Biological Drug Approvals by the FDA in 2015–2021

Subjects: Pharmacology & Pharmacy

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Despite belonging to a relatively new class of pharmaceuticals, biological drugs have been used since the 1980s, when they brought about a breakthrough in the treatment of chronic diseases, especially cancer. They conquered a large space in the pipeline of the pharmaceutical industry and boosted the innovation portfolio and arsenal of therapeutic compounds available. From 2015 to 2021, the number of drugs included in this class grew over this period, totaling 90 approvals, with an average of 13 authorizations per year.

Food and Drug Administration | FDA approvals | monoclonal antibody | antibody–drug conjugate | biological drugs

1. Introduction

Biological drugs (or biopharmaceuticals) derive from living organisms. They are highly selective, high-cost, typically susceptible to microbial contamination, and generally temperature-sensitive drugs. They can also be used as advanced alternatives when conventional synthetic drugs no longer have the desired effect [1].

Biopharmaceuticals can be isolated from microorganisms, humans, animals or they can be isolated from compounds of nucleic acids, sugars and proteins. Here, we will address authorizations given by the U.S. Federal Drug Administration (FDA) to biologicals classified as monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), and proteins, which encompass enzymes and hormones [2]. All product references cited in this work hold a Biologics License Application (BLA) number. Although we will not include biosimilars in the quantitative analysis, they will be briefly commented on.

Advances in biological drug development by the pharmaceutical industry have given rise to new treatments to meet urgent medical needs, among them cancer. For example, regarding biologicals to treat diseases like cancer and autoimmune conditions, in 2014, four mAbs were indicated for cancer. More recently, in 2020, this figure had doubled, with eight mAbs for the treatment of this disease, while in 2021 there were five mAbs for this purpose. In the context of autoimmune diseases, in 2014, there was only one mAb and one enzyme approved, while in 2016 there were two mAbs, and in 2017 four [3][4]. It was only from 2015 onward that the number of approvals of biologicals per year jumped to a 2-digit figure as prior to 2015 such approvals did not reach 10 per year.

2. Timeline for FDA-Approved Biological Drugs

The data collected in the present work point to an undeniable growth of biological therapies. In the period from 2015 to 2021, the FDA authorized new mAbs, ADCs and proteins. Of note, the total number of approvals remained in double figures every

year except 2016, in which only seven biopharmaceuticals, all mAbs, were approved (**Figure 1**). Analysis of the data also revealed the prominence of the authorization of mAbs compared to other biologicals.

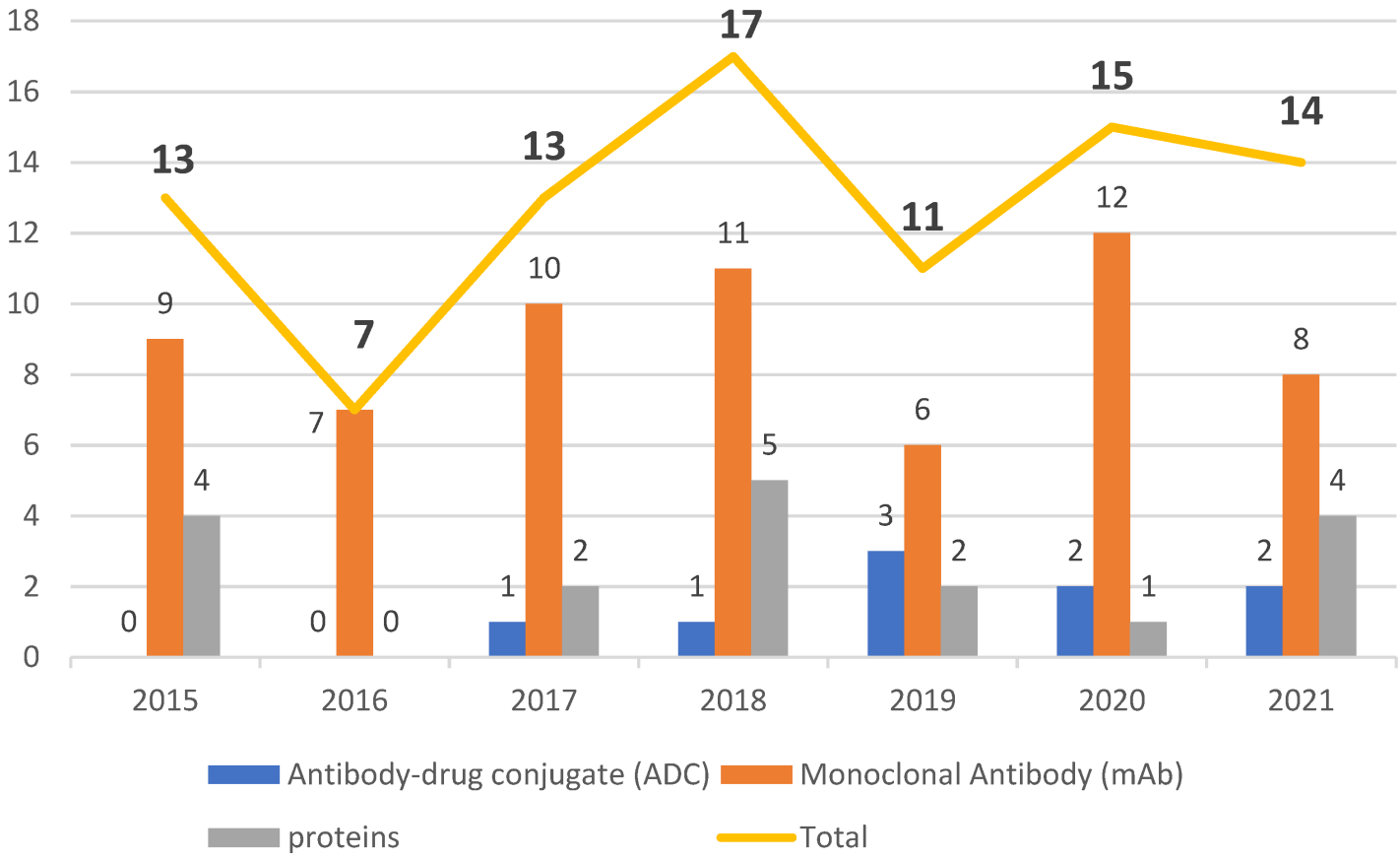

Figure 1. Biologicals approved by the Food and Drug Administration (FDA) from 2015 to 2021 [2][5][6][7][8][9][10][11].

The number of mAbs authorized each year between 2015 and 2021 has never been below 50% of total approvals (2015, 69.2%; 2016, 100%; 2017, 76.9%; 2018, 64.7%; 2019, 53%; 2020, 80%; and 2021, 57.1%). The next category of drugs in terms of the number of approvals in this period is enzymes (11%), followed by ADCs (10%), proteins and fusion proteins (6%), and finally hormones (3%) (**Figure 2**).

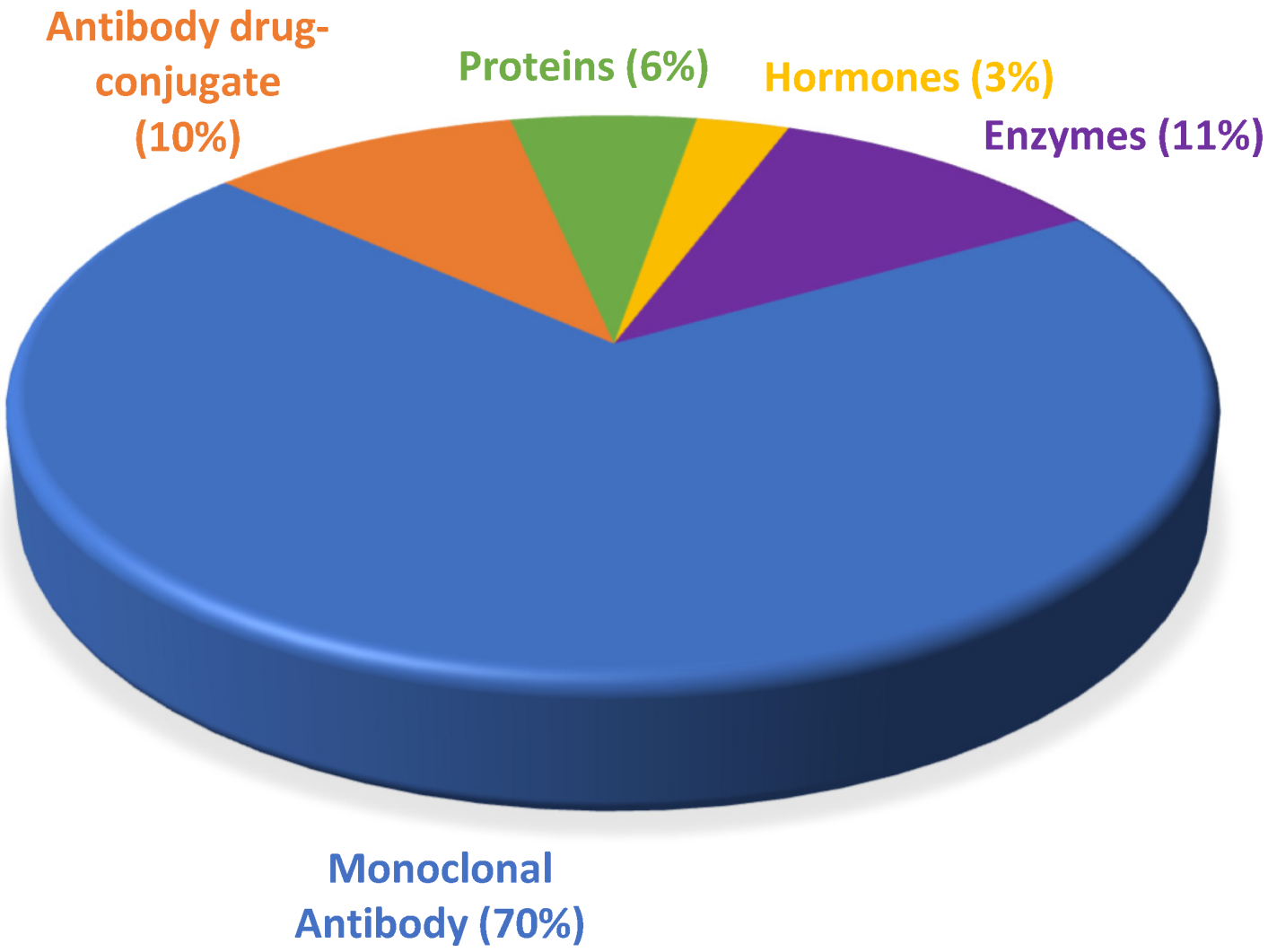

Figure 2. Percentage of new biopharmaceuticals approved by the Food and Drug Administration (U.S. FDA) from 2015 to 2021 [2][7][8][9][10][11].

3. Therapeutic Indications

3.1. Cancer

Considering all the therapeutic targets found, the approvals of biopharmaceuticals for the treatment of cancer are highlighted in the period 2015–2021. A total of 32 biologicals were authorized for the treatment of a variety of cancers (cervical cancer, lymphomas, leukemias, and other blood cancers, lung cancer, endothelial cancer, sarcomas, carcinomas, breast cancer, multiple myeloma, neuroblastoma, skin cell cancers, among others). Of these, 62.5% (20) are mAbs, 30% (9) ADCs, and 9.37% (3) fall into the class of proteins (proteins and enzymes). Of note, the biologicals for the treatment of different types of cancer varied greatly from year to year, although mAbs were on the rise. In this context, in 2015, four out of the nine approved mAbs were for cancer, and in 2016 all six mAbs were for this indication. In 2017, of the three biopharmaceuticals for cancer, two were mAbs and one was an ADC. In 2018, of the five approvals for cancer, only two were mAbs, one was an ADC, and two were proteins. In 2019, of the four approvals for this indication, only one was a mAb, while the remaining three were ADCs. In 2020, six mAbs and two ADCs were authorized for the treatment of this disease. In 2021, only one mAb was approved, while two ADCs and one enzyme received the green light.

3.2. Mechanisms of Action and Therapeutic Indications of ADCs and mAbs for Cancer

3.2.1. mAbs for Cancer

Both IgG1k Daratumumab Darzalex™ and the IgG1 Isatuximab Sarclisa™ bind to CD38 [12][13]. Like other conventional medicines, biologicals can undergo changes. One example is Darzalex™ (given intravenously), which was modified and approved in 2020 as Daratumumab and hyaluronidase (Darzalex Faspro™) (given subcutaneously), the latter containing the same combined human mAb with a recombinant human enzyme called hyaluronidase, which enhances the absorption of injectables, allows faster infusions, and a lower rate of reactions related to infusions [14]. Both Darzalex™ and Darzalex Faspro™ target CD38. Approved by the FDA in 2005, human hyaluronidase injections alter the permeability of human tissue, and they are used as an adjuvant to improve the characteristics of injectables [15]. Other examples of mAb modification include Rituximab and hyaluronidase (Rituxan Hycela™), approved in 2017, also given subcutaneously. However, it was first approved back in 1997 by the trade name Rituxan™, being administered intravenously [16]. Trastuzumab and hyaluronidase (Herceptin Hylecta™) [17] and Pertuzumab, trastuzumab, and hyaluronidase (Phesgo™) [15] underwent the same modification with the addition of hyaluronidase, both being administered subcutaneously and both for breast cancer. Margenza™ is directed at the same target, HER2, for breast cancer [18], and all breast cancer biologicals currently on the market were approved between 2019 and 2020.

Lartruvo™ was the only drug approved for soft tissue sarcoma during the period of interest [19]. Tecentriq™, Bavencio™ and Imfinzi™ have the same target (PD-L1), and all three are biologicals that can be used to treat the highest number of different types of cancer [20][21][22]. Portrazza™ targets EGFR, and Rybrevant™ has the same target plus the MET proto-oncogene. Therefore, Rybrevant™ is the only bispecific mAb for cancer approved to date [23][24]. Another breakthrough in the period 2015–2021 was Poteligeo™, a first-in-class biopharmaceutical that targets the CC chemokine receptor 4 (CCR4) [25]. In this period, we found four biologicals approved for multiple myeloma, but one of them (Empliciti™) has a distinct mechanism of action in that it binds to the cell surface receptor signaling lymphocytic activation molecule F7 (SLAMF7), whereas Darzalex™, Darzalex Faspro™ and Sarclisa™ target CD38 [12][13][14].

3.2.2. Antibody–Drug Conjugates

Enfortumab Vedotin Padcev™ is the first biological to target the protein Nectin-4 [26]. Tisotumab Vedotin Tivdak™ is a Biological specific for tissue factor (TF-011) and Polatuzumab Vedotin Polivy™, an antibody whose target is the CD79b (a component of the B cell receptor). These three ADCs, which have different targets but the same suffix Vedotin, carry the same drug, namely monomethyl auristatin E (MMAE) [27][28][29]. MMAE is released into the cell after binding to the target, with subsequent induction of cell apoptosis by the drug, which also inhibits mitosis. These drugs also have different types of linkers. For example, the linker in Padcev™ is the protease-cleavable maleimidocaproyl valine-citrulline [26], while Tisotumab Vedotin has a Valine citrulline linker, which is also protease-cleavable [28]. It is interesting how these ADCs carrying MMAE have such unique targets, a feature not seen among mAbs.

Fam-Trastuzumab deruxtecan Enhertu™ targets human epidermal growth factor receptor 2 (HER2) for the treatment of gastric cancer, breast cancer and gastroesophageal junction adenocarcinoma. Its ligand is a topoisomerase inhibitor, which blocks DNA replication [17]. Sacituzumab govitecan Trodelvy™, indicated to treat solid tumors, has the hydrolysis-cleavable CL2A as the linker, and it also carries a topoisomerase inhibitor [30]. Loncastuximab tesirine Zynlonta™ includes an antibody against CD19. This antibody carries the antitumor drug pyrrolobenzodiazepine, and its linker is protease-cleavable [31].

Besponsa™ has a linker that can be cleaved by acid [32]. Enhertu™ has a protease-cleavable tetrapepitide linker [17][33]. Trodelvy™ has the hydrolysis-cleavable CL2A as linker [30]. The linker present in Zynlonta™ is also protease-cleavable [31] while that of Blenrep™ is maleimidocaproyl [34].

Besponsa™ and Lumoxiti™ target CD22, but they are indicated for different types of cancer [32][35]. They carry distinct drugs/toxins, Besponsa™ carrying Calich-DMH, an antitumor antibiotic produced by a bacterium, and Lumoxiti™ being conjugated to a fragment of *Pseudomonas exotoxin,* also found as PE38. When internalized, PE38 stimulates apoptosis and the inhibition of protein synthesis.

In 2015 and 2016, no ADCs were approved, while 2017 and 2018 registered the lowest number of authorizations of these drugs in the period of interest. In 2019, the highest number of approvals for ADCs were for the treatment of three types of cancer. In this regard, Padcev™ was authorized for the treatment of metastatic urothelial cancer [26], Polivy™ for diffuse large B-cell lymphoma [29], and Enhertu™ for breast cancer [17]. Then, the following two years registered two approvals each year. Thus, in 2020, Blenrep™ received the green light for the treatment of multiple myeloma [34] and Trodelvy™ for metastatic triple-negative breast cancer [30]. In the following year, Zynlonta™, another drug for the treatment of large B-cell Lymphoma [31], was approved, as was Tivdak™ for metastatic cervical cancer [28].

4. Autoimmune Diseases

The biologics for autoimmune diseases (psoriasis, plaque psoriasis, psoriatic arthritis, multiple sclerosis, myasthenia gravis, lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and neuromyelitis optic spectrum disorder) in the period of interest included 13 biologics, 12 of which were mAbs, and a new class of biological, namely an antibody fragment (Efgartigimod alfa Vyvgart™), which is detailed in **Table 1**.

Table 1. Biopharmaceuticals for autoimmune diseases approved by the Food and Drug Administration from 2015 to 2021.

Active Ingredient and Trade Name	mAb Class	Targets/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Cosentyx™ (Secukinumab) [6] [36]	Human	IL-17A inhibitor	2015	Novartis Pharmaceuticals	Plaque psoriasis, Psa, and AS
Zinbryta™ (daclizumab) [37] [38]	Humanized	IL-2R inhibitor	2016	Biogen Inc	Multiple sclerosis
Taltz™ (ixekizumab) [37] [39]	Humanized	IL-17A inhibitor	2016	Eli Lilly and Company	Plaque psoriasis and Psa
Tremfya™ (guselkumab) [8] [40]	Human	IL-23 and IL-17A inhibitor	2017	Janssen Biotech, Inc	Plaque psoriasis
Ocrevus™ (Ocrezilumab) [41] [42]	Humanized	Anti-CD-20	2017	Genentech, Inc	Multiple sclerosis

Active Ingredient and Trade Name	mAb Class	Targets/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Kevzara™ (sarilumab) [41][43]	Human	IL-6 inhibitor	2017	Sanofi-Aventis U.S LLC	Rheumatoid arthritis
Siliq™ (brodalumab) [41][44]	Human	IL-17A, IL-17F, and other IL-17 isoform inhibitors	2017	Valeant Pharmaceuticals Luxembourg S.à.r.l	Plaque psoriasis
Ilumya™ (tildrakizumab) [45][46]	Humanized	IL 23p19	2018	Sun Pharma Global FZE	Plaque psoriasis
Skyrizi™ (risankizumab) [47][48]	Humanized	IL-23p19 inhibitor	2019	AbbVie Inc.	Plaque psoriasis and Psa
Uplizna™ (inebilizumab) [49][50]	Humanized	Depletes CD-19	2020	Horizon Therapeutics Ireland DAC	NMOSD
Enspryng™ (satralizumab) [11][51][52]	Humanized	Anti-IL -6R	2020	Genentech, Inc.	NMOSD
Saphnelo™ (anifrolumab) [2][53]	Human	Blocks the action of type 1 interferon receptor	2021	AstraZeneca AB	Lupus erythematosus
Vyvgart™ (efgartigimod alfa) [2][54]	Human monoclonal ARGX-113 fc fragment	Neonatal Fc receptor antagonist	2021	Argenx BV	Generalized myasthenia gravis

IL—Interleukin; CD—Cluster of Differentiation; Psa: Psoriatic Arthritis; NMOSD: Neuromyelitis Optica Spectrum Disorder.

Of the approvals of autoimmune biopharmaceuticals from 2015 to 2021, six are indicated for psoriasis, plaque psoriasis, and psoriatic arthritis. Brodalumab Silic™ is indicated for moderate to severe plaque psoriasis [44]. While this drug acts by antagonizing the IL-17A Receptor, Cosentyx™ and Taltz™ antagonize the pro-inflammatory cytokine IL-17A, which plays a role in psoriasis and Psa [36][39]. Ixekizumab Taltz™ is used for the treatment of psoriasis and Psa. It is an antibody that blocks the activity of two interleukins (Il-23, IL-17A) that are overexpressed in these diseases [42]. Tildrakizumab Ilumya™ is an IgG1 antibody that selectively binds to interleukin-23-p19 (IL-23A p19) [46] and, through the same mechanism, Risankizumab Syrizi™ also binds to the same p19 subunit of this interleukin. In some countries, there are trials underway to evaluate Risankizumab for the treatment of Crohn's disease and ulcerative colitis [48][55][56].

5. Other Therapeutic Indications

In the period of interest, some therapeutic indications appear only once among FDA approvals, while others appear between two to four times. Of a total of four FDA-approved mAbs for the treatment of migraine, three are humanized mAbs and only one is fully human (**Table 2**). The humanized ones, Vyepti™, Emgality™ and Ajovy™, have the same mechanism of action. In

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this regard, they bind to CGRP, a potent vasodilator, preventing it from adhering to the receptor [57][58][59]. In contrast, the fully human antibody Aimovig™ binds to CGRPR, preventing the molecule from binding to the receptor [60].

Table 2. Monoclonal antibodies for migraine approved by the Food and Drug Administration from 2015 to 2021.

Active Ingredient and Trade Name	mAb Class	Target/Mechanism of Action	Original Approval Date	Manufacturer
Emgality™ (Galcanezumab) [45][60]	Humanized	CGRP antagonist	2018	Eli Lilly and Company
Ajovy™ (Fremanezumab) [45][59]	Humanized	CGRP antagonist	2018	Teva Branded Pharmaceutical Products R&D, Inc.
Aimovig™ (Erenumab) [45][60]	Human	CGRPR antagonist	2018	Amgen, Inc.
Vyepti™ (Eptinezumab) [11][57]	Humanized	CGRP antagonist	2020	Lundbeck Seattle Pharmaceuticals, Inc.

CGRP: Calcitonin Gene-Related Peptide; CGRPR: Calcitonin Gene-Related Peptide Receptor.

For asthma and severe asthma (**Table 3**), two fully human antibodies were approved from 2015 to 2021. Dupixent™ is an antibody directed against the α subunit of the interleukin 4 receptor (IL-4R-α) [61], and the Tezspire™ blocks thymic stromal lymphopoietin (TSLP), which plays a key role in asthma [62][63]. Furthermore, in the same period, three humanized antibodies received the green light. In this regard, Nucala™ and Cinqair™ are mAbs against IL-5 [64][65], while Fasenra™ acts by binding to the α subunit of the receptor of IL-5 (IL-5R-α) [63][66].

Table 3. Monoclonal antibodies for asthma and severe asthma approved by the Food and Drug Administration from 2015 to 2021.

Active Ingredient and Trade Name	mAb Class	Target/Mechanism of Action	Original Approval Date	Manufacturer
Nucala™ (Mepolizumab) [6][64]	Humanized	IL-5	2015	GlaxoSmithKline LLC
Cinqair™ (Reslizumab) [37][65]	Humanized	IL-5	2016	Teva Respiratory LLC
Fasenra™ (Benralizumab) [41][66]	Humanized	IL-5R-α	2017	AstraZeneca AB
Dupixent™ (Dupilumab) [41][61]	Human	IL-4R-α	2017	Regeneron Pharmaceuticals, Inc.
Tezspire™ (Tezepelumab) [2][63]	Human	Blocks TSLP	2021	AstraZeneca AB

IL: Interleukin; IL-R-α: Interleukin Receptor α; TSLP: Thymic Stromal Lymphopoietin.

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One of the key aspects of biologicals is their potential for the treatment of rare diseases, such as type 2 neuronal ceroid lipofuscinosis, which causes symptoms ranging from seizures and loss of motor coordination to vision failure. The diagnosis of this condition can be delayed due to the similarity of symptoms with other diseases. This disease causes blindness in children, a patient cohort that can make it difficult to conduct clinical trials due to a smaller population for initial studies [67]. For this disease, also known as Batten's disease, only one biological, an enzyme (Cerliponase alfa Brineura™), was approved during the period of interest [68].

The 2021 Biological of the year is Aducanumab Aduhelm™, which was authorized in the midst of the COVID-19 pandemic through an accelerated FDA approval, despite controversy regarding phase three studies, which showed that the drug is associated with a decrease in beta-amyloid plaques. However, these studies have not proved satisfactorily that the drug delays cognitive and functional decline in patients with AD. New FDA submissions of biologicals to treat AD will soon emerge, such as Lecanemab and Donanemab, which are currently in the testing phase. However, these two drugs still need further supporting clinical evidence to compete with Aducanumab and enter the market [69][70][71]. As mentioned earlier, the EMA withdrew marketing authorization for Aducanumab.

Between 2015 and 2021, biologicals were also approved for the treatment of *Bacillus anthracis* (Obiltoxaximab Anthim™), Pseudomembranous Colitis (Bezlotoxumab Zinplava™), Hemophilia A (Emicizumab Hemlibra™), Sly Syndrome (Vestronidase alfa Mepsevii™), X-linked hypophosphatemic rickets (Burosumab Crysvita™), neurotrophic keratitis (Cenegermin Oxervate™), drug-resistant HIV-1 (Ibalizumab Trogarzo™), phenylketonuria (Pegvaliase Palynziq™), temporary smoothing of fine lines (Prabotulinumtoxin Jeuveau™), growth deficiency (Somapacitan Sogroya™, Lonapegsomatropin Skytrofa™), and Ebola virus (Atoltivimab, Maftivimab, and Odesivimab Inmazeb™ and Ansuvimab Ebanga™), among others. Within the context of 'biological treatment', it can be concluded that one of the perspectives is to increasingly promote options for the treatment of patients with chronic diseases, including rare conditions [72].

6. Conclusions

The period 2015 to 2021 witnessed a growth in FDA approval of biologicals in general, with mAbs being the class with the greatest presence. During this period, the number of authorizations of biopharmaceuticals remained in the double figures, except in 2016, when only seven were given the green light. The years 2020 and 2021 did not show considerable variation, with one less biological being approved in 2021 than in 2020, while 2018 was the year with the highest number of approvals. Of note, even in the midst of the COVID-19 pandemic, the potential for these therapies to receive approval remained steady.

Biological medicines show high selectivity and high versatility and are therefore valuable. Their versatility is reflected in indications that range from the treatment of chronic or rare diseases to more aesthetic purposes such as the treatment of frown lines. These drugs offer great potential to be exploited for other therapeutic indications beyond what they were initially authorized for. In this regard, they offer a solid starting point from which to explore their capacity in clinical trials. For example, over the years, new applications have been discovered for Adalimumab Humira™, and today this drug has more than ten therapeutic indications listed in the directions of use [73]. Daratumumab Darzalex™ is also undergoing evaluation for other types of cancer, including refractory or relapsed non-Hodgkin's Lymphoma [12]. mAbs can also be conjugated to toxins or drugs without compromising healthy tissues around the target fragment or at least minimizing effects in other tissues [74].

Between 2015 and 2021, in addition to the increase in the number of drug approvals, several breakthroughs and innovations took place, such as Aducanumab Aduhelm™, although still controversial, and also Tagraxofusp Elzonris™, which the FDA granted the status of Orphan Drug to treat rare diseases. In 2021, we witnessed the authorization of a different class of

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biological, Efgartigimod and Hemlibra™ antibody fragment, both also had Orphan Drug status [54], and the bispecific antibody approved within the period of interest Hemlibra™. Of note only two bispecific antibodies were approved in the period of interest Hemlibra™ and Rybrevant™.

However, one of the great challenges for the development of biopharmaceuticals is the high technology required to produce these drugs, which makes them very expensive, but, in the near future, this class of drugs will become increasingly accessible and new drugs will be developed. Moreover, more biosimilars will become accessible thanks to the development of new technologies that will impact production. These advancements will make these drugs increasingly more profitable and less expensive, which in turn will widen the accessibility of biological therapies, thereby expanding the therapeutic arsenal and transforming the management of diseases for which no treatment is available or diseases for which current treatments are not effective.

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