoma, granulomatosis with polyangiitis, microscopic polyangiitis	2017 (EU)
Rituxan Hycela (rituximab and hyaluronidase human), both produced in CHO cells	Biogen (Cambridge, MA, USA), Genentech	Follicular lymphoma, diffuse large B-cell lymphoma, CLL	2017 (US)
Rituzena (previously Tuxella) (rituximab), produced in CHO cells, biosimilar to MabThera. Same product as Blitzima, Ritemvia and Truxima (see above and below)	Celltrion Healthcare Hungary	Non-Hodgkin lymphoma, CLL, granulomatosis with polyangiitis	2017 (EU)
Rixathon (rituximab), chimeric IgG1 against cell surface antigen CD20, produced in CHO cells, biosimilar to MabThera. Same product as Riximyo (see below)	Sandoz	Various conditions including non-Hodgkin lymphoma, CLL, rheumatoid arthritis	2017 (EU)
Riximyo (rituximab), chimeric IgG1 against cell surface antigen CD20, produced in CHO cells, biosimilar to MabThera. Same product as Rixathon (see above)	Sandoz	Various conditions including non-Hodgkin lymphoma and rheumatoid arthritis, but excluding CLL	2017 (EU)
Solymbic (adalimumab), anti-TNF human IgG1 produced in CHO cells, biosimilar to Humira. Same product as Amgevita and Amjevita (see above and below)	Amgen Europe	Rheumatoid arthritis and selected additional inflammatory diseases	2017 (EU)
Tecentriq (atezolizumab), humanized IgG1 specific for programmed death ligand 1 (PD-L1), engineered to lack Fc glycosylation, produced in CHO cells	Roche Registration (Grenzach-Wyhlen, Germany) Genentech (South San Francisco, CA, USA)	Urothelial carcinoma, non-small-cell lung cancer	2017 (EU) 2016 (US)
Tremfya (guselkumab), human IgG1 that selectively binds the p19 subunit of IL-23, produced in CHO cells	Janssen-Cilag (Beerse, Belgium) Janssen Biotech (Horsham, PA, USA)	Psoriasis	2017 (EU & US)
Truxima (rituximab) chimeric IgG1 against cell surface antigen CD20, produced in CHO cells, biosimilar to MabThera. Same product as Blitzima, Ritemvia, and Truxima (see above)	Celltrion	Selected cancers and autoimmune disorders	2017 (EU)
Zinplava (bezlotoxumab), human IgG directed against *Clostridium difficile* toxin B, produced in CHO cells	Merck Sharp & Dohme Merck (Whitehouse Station, NJ, USA)	*C. difficile* infection	2017 (EU) 2016 (US)
Amjevita (adalimumab-atto), rh IgG1 specific for TNF, produced in CHO cells, biosimilar to Humira. Same product as Solymbic and Amgevita (see above)	Amgen (Thousand Oaks, CA, USA)	Rheumatoid arthritis and selected additional inflammatory diseases	2016 (US)
Anthim (obiltoxaximab), chimeric IgG1 against *Bacillus anthracis* toxin, produced in NS0 cells	Elusys Therapeutics (Pine Brook, NJ, USA)	Inhalational anthrax	2016 (US)
Cinqair in US, Cinqaero in EU (reslizumab), humanized IgG4 against IL-5, produced in NS0 cells	Teva Respiratory (Frazer, PA USA) Teva (Haarlem, the Netherlands)	Asthma	2016 (US) 2016 (EU)
Darzalex (daratumumab), human IgG1 against CD-38, produced in CHO cells	Janssen-Cilag Janssen Biotech	Multiple myeloma	2016 (EU) 2015 (US)
Empliciti (elotuzumab) humanized IgG1 against the cell surface receptor SLAMF7, produced in NS0 cells	Bristol-Myers Squibb (Uxbridge, UK, & Princeton, NJ, USA)	Multiple myeloma (in combination with lenalidomide and dexamethasone)	2016 (EU) 2015 (US)
Flixabi (infliximab), chimeric IgG1 against TNF-α, produced in CHO cells, biosimilar to Remicade. Same product as Renflexis (see above)	Samsung Bioepis (Chertsey, UK)	Various forms of arthritis, psoriasis, colitis, Crohn's disease, ankylosing spondylitis	2016 (EU)
Inflectra in EU and US, Remsima in EU (infliximab in EU, infliximab-dyyb in US), chimeric IgG1 specific for TNF-α, produced in murine Sp2/0 cells, biosimilar to Remicade	Inflectra: Hospira (Lake Forest, IL, USA), Celltrion (Incheon, Republic of Korea) and Hospira (Royal Leamington Spa, UK); Remsima: Celltrion (Budapest)	Certain forms of arthritis and psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis	2016 (US) 2013 (EU)
Lartruvo (olaratumab), rh IgG1 specific for human platelet-derived growth factor receptor-α, produced in NS0 cells	Eli Lilly (Utrecht, the Netherlands, & Indianapolis)	Sarcoma	2016 (EU & US)
Portrazza (necitumumab), human IgG1 against the ligand binding site of human EGF receptor, produced in NS0 cells	Eli Lilly (Utrecht, the Netherlands, & Indianapolis)	Non-small-cell lung cancer (in combination with gemcitabine and cisplatin)	2016 (EU) 2015 (US)
Taltz (ixekizumab), humanized IgG4 against hIL-17A, produced in CHO cells	Eli Lilly (Utrecht, the Netherlands, & Indianapolis)	Psoriasis	2016 (EU & US)
Zinbryta (daclizumab), humanized IgG1 against IL-2Rα, produced in NS0 cells	Biogen (Cambridge, MA US) Biogen Idec (Maidenhead, UK)	Multiple sclerosis	2016 (EU & US) Withdrawn 2018 (EU & US)

Table 1 Continued

Product	Company (location)	Therapeutic indication	Date approved
Blincyto (blinatumomab), bispecific T-cell engager antibody construct (BiTE), produced in CHO cells	Amgen Europe Amgen (Thousand Oaks, CA, USA)	Acute lymphoblastic leukemia	2015 (EU) 2014 (US)
Cosentyx (secukinumab), human IgG1 selectively binding human IL-17a, produced in CHO cells	Novartis Europharm (Camberley, UK) Novartis (East Hanover, NJ, USA)	Moderate to severe plaque psoriasis in adults	2015 (EU & US)
Keytruda (pembrolizumab), humanized IgG4 capable of binding to the receptor PD-1, produced in CHO cells	Merck Sharp & Dohme Merck (Whitehouse Station, NJ, USA)	Advanced (unresectable or metastatic) melanoma in adults	2015 (EU) 2014 (US)
Nivolumab BMS (nivolumab), human IgG4 against the receptor PD-1, produced in CHO cells. Same product as Opdivo (see below)	Bristol-Myers Squibb (Uxbridge, UK)	Locally advanced or metastatic squamous non-small-cell lung cancer after prior chemotherapy in adults	July 2015 (EU) Withdrawn November 2015
Nucala (mepolizumab), humanized IgG1 capable of binding human IL-5, produced in CHO cells	GlaxoSmithKline (Cork, Ireland) GSK (Research Triangle Park, NC, USA)	Add-on treatment for severe refractory eosinophilic asthma in adult patients	2015 (EU & US)
Opdivo (nivolumab), human IgG4 against the receptor PD-1, produced in CHO cells. Same product as nivolumab BMS (see above)	Bristol-Myers Squibb (Uxbridge, UK, & Princeton, NJ, USA)	Melanoma (as monotherapy or in combination with ipilimumab), non-small-cell lung cancer, renal cell carcinoma	2015 (EU) 2014 (US)
Praluent (alirocumab), human IgG1 targeting PCSK9, produced in CHO cells	Sanofi-Aventis (Paris & Bridgewater, NJ, USA) Regeneron Pharmaceuticals (Tarrytown, NY, USA)	Primary hypercholesterolemia or mixed dyslipidemia, as an adjunct to diet	2015 (EU & US)
Praxbind (idarucizumab), humanized IgG1 Fab fragment capable of binding the anticoagulant drug dabigatran, produced in CHO cells	Boehringer Ingelheim (Rhein, Germany, & Ridgefield, CT, USA)	Rapid reversal agent for the anticoagulant drug dabigatran	2015 (EU & US)
Repatha (evolocumab), human IgG2 capable of binding human PCSK-9, produced in CHO cells	Amgen Europe Amgen (Thousand Oaks, CA, USA)	Hypercholesterolemia and mixed dyslipidemia	2015 (EU & US)
Unituxin (dinutuximab), chimeric IgG1 targeting human disialoganglioside (GD2), produced in Sp2/0 cells	United Therapeutics (Chertsey, UK, & Silver Spring, MD, USA)	Neuroblastoma (administered in combination with GM-CSF, IL-2 and isotretinoin)	2015 (EU & US) Withdrawn 2017 (EU)
Cyramza (ramucirumab), human mAb that binds the VEGF-2 receptor, produced in NS0 cells	Eli Lilly Nederland (Utrecht, the Netherlands) Eli Lilly (Indianapolis)	Gastric cancer	2014 (EU & US)
Entyvio (vedolizumab), humanized IgG targeting the human α4β7 integrin, produced in CHO cells	Takeda Pharmaceuticals (Deerfield, IL, USA) Takeda Pharma (Taastrup, Denmark)	Ulcerative colitis, Crohn's disease	2014 (EU & US)
Gazyva in US, Gazyvaro in EU (obinutuzumab), humanized, glycoengineered mAb specific for B-cell antigen CD20, produced in CHO cells	Roche/Genentech Roche (Welwyn Garden City, UK)	CLL	2014 (EU) 2013 (US)
Sylvant (siltuximab), chimeric mAb that binds human IL-6, produced in CHO cells	Janssen Biotech	Multicentric Castleman disease	2014 (EU & US)
Kadcyla (trastuzumab emtansine), humanized mAb specific for HER2 antigen, produced in CHO cells and conjugated to the small molecule cytotoxin DM1	Roche (Welwyn Garden City, UK)	Breast cancer	2013 (EU & US)
Simponi Aria (golimumab). Active substance same as that in Simponi (see below); different strength and mode of administration	Janssen Biotech	Rheumatoid arthritis	2013 (US)
Perjeta (pertuzumab), human mAb specific for HER2, produced in CHO cells	Roche/Genentech	Breast cancer	2013 (EU) 2012 (US)
Abthrax (raxibacumab), human IgG mAb against the protective antigen (PA) of *B. anthracis*, produced in NS0 cells	GSK/Human Genome Sciences (Rockville, MD, USA)	Inhalational anthrax	2012 (US)
Adcetris (brentuximab vedotin), chimeric mAb conjugate specific for human CD30 (expressed on the surface of lymphoma cells), produced in CHO cells	Takeda Pharma (Roskilde, Denmark) Seattle Genetics	Lymphoma	2012 (EU) 2011 (US)
Benlysta (belimumab), human mAb that targets human B-lymphocyte stimulator (BLyS), a B cell survival factor. produced in NS0 cells	Human Genome Sciences Glaxo Group (Greenford, UK)	Lupus	2011 (EU & US)
Xgeva (denosumab) (see Prolia)	Amgen Europe	Bone loss associated with cancer	2011 (EU) 2010 (US)
Yervoy (ipilimumab), human mAb binding to CTLA-4 (a negative regulator of T-cell activation), thereby enhancing T cell activation and proliferation, produced in CHO cells	Bristol-Myers Squibb (Uxbridge, UK)	Melanoma	2011 (EU & US)
Actemra in US, RoActemra in EU (tocilizumab), humanized mAb specific for IL-6, produced in a mammalian cell line	Roche (Welwyn Garden City, UK)	Rheumatoid arthritis	2010 (US) 2009 (EU)
Arzerra (ofatumumab), human mAb specific for CD20, produced in NS0 hybridoma cells	Novartis (East Hanover, NJ, USA), Genmab (Greenford, UK)	CLL	2010 (EU) 2009 (US)
Prolia (denosumab), human mAb specific for receptor activator of nuclear factor κB ligand (RANKL), produced in CHO cells	Amgen Europe	Osteoporosis in postmenopausal women	2010 (EU & US)
Scintimun (besilesomab), murine mAb against nonspecific cross-reacting antigen-95 (found on surface of granulocytes), produced in hybridoma cells	CIS Bio International (Gif-sur-Yvette, France)	*In vivo* diagnosis or investigation of sites of inflammation or infection via scintigraphic imaging	2010 (EU)
Cimzia (certolizumab pegol), anti-TNF-α humanized and PEGylated antibody Fab′ fragment, produced in *E. coli*	UCB Pharma (Brussels, Belgium)	Crohn's disease, rheumatoid arthritis	2009 (EU) 2008 (US)
Ilaris (canakinumab), human mAb specific for IL-1β, produced in Sp2/0 cells	Novartis Pharmaceuticals (East Hanover, NJ, USA) Novartis Europharm (Dublin)	Cryopyrin-associated periodic syndromes (CAPS)	2009 (EU & US)
Removab (catumaxomab), bispecific engineered antibody targeting the human epithelial cell adhesion molecule and human CD3 expressed on T-lymphocytes, produced in hybridoma cells	Neovii Biotech (Gräfelfing, Germany)	Malignant ascites in patients with carcinomas expressing epithelial cell adhesion molecule	2009 (EU) Withdrawn 2017
Simponi (golimumab), human mAb specific for TNF-α, produced in Sp2/0 cells	Janssen Biologics (Leiden, the Netherlands) Janssen Biotech (Horsham, PA, USA)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	2009 (EU & US)
Stelara (ustekinumab), human MAb specific for the p40 subunit of IL-12 and IL-23, produced in Sp2/0 cells	Janssen-Cilag	Moderate to severe plaque psoriasis	2009 (EU & US)
Lucentis (ranibizumab), humanized IgG fragment that binds and inactivates VEGF-A, produced in E. coli	Roche/Genentech	Neovascular (wet) age-related macular degeneration	2007 (EU) 2006 (US)
Soliris (eculizumab), humanized IgG that binds human C5 complement protein, produced in a murine myeloma cell line	Alexion Pharmaceuticals (Cheshire, CT, USA, & Paris)	Paroxysmal nocturnal hemoglobinuria	2007 (EU & US)
Vectibix (panitumumab), human mAb that binds to human EGF receptor, produced in CHO cells	Amgen Europe Abgenix	EGF receptor–expressing colorectal carcinoma	2007 (EU) 2006 (US)
Tysabri (natalizumab), humanized mAb against selected leukocyte integrins, produced in murine myeloma cells	Biogen Inc. (Cambridge, MA, USA) Biogen Netherlands (Badhoevedorp, the Netherlands)	Relapsing forms of multiple sclerosis	2006 (EU) 2004 (US) Suspended 2005 (US) Resumed 2006 (US)
Xolair (omalizumab), humanized mAb that binds IgE at the site of high-affinity IgE receptor binding, produced in CHO cells	Roche/Genentech	Moderate to severe persistent asthma in adults and adolescents	2005 (EU) 2003 (US)
Zevalin (ibritumomab tiuxetan), murine mAb against the CD20 antigen, produced in CHO cells	Spectrum Pharmaceuticals (Amsterdam)	Non-Hodgkin lymphoma	2004 (EU) 2002 (US)
Erbitux (cetuximab), chimeric mAb against human EGF receptor, produced in Sp2/0 cells	Merck KGaA (Darmstadt, Germany) Eli Lilly (Indianapolis)	EGF receptor–expressing metastatic colorectal cancer	2004 (EU & US)
Raptiva (efalizumab), humanized mAb that binds to LFA-1, which is expressed on all leukocytes; produced in CHO cells	Serono (London, UK) Genentech	Chronic moderate to severe plaque psoriasis in adults	2004 (EU) 2003 (US) Withdrawn 2009
Avastin (bevacizumab), humanized mAb against VEGF, produced in CHO cells	Roche/Genentech (Welwyn Garden City, UK)	Metastatic colorectal cancer, glioblastoma, metastatic renal carcinoma	2005 (EU) 2004 (US)
NeutroSpec (fanolesomab), murine mAb against CD15, a surface antigen of selected leukocytes, produced in hybridoma cells	Palatin Technologies (Cranbury, NJ, USA), Mallinckrodt Pharmaceuticals (Hazelwood, MO, USA)	Imaging of equivocal appendicitis	2004 (US) Withdrawn 2005
Humira in EU & US, Trudexa in EU (adalimumab), anti-TNF human mAb, produced in CHO cells	AbbVie (Maidenhead, UK)	Rheumatoid arthritis	2003 (EU) 2002 (US) Trudexa withdrawn 2007 (EU)
Bexxar (tositumomab), radiolabeled mAb against CD20, produced in murine hybridoma cells	GSK	CD20-positive follicular non-Hodgkin lymphoma	2003 (US) Withdrawn 2014
Mabcampath (EU) or Campath (US) (alemtuzumab), humanized mAb against CD52, a surface antigen of B lymphocytes, produced in CHO cells	Genzyme (Naarden, the Netherlands) Millennium (Cambridge, MA, USA)	CLL	2001 (EU & US) Withdrawn (EU) 2012
Herceptin (trastuzumab), humanized mAb against HER2, produced in a murine cell line	Roche (Welwyn Garden City, UK)	Treatment of metastatic breast cancer overexpressing HER2 protein	2000 (EU) 1998 (US)
Remicade (infliximab), chimeric mAb against TNF-α, produced in Sp2/0 cells	Janssen (Leiden, the Netherlands)	Crohn's disease	1999 (EU) 1998 (US)
Synagis (palivizumab) humanized mAb directed against an epitope on the surface of respiratory syncytial virus, produced in a murine myeloma cell line	MedImmune (Gaithersburg, MD, USA) AbbVie Deutschland (Ludwigshafen, Germany)	Prophylaxis of lower respiratory tract disease caused by syncytial virus in children	1999 (EU) 1998 (US)
Zenapax (daclizumab), humanized mAb against the IL-2 receptor α-chain, produced in NS0 cells	Roche (Welwyn Garden City, UK) Biogen (Cambridge, MA, USA)	Prevention of acute kidney transplant rejection	1999 (EU) 1997 (US) Withdrawn 2009 (EU)

Table 1 Continued

Product	Company (location)	Therapeutic indication	Date approved
Humaspect (votumumab), human mAb against cytokeratin tumor-associated antigen, produced in a human lymphoblastoid cell line	KS Biomedix (Farnham, UK)	Detection of carcinoma of the colon or rectum	1998 (EU) Withdrawn 2004
MabThera in EU, Rituxan in US (rituximab), chimeric mAb against CD20 surface antigen of B lymphocytes, produced in CHO cells	Roche (Welwyn Garden City, UK)	Non-Hodgkin lymphoma	1998 (EU) 1997 (US)
Simulect (basiliximab), chimeric mAb directed against the α-chain of the IL-2 receptor, produced in a murine myeloma cell line	Novartis (Horsham, UK)	Prophylaxis of acute organ rejection in allogeneic renal transplantation	1998 (EU)
LeukoScan (sulesomab), murine mAb Fab fragment against granulocyte surface nonspecific cross-reacting antigen-90, produced in Sp2/0 cells	Immunomedics (Darmstadt, Germany)	Diagnostic imaging for infection and inflammation in bone of patients with osteomyelitis	1997 (EU) Withdrawn 2018
Verluma (nofetumomab), murine mAb Fab fragment directed against carcinoma-associated antigen, produced in a murine cell line	Boehringer Ingelheim, NeoRx (Seattle)	Detection of small-cell lung cancer	1996 (US) Withdrawn 1999
Tecnemab KI (antimelanoma Mab fragments), murine mAb fragments (Fab/Fab_2 mix) against HMW-MAA, produced in murine ascites culture	Amersham Sorin (Milan)	Diagnosis of cutaneous melanoma lesions	1996 (EU) Withdrawn 2000
ProstaScint (capromab pentetate), murine mAb against the tumor surface antigen PSMA, produced in a murine cell line	EUSA Pharma USA (Langhorne, PA, USA)	Detection, staging and follow-up of prostate adenocarcinoma	1996 (US)
MyoScint (imiciromab pentetate), murine mAb fragment directed against human cardiac myosin, produced in a murine cell line	Centocor	Myocardial infarction imaging	1996 (US) Withdrawn 1999
CEA-scan (arcitumomab), murine mAb Fab fragment against human carcinoembryonic antigen (CEA), produced in mouse ascites	Immunomedics	Detection of recurrent or metastatic colorectal cancer	1996 (EU & US) Withdrawn 2005 (EU & US)
Indimacis 125 (igovomab), murine mAb Fab_2 fragment against the tumor-associated antigen CA125, produced in a murine cell line	CIS Bio (Gif-sur-Yvette, France)	Diagnosis of ovarian adenocarcinoma	1996 (EU) Withdrawn 2009
ReoPro (abciximab), Fab fragments derived from a chimeric mAb against the platelet surface receptor $GPII_b/III$, produced in a mammalian cell line	Janssen Biologics (Leiden, the Netherlands), Centocor	Prevention of blood clots	1994 (US)
OncoScint CR/OV (satumomab pendetide), murine mAb against the tumor-associated glycoprotein TAG-72, produced in a murine cell line	Cytogen (Princeton, NJ, USA)	Detection, staging and follow-up of colorectal and ovarian cancers	1992 (US) Withdrawn 2002
Orthoclone OKT3 (muromomab CD3), murine mAb against the T-lymphocyte surface antigen CD3, produced in a murine cell line	Centocor Ortho Biotech Products (Raritan, NJ, USA)	Reversal of acute kidney transplant rejection	1986 (US)
Other recombinant products			
Bone morphogenetic proteins			
Opgenra (eptotermin alfa), rh BMP-7, produced in CHO cells	Olympus Biotech (Limerick, Ireland)	Posterolateral lumbar spinal fusion	2009 (EU) Withdrawn 2016
Infuse bone graft, containing dibotermin alfa, a rh BMP-2 produced in CHO cells, placed on an absorbable collagen sponge. Active substance same as that in Infuse (see below)	Wyeth (Madison, NJ, USA)	Acute open tibial shaft fracture	2004 (US)
Inductos (dibotermin alfa), rh BMP-2, produced in CHO cells	Medtronic BioPharma (Heerlen, the Netherlands) Wyeth Europa Genetics Institute	Acute tibia fractures	2002 (EU)
Infuse (rh BMP2), produced in CHO cells	Medtronic Sofamor Danek (Memphis, TN, USA)	Promotes fusion of lower spine vertebrae	2002 (US)
OP-1 implant in US, Osigraft in EU (eptotermin alfa), rh BMP-7, produced in CHO cells	Olympus Biotech (Limerick, Ireland) Stryker Biotech (Hopkinton, MA, USA)	Non-union of tibia	2001 (EU & US) Withdrawn 2015 (EU)
Recombinant enzymes			
Palynziq (pegvaliase-pqpz), r phenylalanine ammonia lyase, produced in *E. coli* and PEGylated	BioMarin (Novato, CA, USA)	Phenylketonuria	2018 (US)
Lamzede (velmanase alfa), rh α-mannosidase, expressed in precursor form in CHO cells	Chiesi Farmaceutici (Parma, Italy	α-mannosidosis	2018 (EU)
Brineura (cerliponase alfa), rh serine tripeptidyl peptidase-1, expresses in proenzyme form in CHO cells	BioMarin (Cork, Ireland), BioMarin	CLN2 disease (tripeptidyl peptidase-1 deficiency)	2017 (EU & US)
Mepsevii (vestronidase alfa-vjbk), r human lysosomal β-glucuronidase, produced in CHO cells	Ultragenyx Pharmaceutical (Novato, CA, USA)	Mucopolysaccharidosis VII	2017 (US)
Oncaspar (pegaspargase), r asparaginase, produced in *E. coli* and conjugated to monomethoxypropylene glycol	Baxalta Innovations	Lymphoblastic leukemia, lymphoma	2016 (EU)
Spectrila (asparaginase), r asparaginase, produced in *E. coli*	Medac Gesellschaft für klinische Spezialpräparate (Wedel, Germany)	Lymphoblastic leukemia, lymphoma	2016 (EU)
Kanuma (sebelipase alfa), rh lysosomal acid lipase, produced in the eggs of transgenic chickens	Alexion Europe (Rueil-Malmaison, France) Alexion Pharmaceuticals (Cheshire, CT, USA)	Enzyme replacement therapy in patients with lysosomal acid lipase deficiency	2015 (EU & US)
Strensiq (asfotase alfa), dimeric fusion protein containing a soluble catalytic domain of human tissue nonspecific alkaline phosphatase linked to an IgG Fc domain and a deca-aspartate peptide domain, produced in CHO cells	Alexion Europe (Rueil-Malmaison, France) Alexion (Cheshire, CT, USA)	Enzyme replacement therapy in patients with pediatric-onset hypophosphatasia	2015 (EU & US)
Vimizim (elosulfase alfa), rh N-acetylgalactosamine-6-sulfatase, produced in CHO cells	BioMarin (London, UK)	Mucopolysaccharidosis IVA (Morquio A syndrome)	2014 (EU & US)
Krystexxal (pegloticase), r urate oxidase, PEGylated after synthesis, produced in *E. coli*	Savient Pharma Ireland (Dublin) Crealta Pharmaceuticals (Lake Forest, IL, USA)	Gout	2013 (EU) 2010 (US) Withdrawn 2016 (EU)
Elelyso (taliglucerase alfa), rh glucocerebrosidase, produced in engineered carrot root cell culture	Pfizer (New York), Protalix BioTherapeutics (Karmiel, Israel)	Gaucher disease	2012 (US)
Voraxaze (glucarpidase), r carboxypeptidase, produced in *E. coli*	BTG International (West Conshohocken, PA, USA)	Toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function	2012 (US)
Lumizyme (alglucosidase alfa), rh acid-α-glucosidase, produced in CHO cells	Sanofi Genzyme	Pompe disease (glycogen storage disease type II)	2010 (US)
VPRIV (velaglucerase alfa), rh glucocerebrosidase, produced in a human fibroblast cell line	Shire Human Genetic Therapies (Danderyd, Sweden)	Gaucher disease	2010 (EU & US)
Elaprase (idursulfase), rh iduronate-2-sulfatase, produced in a human cell line	Shire Human Genetic Therapies	Mucopolysaccharidosis II (Hunter syndrome)	2007 (EU) 2006 (US)
Naglazyme (galsulfase), rh N-acetylgalactosamine-4-sulfatase, produced in CHO cells	BioMarin (London & Novato, CA, USA)	Long-term enzyme replacement therapy in mucopolysaccharidosis VI	2006 (EU) 2005 (US)
Myozyme (algulcosidase alfa), rh acid glucosidase, produced in CHO cells	Sanofi Genzyme (Naarden, the Netherlands)	Pompe disease	2006 (EU & US)
Aldurazyme (laronidase), r α-L-iduronidase, produced in CHO cells	BioMarin	Long-term replacement in mucopolysaccharidosis I	2003 (EU & US)
Hylenex (hyaluronidase), rh hyaluronidase, produced in CHO cells	Halozyme Therapeutics (San Diego)	Adjuvant to increase absorption and dispersion of other drugs	2005 (US)
Fabrazyme (agalsidase beta), rh α-galactosidase, produced in CHO cells	Sanofi Genzyme (Naarden, the Netherlands)	Fabry disease (α-galactosidase A deficiency)	2003 (US) 2001 (EU)
Replagal (agalsidase alfa), rh α-galactosidase, produced in a human cell line	Shire Human Genetic Therapies, TKT Europe	Fabry disease (α-galactosidase A deficiency)	2001 (EU)
Fasturtec in EU, Elitex in US (rasburicase), r urate oxidase, produced in *S. cerevisiae*	Sanofi (Paris)	Hyperuricemia	2002 (US) 2001 (EU)
Cerezyme (imiglucerase), rh β-glucocerebrosidase, produced in CHO cells	Genzyme (Naarden, the Netherlands)	Gaucher disease	1997 (EU) 1994 (US)
Pulmozyme (dornase alpha), r DNase, produced in CHO cells	Roche/Genentech	Cystic fibrosis	1993 (US)
Fusion proteins			
Erelzi (etanercept in EU, etanercept-szzs in USA), r dimeric fusion protein consisting of TNF receptor extracellular domains linked to an IgG1 Fc region, produced in CHO cells, biosimilar to Enbrel	Sandoz (Kundl, Austria, & Princeton, NJ, USA)	Rheumatoid arthritis, selected other inflammatory diseases	2017 (EU) 2016 (US)
Lifmior (etanercept), r dimeric fusion protein consisting of TNF receptor extracellular domains linked to an IgG1 Fc region, produced in CHO cells. Same product as Enbrel (see below)	Pfizer Europe (Brussels)	Rheumatoid arthritis, selected other inflammatory diseases	2017 (EU)
Benepali (etanercept), rh TNF receptor–IgG Fc fusion protein, produced in CHO cells, biosimilar to Enbrel	Samsung Bioepis (Chertsey, UK)	Arthritis, psoriasis, axial spondyloarthritis	2016 (EU)
Zaltrap (aflibercept), combination drug consisting of binding domains of VEGF receptors 1 and 2 fused to an IgG Fc, produced in CHO cells. Same active substance as in Eylea (see below)	Sanofi (Paris) Sanofi-aventis US (Bridgewater, NJ, USA)	Metastatic colorectal cancer	2013 (EU) 2012 (US)
Eylea (aflibercept), fusion protein consisting of extracellular ligand binding domains of VEGF receptor fused to IgG Fc, produced in CHO cells). Same active substance as in Zaltrap (see above)	Bayer (Berlin) Regeneron Pharmaceuticals (Tarrytown, NY)	Neovascular (wet) age-related macular degeneration	2012 (EU) 2011 (US)
Nulojix (belatacept), fusion protein consisting of the extracellular domain of human CTLA4 fused to IgG Fc; binds CD80 and CD86 on antigen-presenting cells, thereby inhibiting T cell activation, produced in CHO cells	Bristol-Myers Squibb (Uxbridge, UK)	Prophylaxis of organ rejection following kidney transplant	2011 (EU & US)
Arcalyst in US, Rilonacept Regeneron in EU (rilonacept), dimeric fusion protein with each monomer consisting of the ligand-binding domains of the human IL-1 receptor and the IL-1 receptor accessory protein along with the Fc region of human IgG-1, produced in CHO cells	Regeneron Pharmaceuticals (London, UK, & Tarrytown, NY, USA)	Cryopyrin-associated periodic syndromes (CAPS)	2009 (EU) 2008 (US) Withdrawn 2012 (EU)
Nplate (romiplostim), dimeric fusion protein with each monomer consisting of two thrombopoietin receptor binding domains and the Fc region of human IgG-1, produced in *E. coli*	Amgen Europe	Thrombocytopenia	2009 (EU) 2008 (US)

Table 1 Continued

Product	Company (location)	Therapeutic indication	Date approved
Orencia (abatacept), fusion protein that links the extracellular domain of human cytotoxic T-lymphocyte associated antigen-4 with modified Fc region of IgG1, produced in a mammalian cell line	Bristol-Myers Squibb (Uxbridge, UK)	Rheumatoid arthritis	2007 (EU) 2005 (US)
Amevive (alefacept), dimeric fusion protein consisting of the extracellular CD2-binding portion of human LFA-3 linked to the Fc region of human IgG1, produced in CHO cells	Astellas Pharma (Deerfield, IL, USA)	Moderate to severe chronic plaque psoriasis in adults	2003 (US) Withdrawn 2011
Enbrel (etanercept), r TNF receptor–IgG fragment fusion protein, produced in CHO cells. Same product as Lifmior (see above)	Amgen (Thousand Oaks, CA, USA) Pfizer (Sandwich, UK)	Rheumatoid arthritis	2000 (EU) 1998 (US)
Ontak (denileukin diftitox), r IL-2–diphtheria toxin fusion protein that targets cells displaying a surface IL-2 receptor, produced in *E. coli*	Eisai (Tokyo), Ligand Pharmaceuticals (San Diego)	Cutaneous T-cell lymphoma	1999 (US)
Gene therapy and nucleic acid–based			
Tegsedi (inotersen), a 20-nucleotide single-stranded oligonucleotide manufactured by direct chemical synthesis	Ionis USA (London)	Hereditary transthyretin amyloidosis	2018 (EU)
Luxturna (voretigene neparvovec-rzyl), a live, nonreplicating adeno-associated virus genetically modified to express the human *RPE65* gene	Spark Therapeutics (Philadelphia)	Retinal dystrophy	2017 (US)
Spinraza (nusinersen sodium), an 18-nucleotide antisense oligonucleotide manufactured by direct chemical synthesis	Biogen Idec (Maidenhead, UK) Biogen (Cambridge, MA, USA)	Spinal muscular atrophy	2017 (EU) 2016 (US)
Exondys 51 (eteplirsen), a chemically synthesized antisense oligonucleotide	Sarepta Therapeutics (Cambridge, MA, USA)	Duchenne muscular dystrophy	2016 (US)
Imlygic (talimogene laherparepvec), an engineered herpes simplex virus type 1 capable of producing GM-CSF	Amgen Europe Amgen	Melanoma	2015 (EU & US)
Kynamro (mipomersen sodium), a chemically synthesized antisense oligonucleotide	Kastle Therapeutics (Chicago)	Familial hypercholesterolemia	2013 (US)
Glybera (alipogene tiparvovec), human *LPL* gene housed in an engineered AAV1 vector	uniQure (Amsterdam)	Lipoprotein lipase deficiency	2012 (EU) Withdrawn 2017
Macugen (pegaptanib sodium injection), a synthetic PEGylated oligonucleotide that specifically binds VEGF	Pfizer, PharmaSwiss Ceska Republika (Prague) Eyetech (Palm Beach Gardens, FL, USA),	Neovascular, age-related macular degeneration	2006 (EU) 2004 (US)
Vitravene (fomivirsen), an antisense oligonucleotide	Novartis Ophthalmics Europe (Farnborough, UK) Isis Pharmaceuticals (Carlsbad, California)	Cytomegalovirus retinitis in AIDS patients	1999 (EU) 1998 (US) Withdrawn 2002 (EU)
Engineered cell–based			
Kymriah (tisagenlecleucel), autologous T cells genetically modified to encode an anti-CD19 chimeric antigen receptor comprising a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3ζ	Novartis (East Hanover, NJ, USA)	Acute lymphoblastic leukemia, large B-cell lymphoma	2017 (US)
Yescarta (axicabtagene ciloleucel), autologous T cells genetically modified to express a chimeric antigen receptor comprising a murine anti-CD19 single-chain variable fragment (scFv) linked to CD28 and CD3ζ co-stimulatory domains	Kite Pharma (Santa Monica, CA, USA)	Large B-cell lymphoma	2017 (US)
Strimvelis, autologous $CD34^+$ cells transduced with an engineered retroviral vector encoding the human adenosine deaminase sequence	GlaxoSmithKline (Cork, Ireland)	Severe combined immunodeficiency	2016 (EU)
Zalmoxis, allogeneic T cells genetically modified to express the herpes simplex thymidine kinase suicide gene and a truncated form of the human low-affinity nerve growth factor receptor gene	MolMed (Milan)	Hematopoietic stem cell transplantation, graft-versus-host disease	2016 (EU)

Data were collected from several sources (http://www.fda.gov/, https://www.ema.europa.eu/en). r, recombinant; rh, recombinant human; CHO, Chinese hamster ovary cell line; HEK, human embryo kidney cell line; BHK, baby hamster kidney cell line; PEG, polyethylene glycol; mAb, monoclonal antibody; tPA, tissue plasminogen activator; hGH, human growth hormone; FSH, follicle stimulating hormone; EPO, erythropoietin; IGF, insulin-like growth factor; BMP, bone morphogenetic protein; EGF, epidermal growth factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; VEGF, vascular endothelial growth factor; IFN, interferon; IL, interleukin; HPV, human papillomavirus; HBsAg, hepatitis B surface antigen; TNF, tumor necrosis factor; GLP, glucagon-like peptide; HER2, human epidermal growth factor receptor 2, CLL, chronic lymphocytic leukemia.