Biopharmaceutical benchmarks 2014

Gary Walsh

Monoclonal antibodies continue their march on the markets, optimized so-called biobetter versions of existing biologics are also gaining ground, but the rate of biosimilar approvals has seen a dramatic slowdown in recent years.

Over the past four years, the rate of biopharmaceutical approvals in the United States and European Union (EU; Brussels) has remained relatively steady compared with previous time periods. The current survey period witnessed the approval of 54 biopharmaceutical (recombinant biologic) products (see **Table 1** for definition). This brings the total number of biopharmaceutical products that have received licenses in these two markets to 246. That said, only 166 of these 246 products have distinct active ingredients. Moreover, with 34 products having been withdrawn from both the US and EU markets subsequent to approval, the number of approved biopharmaceuticals marketed in the United States and/or EU now stands at 212. Annual approval numbers over the four-year period ranged from a low of 6 in 2011 to a high of 20 in 2013 (**Fig. 1a**).

Overall, comparatively few novel therapies gained approval over the period of this study, with monoclonal antibodies (mAbs) accounting for an increasing fraction of approvals; however, 2012 did witness the first approvals of a gene therapy in the EU and the first US approval of a plant-produced biologic. Somewhat surprisingly, the rate of approvals of biosimilars has waned during the most recent survey period, with only a handful gaining approval in the EU (the biosimilar pathway has still not been fully implemented in the United States).

Here, I provide an update on previous surveys of biopharmaceuticals[1,2]; I list all recombinant biologics approved during the past four and a half years (from January 2010 until July 2014), examining the types of biopharmaceutical drugs that have reached the US and EU market as well as the indications for which they are registered. As in previous articles, I have not included tissue-engineering products, which the US Food and Drug Administration (FDA) classifies as pure medical devices.

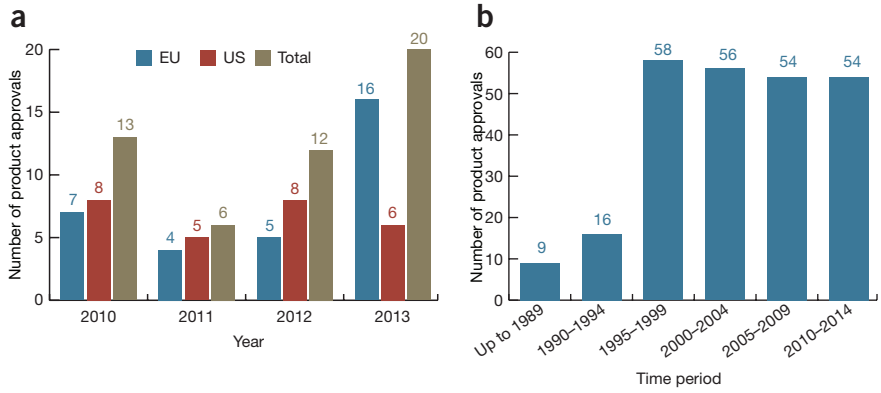

Figure 1 Approvals by region and by date. (**a**) Approvals in US and EU for each of four years in this study period. (**b**) Approval numbers over the indicated periods. Note that both regions experienced a lull in approvals, but in different years. In several instances, the same product has been registered in both regions, but in different years (**Table 1**), hence the yearly totals appear greater than the cumulative number of individual products approved from 2010-2013.

In a snapshot

Over the current four-year period in which 54 biologics were approved, 17 were mAbs, 9 were hormones, 8 were blood-related proteins, 6 were enzymes, 4 were vaccines, fusion proteins and granulocyte-colony stimulating factors (G-CSFs; filgrastims), 1 was interferon and one was a gene therapy-based product. In terms of indications, new approvals followed relatively predictable lines, with cancer representing the single most common indication with nine products. Other common indications included various inflammation-related conditions and hemophilia (six products each), metabolic disorders and diabetes (five products each), as well as neutropenia and vaccines against infectious diseases (four products in each case).

Thirty-two of the new products approved (59%) are genuinely new to the market; the remaining products represent biosimilars, me-too products, as well as products previously approved elsewhere (**Table 2**). Those 32 new products contained a total of 30 genuinely new active biopharmaceutical ingredients. Of the remaining two active biopharmaceutical ingredients, Eylea and Zaltrap (both developed by Regeneron, Tarrytown, NY, USA) share their novel active ingredient (aflibercept), as do Tresiba (Novo Nordisk, Bagsvaerd, Denmark) and Ryzodec (insulin degludec).

Both the United States and the EU approved nearly the same number of products (39 in the case of the United States, 41 in Europe). Over the same period, US regulators approved a grand total of 147 pharmaceutical products containing novel (bio)molecular entities (NMEs). These numbers indicate

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Table 2 Biopharmaceuticals approved in the United States and/or EU during the current survey period (January 2010–July 2014) by category

Category	Products (by trade name)
Genuinely new biopharmaceuticals	Abthrax, Adcetris, Alprolix, Benlysta, Bexsero, Cyramza, Eloctate, Elonva, Entyvio, Eperzan/Tanzeum, Eylea & Zaltrap, Flublok, Gattex/Revestive, Gazyva/Gazyvaro, Glybera, Jetrea, Kadcyla, Krystexxal, Myalept, NovoEight, Nulojix, Provenge, Ruconest, Tresiba & Ryzodec, Sylvant, Tretten/NovoThirteen, Vimizim, Voraxaze, Xgeva/Prolia and Yervoy
Biosimilars	Grastofil, Inflectra/Remsima, Nivestim and Ovaleap
Reformulated, 'me-too' & related	Afrezza Elelyso, Granix, Hexacima/Hexyon, Lonquex, Lumizyme, Nuwiq, Perjeta, Plegridy, Rixubis, Simponi Aria, Somatropin Biopartners and Vpriv
Previously approved elsewhere	Actemra/Roactemra, Arzerra, Scintium and Victoza

that roughly a quarter (26%) of all genuinely new drug approvals in the United States were biopharmaceuticals, which is in line with the value reported in previous surveys (21–24%). Changes made to the reporting system in the EU preclude making analogous calculations for Europe.

Overall product trends

Compared with earlier periods, approvals in the current survey reveal some interesting, albeit predictable, trends. Following the first approval of a biopharmaceutical in 1982 (Humulin; recombinant human insulin; Eli Lilly, Indianapolis), only eight other products came onstream over the rest of that decade. Approval numbers then began to grow dramatically throughout the 1990s as the industry matured. Within each five-year period since 1995, approval rates have remained remarkably constant (**Fig. 1b**). The figure for 2010–2014 currently stands at 54 approvals, but likely will be close to 60 by year's end.

The overall dominance of mAb approvals since the end of the 1990s has continued into the second decade of the twenty-first century, with the increasing prevalence of humanized and human forms over chimeric (and particularly murine) mAbs. Thus, by the end of the 1980s, mAbs represented just a little over 10% of all biologic products approved, whereas between 2010 and April this year they represent almost 27% of all approvals (**Fig. 2**). With one blip (1995–1999), the increase in the proportion of mAb-based products approved has been remarkably steady over time.

The current period has also witnessed an absence of approvals (and thus drop-off in approval rates) for a range of traditional product classes (**Fig. 3**). For example, no recombinant thrombolytic agent, anticoagulant, interleukin or erythropoietin has been approved since 2010, likely reflective of market saturation relative to demand in the case of these products.

At the same time, after an initial burst of EU approvals for biosimilars from 2006–2008, the approval rate has slowed considerably (see below). In contrast, the class of biobetters—forms of existing approved biologics that have been modified to optimize their delivery, pharmacokinetics or pharmacodynamics—has continued to see approvals in recent years. Examples include albumin fusions like GlaxoSmithKline's Eperzan (a GLP-1 fusion) and the continuing development of long-acting, polyethylene glycol (PEG)-derivatized versions of proteins, such as Biogen Idec's (Cambridge, MA, USA) Plegridy (PEGylated interferon (IFN)-beta b1) and Teva's (Petach Tikva, Israel) Lonquex (PEGylated G-CSF). In some cases, manufacturers are launching such products to allow differentiation from competitor products in crowded markets on the basis of

Box 1 Traditional biotech product approvals

It is sometimes easy to forget that biotech-based products (products produced in biological systems, as opposed to by chemical synthesis) represented an important category of pharmaceutical product before the molecular biology era. Such products include traditional vaccines, as well as proteins (e.g., blood factors and immunoglobulins) or other biomolecules extracted directly from biological source material (e.g., certain antibiotics, blood, bacterial or plant material). The term biopharmaceutical was coined in the 1980s specifically to describe products generated or produced by modern molecular biological methods and to distinguish them from the traditional biological products. In terms of technical and medical innovation, biopharmaceuticals quickly and permanently dominated the pharmaceutical biotech sector. In parallel with the approval of biopharmaceuticals, traditional biotech products continue to come on the market. Indeed, some now classify all biosynthesized products, traditional and molecular biology–derived, as 'biotech products' or 'biopharmaceuticals', although we retain the original distinction.

The current survey period witnessed the approval of 45 traditional biotech (nonrecombinant) products within the United States and EU, which were classified as new in terms of active substance by the regulatory authorities (**Supplementary Table 1**). Technologically, most are variants or follow-on versions of already approved traditional products. Almost half of these new products are vaccine-based, mainly viral vaccines produced by traditional culture in embryonated hen's eggs, with follow-on extraction and purification of the whole virus or its surface components. Additional approvals include a range of blood-derived proteins (mainly immunoglobulins and blood factors) as well as proteins extracted from various animal (e.g., pancrealipase), bacterial (e.g., asparaginase) or plant (e.g., bromelain) sources. Approvals also included four whole-cell-based products (Hemacord, LaViv, Gingtuit and Maci), all of which contain nonengineered cells recovered directly from harvested human tissue.

In commercial terms, the majority of traditional biotech products command relatively modest market values, particularly when compared with biopharmaceuticals. Even so, some exceptions exist, with several having reached blockbuster status; in the survey period of this article, two products are notable. Pfizer's meningitis vaccine generated estimated global sales of $4 billion in 2013, making it the best-selling vaccine last year, and one of only six vaccine products to reach blockbuster status (http://www.fiercevaccines.com/). Another was Sanofi's Fluzone, which had an estimated $1.4 billion of sales in 2013. The single most-valuable nonvaccine traditional biotech product currently on the market is Allergan's Botox (onabotulinumtoxin A); purified botulinum toxin, produced by fermentation of Hall strain *Clostridium botulinum* type A. Initially approved in 1989, it is used for various cosmetic as well as therapeutic indications and generated $1.98 billion in 2013 global sales, according to company annual report data. One onabotulinumtoxin A–based product (Xeomin), indicated for cervical dystonia (involuntary contraction of neck muscles) and blepharospasm (eyelid twitch) gained approval during the current period.

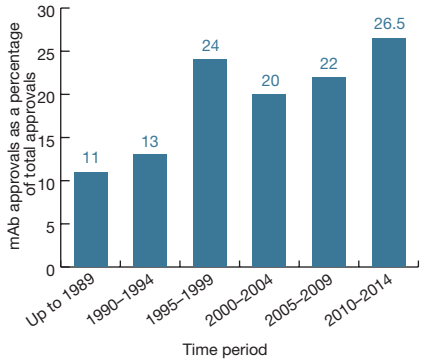

Figure 2 mAbs approved within the indicated periods, expressed as a percentage of total biopharmaceutical product approvals within the same period. Fc-based fusion products are not categorized as mAbs in these data.

ease of administration or ease of compliance.

During the current survey period, the market value of biopharmaceuticals has been steadily rising, reaching a total cumulative sales value of $140 billion for 2013 (**Fig. 4**), a value which exceeds the reported gross domestic product (GDP) of three-quarters of the economies included in the World Bank GDP ranking database (156 of the 214 countries) (http://data.worldbank.org/data-catalog/GDP-ranking-table). Data from various La Merie financial reports (http://www.lamerie.com) indicate cumulative sales over the most recent survey period for which statistics are available (2010–2013 inclusive) reached just short of half a trillion dollars.

The single most lucrative product in 2013 was Humira (adalimumab), generating global sales of $11 billion (**Table 3**), whereas a total of 37 individual biopharmaceuticals recorded blockbuster sales (>$1 billion). Humira, also the top-selling biopharmaceutical in 2011–2012, generated $35 billion in sales over the period 2010–2013. The top ten taken together generated sales of $69.8 billion in 2013, representing 50% of total biopharmaceutical drug product revenues last year. mAbs again represented the most lucrative single product class. Total mAb sales (excluding Fc-fusion–based, antibody-like traps, such as Enbrel (etanercept)) reached $63 billion last year ($75.7 billion if such Fc fusion products are included). Moreover, mAbs are six of the top ten product sales in 2013 (seven if Enbrel is included).

In terms of target indications, the majority of antibody and antibody-like products target inflammatory and/or autoimmune conditions (cumulative 2013 sales of $41 billion, with products targeting tumor necrosis factor (TNF) alone generating $30.5 billion and cancer (2013 cumulative sales of $26 billion, ~29% of the 2013 total overall global oncology market, estimated at $91 billion). Among nonantibody–based products, insulins are the next most lucrative product class, collectively generating sales of $21.5 billion in 2013, some 60% of the total global diabetes drug market.

Interestingly, only 1 of the top 20 biopharmaceuticals in sales was approved in the current survey period (Eylea, number 20). In fact, 18 of the top 20 were first approved a decade or more ago, with over half (11 products) having gained initial approval in the 1980s or 1990s. In part, this can be explained by the fact that the majority of products approved in the current period have relatively limited market size and/or value. As previously mentioned, 40% of approvals were me-too drugs or biosimilars whereas, of the 30 genuinely novel products approved, 15 have orphan status. However, aggressive marketing and potential expanded indications will likely render at least a few of these products blockbusters in the long run.

Although not considered in the same detail herein as biopharmaceuticals, it is worth noting that a steady stream of traditional biological products continues to come on the market (**Box 1**). Those that gained marketing approval in the United States and EU over the current survey period are listed in **Supplementary Table 1.**

Manufacturing platforms

Another trend evident over the years is the steady increase in the prominence of mammalian over nonmammalian-based expression systems used for the production of approved products (**Fig. 5a**). This trend tallies with the ongoing increase in the proportion of molecules that harbor post-translational modifications, particularly glycosylation. Quantitatively, however, microbial production still predominates. Advisory firm BioProcess Technology Consultants (Woburn, MA, USA) estimates that total biopharmaceutical manufacturing activity in 2010 equated to some 26.4 metric tonnes (26,400 kg) of pure protein (active pharmaceutical ingredients) of which some 17.9 metric tonnes (68%) were derived from microbial systems, with the remaining 8.5 metric tonnes (32%) derived from mammalian systems. Insulins constitute the bulk of product produced in microbial systems, whereas mAbs constitute the vast bulk of product produced in mammalian systems. At a quantitative level too, the trend is toward mammalian-based production, with demand for mAb-based products projected to reach some 13.4 metric tonnes by 2016, almost double the 2010 value.

Within mammalian expression platforms, Chinese hamster ovary (CHO) cell–based systems remain the most commonly used expression system (**Fig. 5b**). A small number of products, mainly replacement enzymes with specific post-translational modifications requirements, are produced in various human cell lines. For example, Xigris (drotrecogin-α; Eli Lilly), Elaprase (rh-idursulfase; Shire Pharmaceuticals, Dublin) and Replagal (rh-alfa galactosidase; Shire) are produced in human cell lines. Other mammalian-based production cells include mouse myeloma cell lines NS0 and Sp2/0, and baby hamster kidney cells.

Although the use of *Escherichia coli* as an expression system continues to decline, it remains the single most common nonmammalian-based production cell type. Indeed, the only other bacterial systems currently in use are *Vibrio cholera* and *Bordetella pertussis*, each for the manufacture of single products: the former for Dukoral (cholera toxin subunit B; Stockholm-based Crucell) and the latter for Triacelluvax (recombinant pertussis toxin; Siena, Italy–based Chiron/Novartis). Eukaryotic microbial expression systems based on yeast (*Saccharomyces cerevisiae* and *Pichia pastoris*) continue to be important and have remained common manufacturing systems, just behind *E. coli* in terms of popularity.

Insect cell lines are also in use for three approved products. Flublok (Protein Sciences; Meriden, CT, USA) is a trivalent influenza vaccine based on hemagglutinin sequences of the three currently circulating flu strains produced in *Spodoptera frugiperda* (*Sf*) cells using a baculovirus expression system. Provenge (sipuleucel-T; Dendreon, Seattle, WA, USA) is a preparation of autologous peripheral blood mononuclear cells loaded with a recombinant fusion containing prostatic acid phosphatase and granulocyte-macrophage (GM)-CSF produced by baculovirus in Sf21 insect cells that are adapted to grow in serum-free media. And Cervarix (GlaxoSmithKline; London) is a divalent human papilloma virus (HPV) vaccine, comprising virus-like particles of truncated major capsid L1 proteins from HPV types 16 and 18, produced in a recombinant baculovirus expression system and the insect cell line Hi-5 Rix4446 derived from *Trichoplusia ni*.

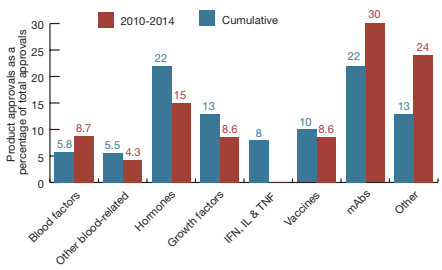

Figure 3 Product approvals, cumulative (1982–2014) and for the current period (2010–July 2014) in the context of product class. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question. IL, interleukin.

Box 2 Plant-based expression

The current survey period was marked by FDA approval of the first biopharmaceutical produced in a plant-based system. Manufactured and marketed by Pfizer on license from Protalix (Carmiel, Israel), Elelyso (taliglucerase alfa) is a recombinant glucocerebrosidase used as a replacement therapy to treat Gaucher disease, a rare lysosomal storage disorder. It is produced in an engineered carrot plant root cell line, grown in a disposable bioreactor system (ProCellEx).

Glycoprotein production in plant-based systems can be problematic in that it typically results in the formation of a hyperglycosylated product, often containing sugar moieties immunogenic in humans. Moreover the sugar chains are devoid of sialic acid caps, which can negatively influence serum half-life. In the case of Elelyso, the recombinant enzyme displays terminal mannose residues in its glycocomponent, neatly facilitating direct product uptake by macrophages (the target cell type) by cell surface mannose receptors.

A marketing authorization application for Elelyso was also submitted to the EMA but was refused. However, European refusal was based not upon technical or medical considerations but rather due to the existence of a ten-year marketing exclusivity granted to a substantially similar product, Shire's Vpriv (velaglucerase alfa), a glucocerebrosidase produced by gene activation technology in a continuous human cell line (HT1080), which was approved by the European Commission in 2010.

Overall, only a handful of plant-produced biopharmaceuticals are in clinical trials. The field suffered a setback in 2012 when Biolex Therapeutics filed for bankruptcy. Biolex pioneered the LEX platform, which uses *Lemna* (duckweed) as a production vehicle for biopharmaceuticals. The company's lead product (Locteron, an interferon alpha) was a casualty of bankruptcy, but the LEX platform has been acquired by Synthon (Nijmegen, the Netherlands).

Transgenic plant-based production platforms have more recently entered the spotlight, this time as a result of Mapp Biopharmaceuticals' (San Diego) experimental Ebola product, ZMapp. ZMapp consists of a combination of three humanized mAbs directed against nonoverlapping epitopes (the mucin-like domain as well as the 6D31 and core epitopes of glycoprotein 1) in the Ebola Zaire virus strain that are produced in a low-nicotine tobacco variety (*Nicotiana benthamiana*) lacking plant-specific N-glycans. ZMapp has been administered on a compassionate basis to three infected individuals from the recent West African outbreak, two of whom recovered. Studies in rhesus macaques have also shown protection from lethal challenge when administered from 48 hours to 5 days after infection[15,16].

Within the therapeutic space perhaps plant-based systems may yet make the most impact upon healthcare applications where a combination of economics and scale of production become particularly important. For example, Ventria Bioscience (Junction City, KS, USA) is developing a plant-synthesized recombinant human lactoferrin product for oral use in the prevention of antibiotic-associated diarrhea. The company estimates a requirement of 30 g protein per patient-treatment period, which (to be cost effective) must be manufactured at a cost of no greater than $3.75/g protein, which they claim their plant system can achieve[17].

In terms of transgenic animal production systems (which express recombinant products in their milk), rabbits have now joined goats as a means of biopharmaceutical production. Ruconest (conestat alfa, Pharming, Leiden, the Netherlands) is a recombinant version of the human C1 esterase inhibitor protein (C1INH) produced in the milk of rabbits harboring genomic human C1INH sequences fused to 5′ bovine αS(1) casein promoter sequences. Ruconest is the second transgenic animal–derived protein to be approved (the first from rabbits); in 2009, the FDA approved Atryn, recombinant antithrombin alpha, produced in the milk of goats under the control of the beta casein promoter[2].

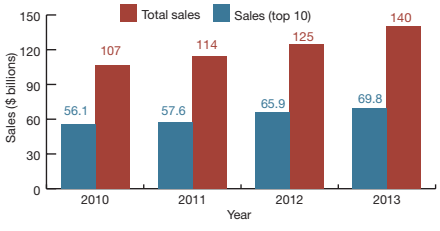

Figure 4 Annual biopharmaceutical sales value (cumulative product sales and sales for the ten top-selling products) for the period 2010 to 2013.

Finally, 2012 also saw the first US approval of a biologic produced in plant cell culture; Protalix Biotherapeutics/Pfizer (New York) Elelyso (taligurase alfa) is a recombinant human glucocerebrosidase produced in cultured carrot root cells. The plant-produced taligurase alfa is targeted to plant cell storage vacuoles during its biosynthesis, using a plant-specific, C-terminal sorting signal. The resulting product naturally displays terminal mannose residues on its glycocomponent, apparently as a result of an endogenous vacuolar carbohydrase. This eliminates the need for a subsequent exoglucosidase-mediated downstream processing step for product derived from placental tissue or by recombinant means using CHO cells (**Box 2**).

Biosimilars stutter

The topic of biosimilars remains the most controversial issue besetting the biopharmaceutical sector. Experience indicates that it takes 7–8 years to bring a biosimilar to market, at a cost of $100–250 million[3], although antibodies likely will cost more. Thus far, 11 different biosimilar active ingredients have been approved within Europe: two somatropins (human growth hormones, hGH), two erythropoietins (EPOs), four filgrastims (G-CSFs), two follitropin alfas (follicle-stimulating hormones, FSHs) and, most recently, an antibody (**Table 4**). By commercial agreement, several of these products are registered under two or more trade names, yielding a total of 19 products by trade name, with each having its own Marketing Authorization.

Within the time surveyed in this article, European regulators approved five biosimilar product applications based upon four distinct active ingredients. Highlights include the approval of the first FSH-based biosimilar (manufactured by BioPartners, a Baar, Switzerland–based subsidiary of Polish biotech company Bioton) and the approval of the first biosimilar mAb, Inflectra/Remsima. These are anti-TNF-α biosimilars of Janssen Biotech's (New Brunswick, NJ, USA) Remicade (infliximab) marketed by Hospira (Lake Forest, IL, USA; Inflectra) and Celltrion (Seoul, South Korea; Remsima) (**Box 3**).

The European experience should also temper commercial expectations for biosimilars in developed markets like the US and Japan. After an initial burst of approvals from 2006–2008, the EU approval rate has slowed and is faltering, certainly relative to hype that so often surrounds the topic. In the current survey

period, there was but one approval in 2010 (Hospira's Nivestim; filgrastim), two in 2013 (Teva's Ovaleap, follitropin alfa) and Hospira's Inflectra and Celltrion's Remsima) and one this year (Balzers, Liechtenstein-based Finox Biotech's Bemfola, FSH)—hardly the opening of the biosimilars' floodgate as some had predicted. Initial market penetration was slow for most products and total sales are modest, though recent data from information consultants IMS Health (Parsippany, NJ, USA) suggest that total 2013 biosimilar sales in the main EU markets stood at around $360 million, with total global sales reaching ~$676 million or 0.4% of the total global biological market[4].

Our survey period also witnessed two biosimilar withdrawals, Filgrastim ratiopharm, (Ratiopharm, Germany) and Valtropin (somatotropin, BioPartners), both for commercial reasons, though neither had been actively marketed in the EU since initial approval. On the positive side, however, European market penetration appears to have finally taken hold. By the end of 2012, biosimilar versions had gained almost 41% of the EU filgrastim market and 19% of the short-acting EPO market, up from start-of-year percentages of 30% and 15%, respectively[5]. Furthermore, none of the products approved has raised unexpected safety issues, and biosimilar prices in the EU have, on average, come in at a 30% discount relative to their reference products[3].

Building on its experiences, including lessons learned from the first wave of biosimilar approvals, the European Medicines Agency (EMA; London) has continued to update and expand their biosimilar guidelines (available at

Box 3 Europe's first biosimilar mAb

On September 10, 2013, the European Commission (Brussels) issued a European Marketing Authorization for the EUs first biosimilar mAb (infliximab) to two companies: Celltrion (under trade name Remsima) and Hospira (Inflectra). It is expected that the product launch will be delayed until Remicade's patent protection expires in early 2015 (**Table 3**).

European biosimilar regulations require the generation of comparative data between the biosimilar and the already approved reference product to which it claims biosimilarity (in this case, Janssen Biotech's Remicade, an $8-billion chimeric mAb that binds TNF-α and is approved to treat a range of TNF-driven inflammatory conditions, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis.

An EU biosimilar marketing authorization application (MAA), relative to a standard MAA, requires a full quality module, which also incorporates comparative quality analysis, as well as reduced comparative clinical and nonclinical data modules. Guiding the development process are various overarching EMA biosimilar guidelines, along with mAb-product-specific guidelines relating to clinical and nonclinical data requirements. Product development effectively occurred in parallel with development of the latter mAb-specific guidelines, which came into effect in December 2012.

EMA regulatory documents provide an insight into the core data and comparative studies that underpinned the biosimilarity approval decision. Both the reference and biosimilar products are expressed in Sp2/0 cell lines. Both share core downstream processing elements, including a protein A capture step, as well as ion exchange and ultrafiltration steps. The finished product composition, strength, route of administration, dosage regimen and indication range is also the same for both products.

Heavy (H) and light (L) chain mass values were determined by liquid chromatography electrospray ionization mass spectrometry (LC-ES-MS). The primary amino acid sequence of both products was shown to be identical using a combination of analytical approaches, including peptide mapping with LC-MS analysis and N- and C-terminal sequencing by tandem MS. Having an identical amino acid sequence to the reference product is in practice an essential EU requirement for biosimilarity; amino acid variations for several other biosimilar candidates have been reported[18].

Each infliximab product heavy chain consists of 450 amino acids and each L chain 214. Disulfide bond locations were determined using peptide mapping under native and reduced conditions. Higher order structures of both products were found to be comparable; higher order structural analysis was undertaken using circular dichroism and Fourier transform infrared spectroscopy as well as X-ray crystallography of the product's Fc domains. Crystallographic studies yielded identical unit cell dimensions and superimposition of all Cα atoms between the two structures.

Comparative structural analysis also incorporated post-translational modifications that, in addition to glycosylation, included C-terminal lysine variability, deamidation and oxidation, which were assessed by methods including isoelectric focusing, liquid chromatography and mass spectrometry. Some differences in the proportion of molecules with and without C-terminal lysines was observed between the two products, but some heterogeneity in C-terminal lysine content is expected with mAbs and the differences observed were considered not clinically relevant and acceptable. Comparative glycoanalysis confirmed the presence of a single N-linked oligosaccharide chain attached at Asn300 of the heavy chain of both products, and the absence of *O*-linked glycosylation. LC-MS analysis of appropriate peptides from peptide maps was used to determine oligosaccharide structures, attachment sites and distribution. Monosaccharide analysis was performed chromatographically subsequent to hydrolysis and high-performance anion exchange chromatography was used to resolve oligosaccharide structures and for sialic acid analysis. Overall oligosaccharide structures were found to be very similar though not identical. For example, Remsima exhibited lower levels of afucosylated glycans than Remicade. This could lower antibody-dependent, cell-mediated cytotoxicity activity through reduced binding affinity for the FcγRIIIa receptor but no actual differences were found by subsequent comparative assessment using clinically relevant assays. The primary mode of infliximab action is, of course (Fab-mediated) direct TNFα binding and thus neutralization, as opposed to Fc-mediated effector activation. No differences considered clinically meaningful between the bioactivity of Remsima and Remicade were detected in *in vitro* assays. A suite of nonclinical pharmacokinetic and toxicity studies in rats also revealed no unacceptable differences between products.

Comparative clinical assessment was undertaken by two pivotal randomized, double-blind, multicenter trials: a comparative pharmacokinetic study in 250 ankylosing spondylitis patients, and an efficacy and safety equivalence trial involving a total of 606 patients with rheumatoid arthritis, with acceptable equivalence margins being attained. The trial results were extrapolated to all other Remicade-approved conditions, presumably on the basis that the therapeutic mode of action would be the same (TNF-α neutralization). However, the applicants also committed to conducting a further comparative study in patients with active Crohn's.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c). In the past few years, EMA developed or revised product-specific guidelines for biosimilar FSH and IFN-β products (enacted in 2013), for mAbs (in 2012) and EPOs (in 2010). Revisions to the original (2005) overarching guidelines on similar biological medicinal products, aimed at clarifying the principle of biosimilarity and spelling out the requirements to demonstrate biosimilarity, are nearly completed, although the final guideline has yet to be published.

During our survey period, several other countries have enacted a biosimilar approval framework, including various Latin American countries and the United States. Although a first US biosimilar product has yet to be approved, the first biosimilar biological license application (BLA) was submitted to the FDA in July of this year (Novartis' biosimilar filgrastim product Zarzio). Even more interestingly, Celltrion filed for US FDA approval of its biosimilar mAb, Resima, in August. At least 17 investigational new drug applications for biosimilar development programs have been received by the FDA's Center for Drug Evaluation and Research, including 10 in 2013 alone. What's more, some companies developing biosimilars have decided to file full BLAs, as demonstrated by the FDA approval of the filgrastim product Granix (TBO-filgrastim, Teva) by this route in 2012, the same product having been approved (under the trade name Tevagrastim) as a biosimilar in Europe in 2008.

The extent to which biosimilars will perform in the United States likely will be dictated by myriad factors, such as how high the biosimilars approval bar will be set by the FDA, physician acceptance, whether automatic substitution will be allowed at the state and federal level, and the response of the originator companies, both at a commercial and a product innovation level. It is perhaps no wonder that estimates of intermediate-term biosimilar sales potential range widely—from $2 billion to $20 billion by 2020 (ref. 6). The positive overall experiences now accrued in highly regulated markets where biosimilars are already available may also provide US healthcare players with sufficient reassurance to facilitate rapid market acceptance.

A gene therapy product at last!

Data provided by *The Journal of Gene Medicine* (http://www.abedia.com/wiley) indicate that 1,992 gene therapy clinical trials have been approved worldwide since 1989, with almost two-thirds (63.9%) based in the United States and a quarter (25.8%) in Europe. Within this survey period, the approval of the first such product in the Western world—UniQure's (Amsterdam) Glybera (alipogene tiparvovec)—represents a historic benchmark for gene-based medicines (**Box 4**).

Glybera's regulatory approval was anything but smooth sailing. The initial marketing application was submitted in December 2009, with the EMAs Committee for Medicinal Products for Human Use (CHMP) recommending refusal of marketing authorization in June 2011, citing a lack of sufficiently convincing data as to the product's long-term efficacy. The company appealed but the CHMP maintained its initial opinion. Following a January 2012 request from the European Commission, the CHMP reassessed its opinion specifically in the context of a subcohort of patients; those displaying severe or multiple pancreatitis attacks, despite dietary fat restrictions. The CHMP finally recommended granting a marketing authorization under exceptional circumstances for that cohort.

Within the nucleic acid space, the period of our survey also witnessed the approval of Isis Pharmaceuticals' (Carlsbad, CA, USA) Kynamro (mipomersen sodium), a 20-nucleotide 2′-*O*-(2-methoxy) ethyl–modified ribose antisense oligonucleotide that binds ApoB mRNA for use in homozygous familial hypocholesterolemia. Although chemically synthesized (as opposed to being produced by recombinant DNA technology), antisense products have historically been included under the biopharmaceutical umbrella. At present, a dozen or more such products have reached mid- or late-stage clinical trials, although a blockbuster molecule is still awaited.

Expanding flavors of mAb

Eleven of the 17 mAbs approved in the current survey period contain a novel active ingredient. Of these, three products are of particular note in terms of technological innovation. Kadcyla (trastuzumab emtansine; Roche/Genentech, Basel) and Adcetris (brentuximab vedotin; Seattle Genetics, Seattle, WA, USA) are newly approved conjugated mAbs; Gazyva (US)/Gazyvaro (EU) (obinutuzumab, Roche/Genentech) is the first glycoengineered antibody to gain approval.

Antibody-drug conjugates (ADCs) are not in themselves new. Mylotarg (gemtuzumab zogamicin; Wyeth, Madison, NJ, USA) was a prototypic ADC, approved back in 2000 (although subsequently withdrawn from the market a decade later due to safety concerns and somewhat underwhelming clinical efficacy). Mylotarg comprised a bacterial toxin (calicheamicin) conjugated to a humanized antibody, targeting the CD33 antigen found on leukemic blast cells and was indicated in the treatment of acute myeloid leukemia. In the intervening years considerable progress has been made in understanding important

Box 4 Gene therapy (barely) makes the grade

Amsterdam-based UniQure's Glybera (alipogene tiparvovec) was approved for the treatment of lipoprotein lipase deficiency (LPLD) by the European Commission on September 25, 2012. LPLD is a rare inherited genetic condition (EU incidence of 0.02 per 10,000 persons) that is caused by mutations in the *LPL* gene, which encodes a key enzyme in the metabolism of circulating triglyceride-rich lipoproteins, with deficiency predictably characterized by high circulating levels of such lipoproteins. The most severe complication is pancreatitis, which can be recurrent and potentially lethal. Current treatment consists of severe dietary fat reduction, with most sufferers finding compliance to be extremely difficult.

Glybera is a replication-deficient, adeno-associated virus type 1 (AVV1) vector, containing a cytomegalovirus promoter and expressing a Ser447X variant of the human *LPL* gene with a woodchuck hepatitis virus post-transcriptional regulatory element and a bovine growth hormone polyadenylation sequence. The AAV capsid displays icosahedral symmetry and a diameter of ~25 nm.

The clinical program upon which Glybera safety and efficacy data was based consisted of three main open-label uncontrolled studies, involving a total of 27 LPL-deficient patients. Patients were administered a single dose of the product as a one-time series of intramuscular injections, with between a 12- and 18-week monitoring phase and follow up for up to five years. Pharmacokinetic studies revealed detectable LPL catalytic activity in 13 of 24 biopsied muscle samples, which were recovered from treated patients between 10 and 52 weeks after administration. The primary efficacy endpoint of the trials related to various threshold reductions in median fasting plasma triglyceride levels. Roughly 50% of treated patients exhibited substantial reductions in plasma triglyceride concentrations over the first several weeks to months, whereas follow-up data showed a subsequent return to baseline levels, suggesting a transient effect over the longer term.

Table 3 The 20 top-selling biopharmaceutical products in 2013

Ranking	Product	Sales ($ billions)[a]	Year first approved	Company	Patent expiry (EU)	Patent expiry (US)
1	Humira (adalimumab; anti-TNF)	11.00	2002	AbbVie & Eisai	2018	2016
2	Enbrel (etanercept; anti-TNF)	8.76	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015	2028
3	Remicade (infliximab; anti-TNF)	8.37	1998	J&J, Merck & Mitsubishi Tanabe Pharma	2015	2018
4	Lantus (insulin glargine)	7.95	2000	Sanofi	2014	2014
5	Rituxan/MabThera (rituximab; anti CD20)	7.91	1997	Biogen-IDEC, Roche	2013	2016
6	Avastin (bevacizumab; anti-VEGF)	6.97	2004	Roche/Genentech	2019	2017
7	Herceptin (anti-HER2)	6.91	1998	Roche/Genentech	2014	2019
8	Neulasta (pegfilgrastim)	4.39	2002	Amgen	2015	2014
9	Lucentis (ranibizumab; anti-VEGF)	4.27	2006	Roche/Genentech, Novartis	2016	2016
10	Epogen/Procrit/Eprex/ESPO (epoetin alfa)	3.35	1989	Amgen, J&J, KHK	Expired	2013
11	Novolog/Novorapid (insulin aspart)	3.13	1999	Novo	2015	2015
12	Avonex (IFN-β-1a)	3.00	1996	Biogen Idec	2015	2015
13	Humalog mix 50:50 (insulin lispro)	2.61	1996	Lilly	2015	2014
14	Rebif (IFN-β-1a)	2.59	1998	Merck Serono	2015	2013
15	Aranesp/Nesp (darbepoetin α)	2.42	2001	Amgen, KHK	2016	2024
16	Advate/Recombinate (Octocog α)	2.37	1992	Baxter		
17	Levemir (insulin detemir)	2.15	2004	Novo	[Levemir]	2014
18	Actrapid/Novolin (insulin)	2.02	1991	Novo	2017	
19	Erbitux (cetuximab; anti-EGF)	1.92	2004	Bristol-Myers Squibb, Merck Serono	2014	2016
20	Eylea (aflibercept; anti-VEGF)	1.88	2011	Regeneron, Bayer	2020	2021

[a]Financial data from LaMerie Business Intelligence. J&J, Johnson & Johnson

considerations pertaining to the development of truly effective ADCs, including appropriate target choice, antibody–conjugate partnering and conjugation chemistry[7].

Adcetris is a CD30-directed ADC, indicated for Hodgkin's lymphoma. The conjugated toxin is monomethyl auristatin E (MMAE), a tubulin disrupter, four molecules of which on average are attached to each antibody molecule. Binding of the ADC to CD30-expressing cells is followed by endocytotic internalization, with subsequent MMAE release by means of proteolytic cleavage.

Kadcyla is an anti-HER2 antibody to which a small cytotoxic molecule (DM1) has been conjugated. Like the parental Herceptin (trastuzumab) product, it is approved for the treatment of HER2-positive metastatic breast cancer. Its approval may also prove convenient for Genentech (S. San Francisco, CA, USA) in terms of staving off inevitable future biosimilar competition, now that Herceptin is nearing the end of patent protection (**Table 3**).

Genentech's Gazyva, which was approved by the FDA last year and in the EU this year, represents another milestone in mAb approvals, being the first glycoengineered mAb to come on the market in the United States. Gazyva's glycocomponent is enriched in nonfucosylated oligosaccharide variants, which enhances the mAb's antibody-dependent, cell-mediated cytotoxicity activity. Like Genentech's already well-established product Rituxan (rituximab), Gazyva targets the CD20 surface protein associated with B lymphocytes and is approved to treat chronic lymphocytic leukemia, one of Rituxan's main indications. Notably, head-to-head clinical trials showed it to be more effective than Rituxan[8]. In addition to the technical innovation, Gazyva will presumably also protect Genentech from inevitable future competition from Rituxan-based biosimilars. It should be noted that although Gazyva is a first in the United States, a glycoengineered, nonfucosylated mAb (Kayowa Hakko Kirin's Poteligeo (Tokyo; mogamulizumab)) has been on the Japanese market since 2012 for the treatment of T-cell leukemia-lymphoma.

Ongoing technological innovations in the mAb sector over the current period were not limited to ADC and glycoengineering. The period also witnessed continued engineering of the Fc domain, bispecific antibody development, antibody fragment technology, as well as continued efforts to develop recombinant polyclonal antibodies.

Fc-based protein engineering targeted at enhancing Fc function is exemplified by Xencor's (Monrovia, CA, USA) XmAb platform technology. The company has applied largely a bioinformatics-based approach to identify and subsequently replace specific amino acid residues playing critical roles in Fc function, thus modulating both effector functions and antibody half-life. Another format with several candidates in the pipeline is bispecific antibodies. This field was buoyed by the approval of Fresnius Biotech's Removab (Munich; catumaxomab) in 2010 (which was featured in our last benchmark's article[2]).

In terms of antibody fragments, thus far, two Fab fragments have been approved: Janssen Biotech's ReoPro (abciximab) and Genentech's Lucentis (ranibizumab). A trend toward development of smaller antigen-binding fragments, such as single-chain Fv (scFv) fragments, diabodies, minibodies and nanobodies is also evident. It is hoped that the small size of these formats may render them more straightforward to manufacture (and in nonmammalian systems), allow them to bind immune-silent targets (targets inaccessible to conventional large mAbs), and enable them to more readily penetrate through tissue and solid tumors. However, even if such advantages materialize in practice, such fragments suffer from a number of potential drawbacks, including lack of Fc effector function and short half-lives due to low mass and lack of Fc-based antibody recycling. The actual impact of such products on the biopharmaceutical armamentarium therefore remains to be seen.

Although recombinant polyclonal anti-

body preparations are by and large further back in product development, they may also prove useful additions to the biologic pharmacopeia. Polyclonal antibody preparations would display several advantages over mAbs, including the ability to simultaneously target several epitopes on the same or different antigens, thereby avoiding the emergence of resistance in cancer and infectious agents and making antigenic drift less likely to render antibody ineffective. Traditional blood-derived polyclonal preparations are characterized by heterogeneity and batch-to-batch variation, whereas recombinant-based polyclonal production could overcome such difficulties[9].

Special delivery

Parenteral administration remains the mainstay of products approved during the current survey period, although the period did witness the approval of one inhaled insulin product, Afrezza (MannKind; Valencia, CA, USA). An earlier inhaled insulin product (Pfizer's Exubera, approved in 2006) was taken off the market within a year, having been disappointing commercially. Underlining poor patient uptake was the rather cumbersome inhalation device along with concerns over the potential for compromised lung function—and potentially even an increased risk of lung cancer. The commercial success of Afrezza remains to be seen; certainly, the inhaler device design is much improved, but general concerns with regard to lung safety remain[10].

Nonparenteral delivery routes offer potentially increased patient convenience and safety, although they are not likely to radically alter the course of treatments in the near to mid-term. Almost 12 billion injections are administered annually, with unsatisfactory delivery leading to over 20 million infections and over 100 million adverse reactions annually. Attempts to develop alternative delivery routes for therapeutic proteins continue with oral delivery seen as particularly attractive[11]. Within this space, for example, Novo Nordisk continues to develop an oral insulin candidate using Merrion (Dublin) technology, whereas Oramed Pharmaceuticals (Jerusalem) are also pursing an oral insulin development program.

Future directions

Given drug discovery timelines and irrespective of technological innovations in the pipeline, it seems likely that approvals over the next few years will continue to be dominated by mAb-based products and by products synthesized using conventional expression systems and administered by means of conventional parenteral delivery. IMS Health projections suggest that biologic-based products will continue to gradually increase in terms of overall pharmaceutical market share (~18% in 2012 to ~20% in 2017), with growth dominated by mAbs and insulins. In terms of target indications, cancer and infectious diseases will continue to dominate the development pipeline.

Despite growing acceptance by the scientific and commercial community of the merits as well as the medical validity of biosimilars, their commercial success is not yet guaranteed. The next wave of biosimilars will target multibillion-dollar blockbuster brands, quite a number of which have lost, or will shortly lose, patent protection particularly from 2015 on (**Table 3**). Biosimilar mAbs, of which there were 73 in development in 2012, 9 having reached phase 3 (ref. 6), will be particularly prominent, boosted by the first such approval in the EU. The potential savings of even modest price discounts afforded by biosimilar competition to healthcare systems will be a strong commercial driver for such products. This will be particularly true in regions such as the United States, which accounts for approximately half of global biopharmaceutical sales, and in which the average daily cost of a biological product is $45 compared with $2 for chemical small-molecule drugs[12].

Whereas the approval of Glybera marks a watershed for gene therapy, it is unlikely to herald an avalanche of gene therapy approvals in the short to medium term. The clinical data supporting its approval were hardly overwhelming, and the largely transient nature of the beneficial effects provides some cause for concern for the field as a whole. It remains to be seen whether the million-dollar price tag for Glybera currently being touted will be sustainable, given shrinking healthcare budgets[13]. Moreover, no more than a handful of gene therapy products are in active, late-stage (phase 3) clinical trials. Examples include Advantagene's (Auburndale, MA, USA) ProstAtak (a replicative-defective human adenovirus type 1–expressing herpes simplex virus 1 (HSV-1) thymidine kinase combined with the oral prodrug valacyclovir) for prostate cancer, Cardium Therapeutics' (San Diego) Generx (a replication-deficient human adenovirus serotype 5 that encodes human fibroblast growth factor 4; FGF4) for myocardial ischemia, and Amgen's (Thousand Oaks, CA, USA) oncolytic herpes simplex virus (talminogene laherparepvec; an HSV-1 engineered to express GM-CSF together with pro-apoptotic deletions in *ICP47* and *ICP34.5* and expression of immediate-early gene *US11* that enhanced selectivity for cancer cells) for malignant melanoma.

The ongoing breadth and depth of research and innovation within the antibody engineering field ensures that mAb-based products will remain the most prominent class of biopharmaceuticals for the foreseeable future. In fact, the sheer range of technological innovations being pursued will likely result in a measure of technological competition within the field. Only time will tell which technologies will underpin the most successful future wave of innovative products. Advances in antibody–drug conjugate design and development has stimulated renewed interest in this area, with over 30 such products now in clinical development. Assuming satisfactory clinical performance, several such products are likely to make it to market over the next few years, along with some promising antibody fragments.

In the area of regenerative medicine, several products based upon tissue-extracted, fully differentiated cells have already made it to market (e.g., Genzyme's (Cambridge, MA, USA) cultured autologous human chondrocytes combined with purified porcine-derived collagen; for a full list, see **Supplementary**

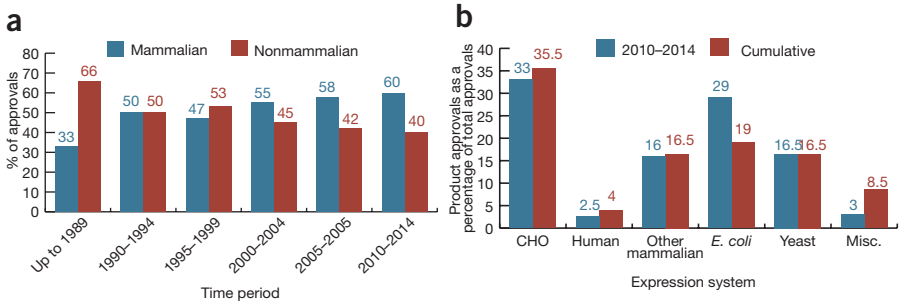

Figure 5 Expression systems used to manufacture biopharmaceutical products. (**a**) Relative application of mammalian versus nonmammalian-based expression systems in the production of biopharmaceuticals approved over the indicated periods. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question. (**b**) Product approvals, cumulative (1982–2014) and for period of this study (2010–July 2014) in the context of expression systems employed. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question.

Table 4 Biosimilar products that have gained European Marketing Authorization within the EU.

Product type	Biosimilar brand	Reference product	Year approved	Marketing authorization sponsor	Manufacturer of active substance
Somatropin (hGH)	Omnitrope	Genotropin	2006	Sandoz (Kundl, Austria)	Sandoz (Kundl, Austria)
	Valtropin	Humatrope	2006 (withdrawn 2012)	Biopartners (Reutlingen, Germany)	LG Life Sciences (Jeonbuk-do, South Korea)
Epoetin alfa (EPO)	Binocrit	Eprex/Erypo	2007	Sandoz (Kundl, Austria)	Rentschler (Laupheim, Germany) & Lek (Menges, Slovenia)
	Epoetin alfa hexal		2007	Hexal (Holzkirchen, Germany)	
	Abseamed		2007	Medice Arzneimittel (Iserlohn, Germany)	
Epoetin zeta (EPO)	Retacrit		2007	Hospira (Warwickshire, UK)	Norbitec (Uetersen, Germany)
	Silapo		2007	Stada (Vilbel, Germany)	
Filgrastim (G-CSF)	Ratiograstim	Neupogen	2008	Ratiopharm (Ulm, Germany)	Sicor (Vilnius, Lithuania)
	Filgrastim ratiopharm		2008 (withdrawn 2011)	Ratiopharm (Ulm, Germany)	
	Biograstim		2008	AbZ pharma (Ulm, Germany)	
	Tevagrastim		2008	Teva (Radebeul, Germany)	
	Zarzio		2009	Sandoz (Kundl, Austria)	Sandoz (Kundl, Austria)
	Filgrastim hexal		2009	Hexal (Holzkirchen, Germany)	
	Nivestim		2010	Hospira (Warwickshire, UK)	Hospira (Zagreb, Croatia)
	Grastofil		2013	Apotex (Leiden, the Netherlands)	Intas Biopharmaceuticals (Gujarat, India)
Follitropin alfa (FSH)	Ovaleap	Gonal F	2013	Teva (Utrecht, the Netherlands)	Merckle Biotech, (Ulm, Germany)
	Bemfola		2014	Finox Biotech (Balzers, Liechtenstein)	Polymun Scientific Immunbiologische Forschung (Klosterneuburg, Austria)
mAb	Remsima	Remicade	2013	Celltrion Hungary Budapest, Hungary	Celltrion (Incheon, Korea)
	Inflectra		2013	Hospira (Warwickshire, UK)	

hGH, human growth hormone

Table 1). Even so, now several types of stem cell and stem cell–derived therapies are also making their way through development, with at least six such products reaching phase 3 trials (**Supplementary Table 2**)[14].

Overall, the current survey period has witnessed some notable milestones, including approval of the first biosimilar mAb, a first gene therapy product and the first product produced in a plant-based system. The number of product approvals and market value remains buoyant, and the current pipeline insures the sector will remain at the technological and commercial forefront of the pharmaceutical sector as a whole.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

Note: Any Supplementary Information are available in the online version of the paper.

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BIOPHARMACEUTICAL Benchmarks

nature biotechnology

Biopharmaceuticals approved in the United States and Europe up to end of July 2014 (listed consecutively from most recent approval in each class). Eight categories are shown: recombinant blood factors, recombinant thrombolytics and anticoagulants, recombinant hormones, recombinant growth factors, recombinant interferons and interleukins, recombinant vaccines, monoclonal antibody (mAb)–based products and miscellaneous recombinant products.

Table 1 Biopharmaceuticals approved in the United States and Europe (listed consecutively from the most recent approval in each class, with post-2010 registrations in bold and withdrawals in red)

Product	Company (location)	Therapeutic indication	Date approved
Recombinant blood factors			
Factor VIII			
Nuwiq (simoctocog alfa; rh blood factor VIII, produced in a human embryonic kidney cell line)	**Octapharma AB (Stockholm, Sweden)**	**Hemophilia A**	**2014 (EU)**
Eloctate (rh B-domain deleted factor VIII Fc fusion protein, produced in a HEK cell line)	**Biogen-Idec (Cambridge, MA, USA)**	**Hemophilia A**	**2014 (US)**
NovoEight (turoctocog alfa), rh factor VIII analog which, when activated, is structurally comparable to endogenous h factor VIIIa produced in a CHO cell line	**Novo Nordisk, (Bagsvaerd, Denmark and Plainsboro, NJ, USA)**	**Hemophilia A**	**2013 (EU & US)**
Xyntha (anti-hemophiliac factor), rh coagulation factor VIII produced in CHO cells	Pfizer/Wyeth (Philadelphia, PA)	Hemophilia A	2008 (US)
Advate (octocog α), rh factor VIII produced in CHO cells	Baxter (Vienna and Deerfield, IL, USA)	Hemophilia A	2004 (EU), 2003 (US)
Helixate NexGen (octocog α), rh factor VIII produced in BHK cells	Bayer (Berlin, Germany)	Hemophilia A	2000 (EU)
Refacto (Moroctocog-α), B-domain-deleted rh factor VIII produced in CHO cells)	Pfizer/Wyeth (Sandwich, UK)/ Genetics Institute (Cambridge, MA, USA)	Hemophilia A	1999 (EU), 2000 (US)
Kogenate/Helixate (anti-hemophiliac factor), rh factor VIII produced in BHK cells. Sold as Helixate by Aventis Behring through a license agreement	Bayer (Leverkusen, Germany, and Berkeley, CA, USA)	Hemophilia A	1993 (US), 2000 (EU)
Bioclate (anti-hemophiliac factor), rh factor VIII produced in CHO cells	Aventis Behring (King of Prussia, PA, USA)	Hemophilia A	1993 (US)
Recombinate (anti-hemophiliac factor), rh factor VIII produced in a CHO cell line)	Baxter Healthcare (Deerfield, IL, USA)/Genetics Institute	Hemophilia A	1992 (US)
Other blood factors			
Alprolix (rh factor IX fused to a human IgG_1 F_C domain), produced in a HEK cell line	**Biogen Idec**	**Hemophilia B**	**2014 (US)**
Rixubis (rh factor IX), produced in CHO cell line	**Baxter Healthcare**	**Hemophilia B**	**2013 (US)**
Tretten (USA); (NovoThirteen in EU); (Catridecog), rh factor XIII A-subunit, produced in *Saccharomyces cerevisiae*	**Novo Nordisk**	**Congenital factor XIII A-subunit deficiency**	**2012 (EU), 2013 (US)**
Recothrom (thrombin) rh factor IIa, produced in CHO cells	Bristol-Meyers Squibb (BMS); Princeton, NJ, USA)/ Zymogenetics (Seattle, WA, USA)	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 and US)
Recombinant thrombolytics, anticoagulants and other blood-related products			
Tissue plasminogen activator (tPA)			
Metalyse (tenecteplase), TNK-tPA, modified rh tPA produced in CHO cells	Boehringer Ingelheim (Ingelheim, Germany)	Myocardial infarction	2001 (EU)
TNKase (tenecteplase) modified rh tPA produced in CHO cells	Roche/Genentech (S. San Francisco, CA, USA)	Myocardial infarction	2000 (US)
Ecokinase (Reteplase) rh 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) rh tPA; see Ecokinase)	Actavis group PTC (Hafnarfjordur, Iceland)/Roche	Acute myocardial infarction	1996 (EU)
Retavase (Reteplase, rh tPA; see –Ecokinase)	Chiesi (Cary, NC, USA)	Acute myocardial infarction	1996 (US)
Activase (Alteplase, rh tPA produced in CHO cells)	Roche/Genentech (S. San Francisco)	Acute myocardial infarction	1987 (US)
Hirudin			
Refludan (lepirudin) rh hirudin produced in *S. cerevisiae* (anticoagulant)	Bayer Healthcare (Leverkusen, Germany)	Anticoagulation therapy for heparin-associated thrombocytopenia	1997 (EU), 1998 (US) Withdrawn (EU) 2012
Revasc (desirudin), rh hirudin produced in *S. cerevisiae* (anticoagulant)	Canyon Pharmaceuticals, (London)	Prevention of venous thrombosis	1997 (EU)
Other			
Jetrea (ocriplasmin) recombinant truncated form of human plasmin, produced in *Pichia pastoris*	**ThromboGenics (Leuven, Belgium)**	**Symptomatic vitreomacular adhesion/vitreomacular traction**	**2013 (EU) 2012 (US)**
***Ruconest (conestat alfa), rh- complement C1 esterase inhibitor, produced in the milk of transgenic rabbits**	**Salix/Santarus (Raleigh, NC, USA), Pharming (Leiden, the Netherlands)**	**Acute angioedema**	**2014 US 2010 (EU)**
Atryn (rh antithrombin), from milk of transgenic goats	GTC Biotherapeutics London, UK), Ovation Pharmaceuticals (Deerfield, IL, USA)	Hereditary antithrombin deficiency	2009 (US), 2006 (EU)
Kalbitor (ecallantide), rh plasma kallikrein inhibitor, produced in *P. pastoris*	Dyax (Cambridge, MA, USA)	Hereditary angioedema	2009 (US)
Xigris (drotrecogin-α), rh activated protein C produced in a human cell line	Eli Lilly (Houten, the Netherlands)	Severe sepsis	2001 (US), 2002 (EU) Withdrawn 2011
Recombinant hormones			
Insulin			
Afrezza (rh insulin, produced in *E. coli*)	**MannKind (Danbury, CT, USA)**	**Diabetes mellitus**	**2014 (USA)**
Tresiba (insulin degludec), engineered long-acting human insulin analog, produced in *S. cerevisiae* (see also Ryzodeg entry)	**Novo Nordisk**	**Diabetes**	**2013 (EU)**
Ryzodeg (insulin degludec/insulin aspart), combination of 2 engineered insulins, produced in *S. cerevesiae*	**Novo Nordisk**	**Diabetes**	**2013 (EU)**
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 (rhInsulin produced in *E. coli*)	Sanofi (Frankfurt, Germany)	Diabetes mellitus	2007 (EU)
Exubera (inhalable rh insulin produced in *E. coli*)	Pfizer (Sandwich, UK)	Diabetes mellitus	2006 (EU and US) Withdrawn 2008
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, Germany)	Diabetes mellitus	2004 (EU and US)
Actrapid/Velosulin/Monotard/Insulatard/Protaphane/Mixtard/ Actraphane/Ultratard (all contain rh insulin produced in *S. cerevisiae* formulated as short/intermediate/long-acting product)	Novo Nordisk	Diabetes mellitus	2002 (EU) Withdrawn (Monotard and Ultratard) 2006 (Velosulin) 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, short-acting rh insulin analog as one ingredient, produced in *S. cerevisiae* (see also Novomix)	Novo Nordisk	Diabetes mellitus	2001 (US)
Novomix 30 (contains insulin aspart, short-acting rh insulin analog, produced in *S. cerevisiae*, as one ingredient)	Novo Nordisk	Diabetes mellitus	2000 (EU)
Lantus (insulin glargine), long-acting rh insulin analog, produced in *E. coli*	Sanofi (Frankfurt, Germany)	Diabetes mellitus	2000 (EU and US)
Optisulin (insulin glargine), long-acting rh insulin analog, produced in *E.coli* (see also Lantus entry)	Sanofi (Frankfurt, Germany)	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	2001 (EU)
Insuman (rh insulin), produced in *E. coli*	Sanofi (Frankfurt, Germany)	Diabetes mellitus	1997 (EU)
Humalog (insulin lispro, rh insulin analog), produced in *E. coli*	Eli Lilly (Houten, the Netherlands)	Diabetes mellitus	1996 (EU and 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	Diabetes mellitus	1982 (US)
Human growth hormone			
Somatropin Biopartners (somatropin), rh growth hormone, produced in *S. cerevisiae*	**BioPartners (Reutlingen, Germany)**	**Growth failure/growth hormone deficiency**	**2013 (EU)**
Accretropin (somatropin) rhGH produced in *E. coli*	Emergent Biosolutions (Rockville, MD, USA)/Cangene (Winnipeg, MB, Canada)	Growth failure or short stature associated with Turner syndrome in pediatric patients	2008 (US)
Valtropin (somatropin) biosimilar r hGH produced in *S. cerevisiae*	Biopartners (Reutling, Germany), LG Life Sciences (Korea)	Certain forms of growth disturbance in children and adults	2007 (US), 2006 (EU) Withdrawn 2012 (EU)
Omnitrope (somatropin) biosimilar (in EU) r hGH produced in *E. coli*	Sandoz (Kundl, Austria)/Novartis (Princeton, NJ, USA)	Certain forms of growth disturbance in children and adults	2006 (EU and US)
Somavert (pegvisomant) PEGylated r hGH analog (antagonist) produced in *E. coli*	Pfizer (Sandwich, UK)/Nektar Therapeutics (San Francisco)	Acromegaly	2003 (US), 2002 (EU)
Nutropin AQ (r hGH produced in *E. coli*), different formulation of Nutropin—see later entry	Ipsen Pharma (Boulogne-Billiancourt, France)	Growth failure/Turner's syndrome	2001 (EU) Withdrawn (EU) 2008, (US) 1994
Serostim (somatropin), r hGH, produced in a mouse C127 cell line	EMD Serono (Geneva)	AIDS-associated catabolism/wasting	1996 (US)
Saizen (somatropin), r hGH, produced in a mouse C127 cell line	EMD Serono	hGH deficiency in children	1996 (US)
Genotropin (somatropin), r hGH produced in *E. coli*	Pfizer	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 USA (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	hGH deficiency in children	1987 (US)
Protropin (somatropin), r hGH, differs from hGH only in containing an additional N-terminal methionine residue, produced in *E. coli*	Genentech	hGH deficiency in children	1985 (US) Withdrawn 2004
Follicle-stimulating hormone			
Ovaleap (follitropin alfa), biosimilar rh FSH, produced in a CHO cell line	**Teva Pharma (Utrecht, the Netherlands)**	**Infertility/subfertility**	**2013 (EU)**
***Elonva (corifollitropin alfa), a modified rh FSH in which the carboxy-terminal peptide of the β subunit of hCG is fused to the FSH β chain produced in CHO cells**	**Merck Sharp Dohme (MSD; Hoddesdon, UK)**	**Controlled ovarian stimulation**	**2010 (EU)**
Fertavid (follitropin β), rh FSH produced in CHO cells. Active identical to 'Puregon'	MSD (Hoddesdon, UK)	Infertility	2009 (EU)
Pergoveris (follitropin α/lutropin α), combination product containing rh FSH and rh LH, both produced in CHO cells	Merck Serono (London)	Stimulation of follicular development in women with severe LH and FSH deficiency	2007 (EU)
Follistim (follitropin-β), rh FSH produced in CHO cells)	Merck (Whitehouse Station, NJ, USA)	Infertility	1997 (US)
Puregon (follitropin-β) rh FSH produced in CHO cells)	N.V. Organon (Oss, the Netherlands)	Anovulation and superovulation	1996 (EU)
Gonal F (follitropin-α), rh FSH produced in CHO cells)	Merck Serono (London); EMD Serono (Rockland, MD, USA)	Anovulation and superovulation	1995 (EU), 1997 (US)
Other hormones			
Myalept (metreleptin), rh leptin analog, produced in *E. coli*	**AstraZeneca (London)/Amylin**	**Some forms of lipodystrophy**	**2014 (US)**
Gattex (in US)/Revestive (in EU); (teduglutide), rh GLP-2 analog, produced in *E. coli*	**NPS Pharma (Dublin)**	**Short bowel syndrome**	**2012 (US and EU)**
Victoza (liraglutide), a GLP-1 analog with attached fatty acid, produced in *S. cerevisiae	**Novo Nordisk**	**Type 2 diabetes**	**2010 (US), 2009 (EU)**
Preotact, rh parathyroid hormone, produced in *E. coli*	NPS Pharma (Dublin)	Osteoporosis	2006 (EU)
Fortical (r salmon calcitonin), produced in *E. coli*	Upsher-Smith Laboratories (Minneapolis, MN, USA)/Unigene (Fairfield, NJ, USA)	Postmenopausal osteoporosis	2005 (US)
Luveris (lutropin α) rh leutinizing hormone produced in CHO cells	EMD Serono	Some forms of infertility	2004 (US) 2000 (EU)
Forsteo(EU)/Forteo (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 (EU)/Ovidrel (US) (choriogonadotropin-α) rhCG produced in CHO cells)	Merck/EMD Serono (London)	Selected assisted reproductive technologies	2001 (EU) 2000 (US)
Thyrogen (thyrotrophin-α), rhTSH 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 (Bushey Herne, UK)	Paget's disease	1999 (EU) Withdrawn 2008
Glucagen (rh glucagon), produced in *S. cerevisiae*	Novo Nordisk	Hypoglycemia	1998 (US)
Glucagon (glucagon, recombinant), rhGlucagon, produced in *E. coli*	Eli Lilly	Hypoglycemia	1998 (US)
Recombinant growth factors			
Erythropoietin			
Biopoin (epoetin theta), rhEPO produced in CHO cells	Teva (Ulm, Germany)	Anemia	2009 (EU)
Eporatio (epoetin theta), rhEPO produced in CHO cells	Teva	Anemia	2009 (EU)
Abseamed (epoietin-α), a biosimilar rhEPO produced in CHO cells	Medice Arzneimittel Putter (Iserlon, Germany)	Anemia associated with chronic renal failure	2007 (EU)
Binocrit (epoetin-α), a biosimilar rhEPO produced in CHO cells	Sandoz (Kundl, Austria)	Anemia associated with chronic renal failure	2007 (EU)
Epoetin ω Hexal (epoietin-α), biosimilar a rhEPO produced in CHO cells	Hexal (Holzkirchen, Germany)	Anemia associated with chronic renal failure	2007 (EU)
Mircera (methoxy polyethylene glycol-epoetin β), PEGylated rh EPO produced in CHO cells	Roche (Welwyn Garden City, UK)	Anemia associated with chronic kidney disease	2007 (EU and US)
Retacrit (epoetin zeta), a biosimilar rh EPO produced in CHO cells	Hospira (Royal Leamington Spa, UK)	Anemia associated with chronic renal failure	2007 (EU)
Silapo (epoetin zeta), a biosimilar rh EPO produced in CHO cells	Stada (Bad Vibel, Germany)	Anemia associated with chronic renal failure	2007 (EU)
Aranesp (darbepoetin α), long-acting rEPO analog produced in CHO cells	Amgen (Breda, the Netherlands; EU)	Anemia	2001 (EU and US)
Nespo (darbepoetin α; see also Aranesp) long-acting rEPO analog produced in CHO cells	Pomme Biotec (Milan, Italy)	Anemia	2001 (EU) Withdrawn 2008
Neorecormon (epoietin β), rh EPO produced in CHO cells	Roche (Welwyn Garden City, UK)	Anemia	1997 (EU)
Procrit (epoietin-α), rh EPO produced in a mammalian cell line	Janssen Biotech (Horsham, PA, USA)	Anemia	1990 (US)
Epogen (epoietin-α), rh EPO produced in a CHO cell line	Amgen	Anemia	1989 (US)
Colony-stimulating factors			
Grastofil (biosimilar filgrastim), rh G-CSF produced in *E. coli*	**Apotex (Leiden, the Netherlands)**	**Neutropenia**	**2013 (EU)**
Lonquex (lipegfilgrastim), PEGylated rh G-CSF produced in *E. coli*	**Teva Pharmaceuticals (Utrecht, the Netherlands)**	**Neutropenia**	**2013 (EU)**
Granix (tbo-filgrastim) (rh G-CSF produced in *E. coli*) (Note: this is identical to the product 'Tevagrastim', approved as a biosimilar in EU in 2008; see Tevagrastim entry below)	**Teva (Frazer, PA, USA)/Cephalon (Malvern, PA, USA)**	**Neutropenia**	**2012 (US)**
***Nivestim (biosimilar filgrastim, rhG-CSF produced in *E. coli*)**	**Hospira (Lemington Spa, UK)**	**Neutropenia**	**2010 (EU)**
Filgrastim hexal biosimilar filgrastim, rh G-CSF produced in *E. coli*)	Hexal (Holzkirchen, Germany)	Neutropenia	2009 (EU)
Zarzio (biosimilar filgrastim, rh G-CSF produced in *E. coli*)	Sandoz (Kundl, Austria)	Neutropenia	2009 (EU)
Biograstim (biosimilar filgrastim, rh G-CSF produced in *E. coli*)	ABZ pharma (Ulm, Germany)	Neutropenia	2008 (EU)
Ratiograstim (biosimilar filgrastim; rh G-CSF produced in *E. coli*)	Ratiopharm (Ulm, Germany)	Neutropenia	2008 (EU)
Tevagrastim (biosimilar filgrastim, rh G-CSF produced in *E. coli*)	Teva (Radebeul, Germany)	Neutropenia	2008 (EU)
Filgrastim ratiopharm (biosimilar filgrastim; rh G-CSF produced in *E. coli*)	Ratiopharm (Ulm, Germany)	Neutropenia	2008 (EU) Withdrawn 2011
Neulasta (pegfilgrastim), PEGylated rh G-CSF. Also marketed in EU as Neupopeg	Amgen (Breda, the Netherlands)	Chemotherapy-induced neutropenia	2002 (EU and US) Withdrawn (EU, Neupopeg) 2008
Leukine (sargramostim), rh GM-CSF, differs from the native human protein by one amino acid, R23→L; produced in *E. coli*	Sanofi/Berlex Laboratories	Autologous bone marrow transplantation	1991 (US) Withdrawn 2008 and reformulated without EDTA since 2008
Neupogen (filgrastim), rh G-CSF differs from human protein by containing an additional N-terminal methionine; produced in *E. coli*	Amgen	Chemotherapy-induced neutropenia	1991 (US)
Other growth factors			
Increlex (mecasermin), rh IGF-1 produced in *E.coli*	Ispen Pharma (Boulogne-Billancourt, France) (formerly Tercica, Brisbane, CA, USA)	Growth failure in children with IGF-1 deficiency or GH gene deletion (long-term treatment)	2007 (EU), 2005 (US)
IPlex (mecasermin rinfabate), a complex of rh IGF-1 and rh IGFBP-3 produced separately in *E. coli*	Insmed (Glen Allen, VA, USA)	Growth failure in children with severe primary IGF-1 deficiency or GH gene deletion (long-term treatment	2005 (US) Withdrawn 2007 for IGF-1 deficiency as per lawsuit filed by Genentech and Tercia
Kepivance (palifermin), a rh KGF produced in *E. coli*	Swedish Orphan Biovitrum (Stockholm, Sweden) (acquired from Amgen since last listed)	Severe oral mucositis in selected patients with hematologic cancers	2005 (EU) 2004 (US)
GEM 21S (growth factor enhanced matrix; contains rh PDGF-BB (Regranex—see entry below) and tricalcium phosphate)	BioMimetic Pharmaceuticals (Franklin, TN, USA)	Periodontally related defects	2005 (US)
Regranex (becaplermin), rh PDGF-BB produced in *S. cerevisiae*	Novartis/Johnson & Johnson (Raritan, NJ, USA)	Lower extremity diabetic neuropathic ulcers	1997 (US) 1999 (EU) Withdrawn (EU) 2012
Recombinant interferons, interleukins and tumor necrosis factors			
Interferon-α			
PEGintron/ribetol combo pack (peginterferon-α), PEGylated rh IFNα-2b produced in *E. coli* and ribavirin	Schering Plough (Kenilworth, NJ, USA)	Chronic hepatitis C	2008 (US)
Pegasys (PEGinterferon α-2a), produced in *E. coli*	Roche/Genentech (Welwyn Garden City, UK)	Hepatitis C	2002 (EU and US)
PegIntron (PEG rIFN-α-2b), produced in *E. coli*	Merck Sharp & Dohem (MSD, Hoddesdon, UK)	Chronic hepatitis C	2000 (EU) 2001 (US)
Viraferon (rIFN-α-2b), produced in *E. coli*)	Schering Plough (Brussels)	Chronic hepatitis B, C	2000 (EU) Withdrawn 2008
ViraferonPeg (PEG rIFN-α-2b), produced in *E. coli*	MSD (Hoddesdon, UK)	Chronic hepatitis C	2000 (EU)
Intron A (also known as Alfatronol) (rIFN-α-2b), produced in *E. coli*	MSD (Hoddesdon, UK)	Cancer, genital warts, hepatitis	1986 (US) 2000 (EU)
Rebetron (combination of ribavirin and rh IFN-α2b) produced in *E. coli*	Schering Plough	Chronic hepatitis C	1999 (US)
Infergen (interferon alficon-1), r IFN-α, synthetic type I IFN produced in *E. coli*	InterMune/Amgen	Chronic hepatitis C	1997 (US) 1999 (EU) Withdrawn (EU) 2006
Roferon A (rh IFN-α2a), produced in *E. coli*	Roche	Hairy cell leukemia	1986 (US) Withdrawn 2007
Interferons β & γ			
Plegridy (rh peginterferon beta 1a), produced in a CHO cell line	**Biogen Idec (Berkshire, UK)**	**Multiple sclerosis**	**2014 (EU)**
Extavia (interferon beta-1b), rh IFN-β1b produced in *E. coli*	Novartis	Multiple sclerosis	2009 (US) 2008 (EU)
Rebif (interferon-β1a), rh IFN-β1a, produced in CHO cells	EMD Serono (London)	Relapsing/remitting multiple sclerosis	2002 (US) 1998 (EU)
Avonex (interferon-β1a), rh IFN-β1a, produced in CHO cells	Biogen-IDEC (Maidenhead, UK)	Relapsing multiple sclerosis	1997 (EU) 1996 (US)
Betaferon (interferon-β-1b), r IFN-β1b, differs from human protein by C17→S, produced in *E. coli*	Bayer Pharma (Berlin)	Multiple sclerosis	1995 (EU)
Betaseron (rIFN-β1b), differs from human protein by C17→S, produced in *E. coli*	Bayer/Berlex Labs (Richmond, CA, USA)/Chiron (Emeryville, CA, USA)	Relapsing/remitting multiple sclerosis	1993 (US)
Actimmune (rh IFN-γ1b, produced in *E. coli*)	Vidara Therapeutics (Dublin)	Chronic granulomatous disease	1990 (US)

Table 1 (continued)

Product	Company (location)	Therapeutic indication	Date approved
Others			
Kineret (anakinra), rh IL-1 receptor antagonist produced in *E. coli*	Swedish Orphan Biovitrum/ Amgen	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), rh IL-11, lacks N-terminal proline of native molecule produced in *E. coli*	Pfizer/Genetics Institute	Prevention of chemotherapy-induced thrombocytopenia	1997 (US)
Proleukin (aldesleukin), rh IL-2, differs from human molecule in absence of an N-terminal alanine and contains C125→S substitution, produced in *E. coli*	Prometheus Therapeutics and Diagnostics (San Diego)/Chiron	Renal cell carcinoma	1992 (US)
Recombinant vaccines			
Hepatitis B			
Hexacima/Hexyon (multicomponent vaccine containing r HBsAg produced in Hansenula polymorpha as one component	Sanofi Pasteur (Lyon, France)	Immunization against several pathogens/toxins	**2013 (EU)**
Ambirix (combination vaccine, containing rHBsAg produced in *S. cerevisiae* as one component)	GlaxoSmithKline (GSK, Rixensart, Belgium)	Immunization against hepatitis A and B	2002 (EU)
Pediarix (combination vaccine containing rHBsAg produced in *S. cerevisiae* as one component)	GSK	Immunization of children against various conditions inducing hepatitis B	2002 (US)
HBVAXPRO (rHBsAg produced in *S. cerevisiae*)	Sanofi (Lyon, France)	Immunization of children and adolescents against hepatitis B	2001 (EU)
Twinrix (adult and pediatric forms in EU; combination vaccine containing rHBsAg produced in *S. cerevisiae* as one component)	GSK (Rixensart, Belgium)	Immunization against hepatitis A and B	2001 (US) 1996 (EU adult) 1997 (EU pediatric)
Infanrix Hexa (combination vaccine, containing rHBsAg produced in *S. cerevisiae* as one component)	GSK (Rixensart, Belgium)	Immunization against diphtheria, tetanus, pertussis, *Haemophilus influenzae* b and hepatitis B and polio	2000 (EU)
Infanrix Penta (combination vaccine, containing rHBsAg produced in *S. cerevisiae* as one component)	GSK (Rixensart, Belgium)	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 rHBsAg produced *S. cerevisiae* as one component)	Sanofi Pasteur (Lyon, France)	Immunization against diphtheria, tetanus, pertussis, hepatitis B, polio and *H. influenza*e type b	2000 (EU) Withdrawn 2012
Procomvax (combination vaccine, containing r HBsAg as one component)	Sanofi Pasteur (Lyon, France)	Immunization against *H. influenzae* type B and hepatitis B	1999 (EU) Withdrawn 2009
Primavax (combination vaccine, containing r HBsAg produced in *S. cerevisiae* as one component)	Sanofi Pasteur (Lyon, France)	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 rHBsAg produced in *S. cerevisiae* as one component)	GSK (Rixensart, Belgium)	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* type B and hepatitis B	1996 (US)
Tritanrix-Hep B (combination vaccine, containing r HBsAg produced in *S. cerevisiae* as one component)	GSK (Rixensart, Belgium)	Immunization against hepatitis B, diphtheria, tetanus and pertussis	1996 (EU) Withdrawn 2014
Recombivax (r HBsAg produced in *S. cerevisiae*)	Merck	Immunization against hepatitis B	1986 (US)
Other			
Bexsero (meningococcal group B vaccine, rDNA component, absorbed). Multicomponent subunit vaccine, produced in *E. coli*.	**Novartis (Siena, Italy)**	**Immunization against invasive meningococcal disease**	**2013 (EU)**
Flublok (recombinant hemagglutinin proteins from 3 influenza strains), produced in an *Spodoptera frugiperda* cells using baculovirus	**Protein Sciences (Meriden, CT, USA)**	**Immunization against influenza**	**2013 (US)**
***Provenge (sipuleucel-T, autologous peripheral blood mononuclear cells in combination with rh prostatic acid phosphatase–GM-CSF produced in an insect cell line)**	**Dendreon (London)**	**Prostate cancer**	**2013 (EU) 2010 (US)**
Cervarix (r, C-terminally truncated major caspid L 1 proteins from human papillomavirus types 16 and 18 produced in a baculovirus-based expression system)	GSK (Rixensart, Belgium)	Prevention of cervical cancer	2009 (US) 2007 (EU)
Gardasil (EU & US). Also marketed as Silgard in EU, (quadrivalent human papillomavirus (HPV) r vaccine; contains major capsid proteins from four HPV types, produced in *S. cerevisiae*)	In EU: Sanofi-Pasteur, Lyon France; (Gardisil), Merck	Therapeutic indication: vaccination against diseases caused by HPX	2006 (EU and US)
Dukoral (*Vibrio cholerae* and r cholera toxin B subunit)	Crucell Sweden (Stockholm, Sweden)	Immunization against disease caused by *V. cholerae* subunit 0 1	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 (mAb)-based products			
Entyvio (vedolizumab), humanized IgG targeting the human $\alpha 4\beta 7$ integrin, produced in CHO cells	**Takeda Pharma/Millennium (Deerfield, IL, for USA; Taastruup, Denmark, for EU)**	**Ulcerative colitis, Crohn's disease**	**2014 (US & EU)**
Sylvant (siltuximab), chimeric mAb that binds human interleukin-6, produced in a CHO cell line	**Janssen Biotech (Horsham, PA, USA)**	**Multicentric Castleman's disease**	**2014 (US & EU)**
Cyramza (ramucirumab), human mAb that binds the VEGF-2 receptor, produced in NS0 cell line	**Eli Lilly**	**Gastric cancer**	**2014 (US)**
Gazyva(US)/Gazyvaro (EU) (obinutuzumab), humanized glycoengineered mAb specific for CD20 expressed on B lymphocytes, produced in a CHO cell line	**Roche (Genentech)/ Roche, Welwyn Garden City, UK (EU)**	**Chronic lymphocytic leukemia**	**2014 (EU) 2013 (US)**
Inflectra/Remsima (infliximab), biosimilar, chimeric mAb specific for TNF-α, produced in Sp2/0 cell line	**Hospira (Royal Leamington Spa, UK; Inflectra) Celltrion (Budapest, Hungary (Remsima)**	**Arthritis, colitis, Crohn's, psoriasis, ankylosing spondylitis**	**2013 (EU)**
Kadcyla (trastuzumab emtansine), humanized mAb specific for HER-2 antigen, produced in CHO cell line and conjugated to the small-molecule cytotoxin, DM1	**Roche/Genentech (Welwyn Garden City, UK)**	**Breast cancer**	**2013 (EU and US)**
Simponi Aria (golimumab), identical active to that in Simponi (see below); different active strength and mode of administration	**Janssen Biotech**	**Rheumatoid arthritis**	**2013 (US)**
Perjeta (pertuzumab), human mAb specific for HER2, produced in a CHO cell line	**Roche/Genentech (Welwyn Garden City, UK)**	**Breast cancer**	**2013 (EU) 2012 (US)**
Abthrax (raxibacumab), human IgG mAb raised against the protective antigen (PA) of Bacillus anthracis, produced in a NS0 cell line	**GSK/Human Genome Sciences**	**Inhalational anthrax**	**2012 (US)**
Adcetris (brentuximab vedotin), chimeric mAb conjugate specific for human CD 30 (expressed on the surface of lymphoma cells), produced in a CHO cell line	**Takeda Pharma (Roskilde, Denmark)/Seattle Genetics**	**Lymphoma**	**2012 (EU) 2011 (US)**
Benlysta (belimumab), human mAb which targets human B-lymphocyte stimulator (BLyS), a B-cell survival factor, produced in an NS0 cell line	**Glaxo Group (Greenford, UK/ Human Genome Sciences (USA)**	**Lupus**	**2011 (US and EU)**
Xgeva (denosumab) (see Prolia entry)	**Amgen (Breda, the Netherlands)**	**Treatment of bone loss associated with cancer**	**2011 (EU) 2010 (US)**
Yervoy (ipilimumab), human mAb. Binds to CTLA-4 (a negative regulator of T-cell activation), thereby enhancing T-cell activation and proliferation, produced in CHO cell line	**Bristol-Myers Squibb (Uxbridge, UK)**	**Melanoma**	**2011 (US and EU)**
Actemra (US)/RoActemra (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/Genmab (Greenford, UK)**	**Chronic lymphocytic leukemia**	**2010 (EU) 2009 (US)**
Prolia (denosumab), human mAb specific for RANK ligand, produced in CHO cells	**Amgen (Breda, the Netherlands)**	**Osteoporosis in postmenopausal women**	**2010 (EU and US)**
Scintimun (besilesomab), murine mAb specific for NCA-95 found on surface of granulocytes, produced in hybridoma cells	**CIS Bio International (Gif sur Yvette Cedex, France)**	***In vivo* diagnosis/investigation of sites of inflammation/infection via scintigraphic imaging**	**2010 (EU)**
Cimzia (certolizumab pegol), anti-TNFα 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 interleukin-1β, produced in murine Sp2/0 cells	Novartis (Horsham, UK)/ Regeneron (Tarrytown, NY, USA)	Cryopyrin-associated periodic syndromes (CAPS)	2009 (EU and US)
Removab (catumaxomab), a bispecific engineered antibody produced in hybrid hybridoma cells	Neovii Biotech (Graefelfing, Germany)	Malignant ascites in patients with EpCAM positive carcinomas	2009 (EU)
Simponi (golimumab) human mAb specific for TNF-α, produced in Sp2/0 cells	Janssen Biotech (Beerse, Belgium)	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis	2009 (EU and US)
Stelara (ustekinumab), human mAb specific for the p40 subunit of IL-12 and IL-23, produced in Sp2/0 cells)	Janssen Biotech (Beerse, Belgium)	Moderate to severe plaque psoriasis	2009 (EU and 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), a humanized IgG that binds human C5 complement protein, produced in a murine myeloma cell line	Alexion (Cheshire, CT, USA, Paris)	Paroxysmal nocturnal hemoglobinuria	2007 (US and EU)
Vectibix (panitumumab), human mAb that binds to hEGFR, produced in a CHO cell line	Amgen (Breda, the Netherlands)/ Abgenix	EGFR-expressing colorectal carcinoma	2007 (EU) 2006 (US)
Tysabri (natalizumab), a humanized mAb raised against selected leukocyte alpha4 beta1/7 integrins, produced in a murine myeloma cell line	Biogen Idec (Maidenhead, UK)/ Elan	Relapsing forms of multiple sclerosis	2006 (EU) 2004 (US); 2005 suspended, 2006 resumed
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 targeted against the CD20 antigen, produced in CHO cells	Spectrum Pharmaceuticals (Amsterdam, the Netherlands)	Non-Hodgkin's lymphoma	2004(EU) 2002 (US)
Erbitux (cetuximab), chimeric mAb against human EGF receptor, produced in Sp2/0 cells	Merck/BMS/Lilly/Imclone Systems (New York)	EGF receptor-expressing metastatic colorectal cancer	2004 (EU and US)
Raptiva (efalizumab), humanized mAb that binds to LFA-1, which is expressed on all leukocytes; produced in CHO cells	Serono (London) Genentech (US)	Chronic moderate to severe plaque psoriasis in adults	2004 (EU) 2003 (US) Withdrawn 2009
Avastin (bevacizumab), humanized mAb raised 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 raised against CD 15 surface antigen of selected leukocytes, produced in hybridoma cells	Palatin Technolgies (Cranbury, NJ, USA)/Mallinckrodt (Hazelwood, MO, USA)		2004 (US) Withdrawn 2005
Humira (EU and US) was also sold as Trudexa in EU (adalimumab) (anti-TNF) human mAb produced in a CHO cell line	AbbVie (Maidenhead, UK)	Rheumatoid arthritis	2003 (EU) 2002 (US) Withdrawn (EU, Trudexa) 2003
Bexxar (tositumomab), radiolabeled mAb directed against CD20, produced in a murine hybridoma cell line	GSK	CD 20 positive follicular non-Hodgkin's lymphoma	2003 (US) Withdrawn 2014
Mabcampath (EU) or Campath (US) (alemtuzumab), humanized mAb directed against CD52 surface antigen of B-lymphocytes, produced in a CHO cell line	Genzyme (Naarden, the Netherlands), Millennium (Cambridge, MA, USA)	Chronic lymphocytic leukemia	2001 (EU and US) Withdrawn (EU) 2012
Mylotarg (gemtuzumab zogamicin) a humanized antibody-toxic antibiotic conjugate targeted against CD33 antigen found on leukemic blast cells, produced in an NS0 cell line	Wyeth (Madison, NJ, USA)	Acute myeloid leukemia	2000 (US) Withdrawn 2010
Herceptin (trastuzumab), humanized mAb directed against HER 2, produced in a murine cell line	Roche/Genentech (Welwyn Garden City, UK)	Treatment of metastatic breast cancer if tumor overexpresses HER2 protein	1998 (US) 2000 (EU)
Remicade (infliximab), chimeric mAb directed against TNF-α, produced in an Sp2/0 cell line	Janssen Biotech (Leiden, the Netherlands)	Crohn's disease	1998 (US) 1999 (EU)
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 (London) AstraZeneca	Prophylaxis of lower respiratory tract disease caused by syncytial virus in pediatric patients	1998 (US) 1999 (EU)
Zenapax (daclizumab), humanized mAb directed against the α-chain of the IL-2 receptor), produced in an NS0 cell line	Roche/(Welwyn Garden City, UK)/ Protein Design Labs	Prevention of acute kidney transplant rejection	1997 (US) 1999 (EU) Withdrawn (EU) 2009
Humaspect (votumumab), human mAb directed 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 (EU)/Rituxan (US) (rituximab), chimeric mAb directed against CD20 surface antigen of B lymphocytes, produced in a CHO cell line	Roche (Welwyn Garden City, UK)/ Biogen-Idec	Non-Hodgkin's 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 fragment (Fab) directed against NCA 90, a surface granulocyte nonspecific cross-reacting antigen, produced in an Sp2/0 cell line	Immunomedics (Darmstadt, Germany)	Diagnostic imaging for infection and inflammation in bone of patients with osteomyelitis	1997 (EU)
Verluma (nofetumomab), murine mAb fragments (Fab) 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, murine mAb fragments (Fab/Fab_2 mix) directed against HMW-MAA, produced in murine ascites culture	Amersham Sorin (Milan, Italy)	Diagnosis of cutaneous melanoma lesions	1996 (EU) Withdrawn 2000
ProstaScint (capromab pentetate), murine mAb-directed against the prostrate-specific membrane antigen (PSMA), produced in a murine cell line	EUSA Pharma/Cytogen (Princeton, NJ, 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 agent	1996 (US) Withdrawn 1999
CEA-scan (arcitumomab), murine mAb fragment (Fab), directed against human carcinoembryonic antigen, CEA, produced in mice ascites	Immunomedics (Darmstadt, Germany)	Detection of recurrent/metastatic colorectal cancer	1996 (EU and US) Withdrawn 2005
Indimacis 125 (igovomab), murine mAb fragment (Fab_2) directed against the tumor-associated antigen CA 125, 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, directed against the platelet surface receptor GPIIb/IIIa, 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 directed against the tumor-associated glycoprotein, TAG-72, produced in a murine cell line	Cytogen	Detection, staging and follow-up of colorectal and ovarian cancers	1992 (US) Withdrawn 2002
Orthoclone OKT3 (muromomab CD3), murine mAb directed against the T-lymphocyte surface antigen CD3, produced in a murine cell line	Janssen-Cilag/Ortho Biotech	Reversal of acute kidney transplant rejection	1986 (US)
Other recombinant products			
Bone morphogenetic proteins			
Opgenra (eptotermin α), rhBMP-7 produced in CHO cells	Olympus Biotech (Limerick, Ireland)	Posterolateral lumbar spinal fusion	2009 (EU)
Infuse bone graft (contains dibotermin-alfa, a rh BMP-2 produced in CHO cells placed on an absorbable collagen sponge. Note: this is the same active ingredient present in the product Infuse)	Wyeth (Madison, NJ, USA)	Acute open tibial shaft fracture	2004 (US)
Inductos (dibotermin alfa); rhBMP-2 produced in CHO cells	Medtronic BioPharma (Heerlen, the Netherlands); Genetics Institute (Cambridge, MA)	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 (US)/Osigraft (EU) (eptotermin alfa), rh BMP-7, produced in CHO cells	Olympus Biotech (Limerick, Ireland); Stryker Biotech (Hopkington, MA, USA)	Non-union of tibia	2001 (EU and US)
Recombinant enzymes			
Vimizim (elosulfase alfa), rh *N*-acetylgalactosamine-6-sulfatase, produced in a CHO cell line	**BioMarin (London)**	**Mucopolysaccharidosis IVA (Morquio A syndrome)**	**2014 (US and EU)**
Krystexxa (pegloticase), r urate oxidase, PEGylated post synthesis, produced in *E. coli*	**Savient (Dublin)/Crealta Pharmaceuticals (Lake Forest, IL, USA)**	**Gout**	**2013 (EU) 2010 (US)**
Elelyso (taliglucerase alfa) rh glucocerebrosidase, produced in engineered carrot root cell culture	**Pfizer/Protalix (Karmiel, Israel)**	**Gaucher disease**	**2012 (US)**
Voraxaze (glucarpidase) r carboxypeptidase, produced in *E. coli*	**BTG International**	**Treatment of 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 a CHO cell line**	**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 Genetics (Danderyd, Sweden)**	**Gaucher disease**	**2010 (US and EU)**
Elaprase (idursulfase), rh iduronate-2-sulfatase, produced in a human cell line	Shire Human Genetic Therapies (Danderyd, Sweden)	Mucopolysaccharidosis II (Hunter's syndrome)	2007 (EU) 2006 (US)
Naglazyme (galsulfase), rh *N*-acetylgalactosamine 4 sulfatase, produced in a CHO cell line	BioMarin (London)/ Novato, CA, USA	Long-term enzyme replacement therapy in patients suffering from Mucopolysaccharidosis VI	2006 (EU) 2005 (US)
Myozyme (algulcosidase α), rh acid glucosidase produced in CHO cells	Sanofi/Genzyme (Naarden, the Netherlands)	Pompe disease	2006 (EU and US)
Aldurazyme (laronidase), r-α-L-iduronidase produced in CHO cells	BioMarin	Long-term replacement in patients with mucopolysaccharidosis I	2003 (EU and US)
Hylenex (rh hyaluronidase), produced in CHO cells	Baxter/ 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 (Danderyd, Sweden)/TKT Europe	Fabry disease (α-galactosidase A deficiency)	2001 (EU)
Fasturtec (Elitex in US) (rasburicase), r urate oxidase, produced in *S. cerevisiae*	Sanof (Paris)	Hyperuricemia	2001 (EU) 2002 (US)
Cerezyme (imiglucerase), rh-β-glucocerebrosidase, produced in a CHO cell line	Sanofi/Genzyme (Naarden, the Netherlands)	Gaucher disease	1997 (EU) 1994 (US)
Pulmozyme (dornase-α), r DNase produced in CHO cells	Roche/Genentech	Cystic fibrosis	1993 (US)
Fusion proteins			
Eperzan (in EU)/ Tanzeum (in USA) (albiglutide), GLP-1 receptor agonist, a fusion protein consisting of two tandem copies of modified human GLP-1 to human albumin, produced in *S. cerevisiae*	**GSK (Cork, Ireland)**	**Type 2 diabetes**	**2014 (EU & US)**
Zaltrap (aflibercept), a combination drug containing a fusion protein, consisting of the extracellular ligand binding domains of VEGF receptors 1 and 2 fused to an IgG Fc, produced in a CHO cell line	**Regeneron/Sanofi (Paris)**	**Metastatic colorectal cancer**	**2013 (EU) 2012 (USA)**
Eylea (aflibercept). Same active biopharmaceutical active as in Zaltrap	**Regeneron/Bayer (Berlin)**	**Neovascular (wet) age-related Macular degeneration**	**2012 (EU) 2011 (USA)**
Nulojix (belatacept), a fusion protein consisting of the extracellular domain of human CTLA4 fused to IgG Fc. It binds CD80 and CD86 on antigen-presenting cells, thereby inhibiting T-cell activation, produced in a CHO cell line	**Bristol-Myers Squibb (Uxbridge, UK)**	**Prophylaxis of organ rejection following kidney transplant**	**2011 (USA and EU)**
Arcalyst (US)/Rilonacept (EU) (rilonacept) dimeric fusion protein with each monomer consisting of the ligand-binding domains of the hIL-1 receptor and the IL-1 receptor accessory protein, and the Fc region of h IgG-1, produced in CHO cells	Regeneron	Cryopyrin-associated periodic syndromes (CAPS)	2009 (EU) 2008 (US) Withdrawn (EU) 2012
Nplate (romiplostim), a dimeric fusion protein with each monomer consisting of two thrombopoietin receptor binding domains and the Fc region of hIgG-1, produced in *E. coli*	Amgen (Breda, the Netherlands)	Thrombocytopenia	2009 (EU), 2008 (US)
Orencia (abatacept), fusion protein which links the extracellular domain of human cytotoxic T-lymphocyte associated antigen-4 with modified Fc region of IgG1, produced in a mammalian cell line	BMS (Uxbridge, UK)	Rheumatoid arthritis	2007 (EU), 2005 (US)
Amevive (alefacept), dimeric fusion protein consisting of the extracellular CD2-binding portion of the human LFA-3 linked to the Fc region of human IgG1; produced in CHO cells	Astellas Pharma/Biogen-Idec	Moderate to severe chronic plaque psoriasis in adults	2003 (US) Withdrawn 2011
Enbrel (etanercept), rTNF receptor–IgG fragment fusion protein, produced in CHO cells	Amgen (Immunex)/Pfizer/Takeda	Rheumatoid arthritis	1998 (US) 2000 (EU)
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			
Kynamro (mipomersen sodium) an 2'-*O*-(2-methoxy) ethyl–modified ribose antisense oligonucleotide)	**Sanofi/Isis (Carlsbad, CA, USA)**	**Familial hypercholesterolemia**	**2013 (USA)**
Glybera (alipogene tiparvovec), h *LPL* gene housed in an engineered AAV1 vector	**uniQure (Amsterdam, the Netherlands)**	**Lipoprotein lipase deficiency**	**2012 (EU)**
Macugen (pegaptanib sodium injection), a synthetic PEGylated oligonucleotide aptamer that specifically binds VEGF protein	Eyetech (New York)/Pfizer (EU)/Valeant Pharmaceuticals (Montreal)	Treatment of neovascular, age-related macular degeneration	2006 (EU) 2004 (USA)
Vitravene (fomivirsen), an antisense oligonucleotide	Isis Pharmaceuticals/Novartis	Cytomegalovirus retinitis in AIDS patients	1998 (US) 1999 (EU) Withdrawn (EU) 2002

Biopharmaceutical defined here as recombinant therapeutic proteins, including mAb-based products and nucleic acid based products used for gene therapy and antisense technology. Data were collected from several industry sources (http://www.fda.gov/; http://eudravigilance.emea.europa.eu/human/index.asp; http://www.phrma.org/). Boldface indicates products approved from 2010 to June 2014. Asterisk indicates 2010 products listed in the previous benchmark article, which covered products approved up to June 2010. Red indicates products that have been withdrawn from the market. Products are listed in chronological order, with the most recent approvals first. Where more than one drug in the same category was approved in a single year, they are listed alphabetically. Several products have been approved for multiple indications, but only the first indication for which it was approved is listed here. Company listed: for EU entries the market authorization holder is listed, as per EMA website, May 2014. For United States, companies listed are taken from the FDA website (http://www.fda.gov/Drugs), BioMedTracker.com or both. Products are listed by trade name. r, recombinant; rh, recombinant human; BHK, baby hamster kidney; CHO, Chinese hamster ovary; EPO, erythropoietin; FSH, follicle stimulating hormone; GM-CSF, granulocyte-macrophage colony stimulating factor; GLP, glucagon-like peptide; HbsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HER 2, human epidermal growth factor receptor 2; hGH, human growth hormone; IFN, interferon; IL, interleukin; mAb, monoclonal antibody; KGF, keratinocyte growth factor; NCA-95, nonspecific cross-reacting antigen 95; PAP-GM-CSF, prostatic acid phosphatase linked to granulocyte macrophage colony stimulating factor; PDGF, platelet derived growth factor; RANKL, receptor activator of nuclear factor kappa-B ligand; tPA, tissue plasminogen activator; TNFR, tumor necrosis factor receptor; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.