2019 FDA Biopharmaceutical Approvals: A Record Year for Follow-on Products, But is Innovation Lagging?

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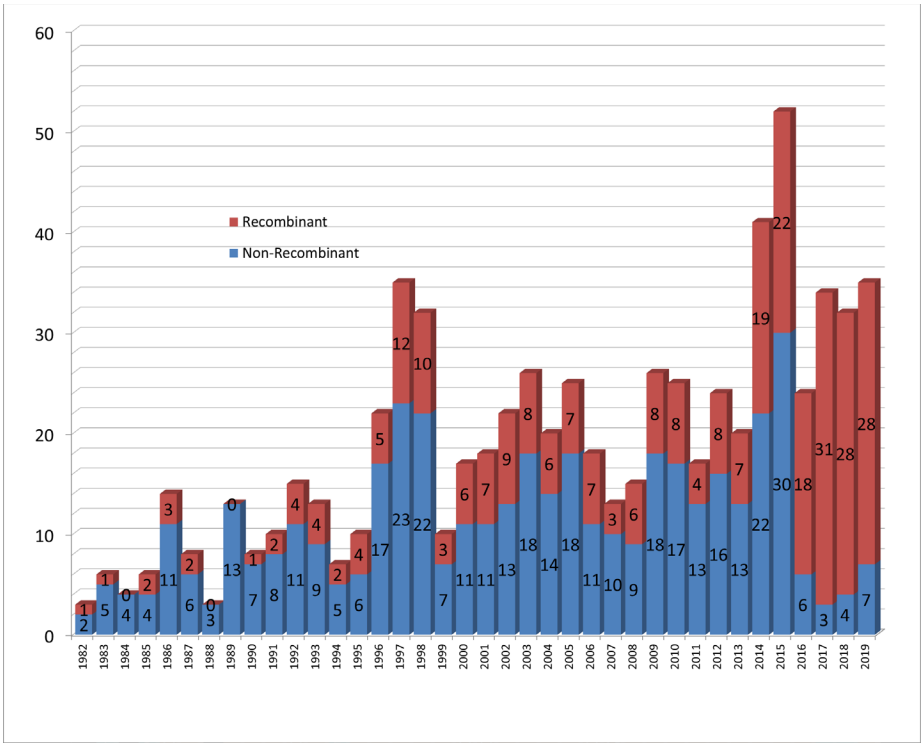
Introduction

Although 2019 was overall a good year for biopharmaceutical product approvals, there was a lower percentage of approvals for fully new, innovative products compared with prior years. This may indicate problems with recent years' pharmaceutical industry increased investment in biopharmaceutical vs. drug R&D, with a relative increase in resulting innovative product approvals not showing up yet. It may be too early to make conclusions regarding the extent of this pipeline trend, but the record portion of follow-on product approvals (63% of approvals) can be viewed as positive or negative for the industry.

Biopharmaceuticals are here defined as prescription therapeutic products containing active agents manufactured using biotechnology methods, i.e., using living organisms (1). Figure 1 shows the numbers of recombinant and non-recombinant biopharmaceuticals approved by FDA since 1981, when the first recombinant protein received approval. Total biopharmaceutical approvals have increased over the years while remaining steady in the past few years.

Figure 1: Numbers of Recombinant and Non-Recombinant Biopharmaceuticals Approved by FDA, 1981-2019



Approvals in 2019

In Table 1 we present approvals during 2019. Several oligonucleotide therapeutics, both antisense and RNAi, also received approval, but these are synthetically manufactured drugs and not considered biopharmaceuticals. Other products not included as biopharmaceuticals include medical devices, allergenic extract products, and diagnostics that receive biologics (BLA) approvals.

Table 1: Biopharmaceuticals Approved by FDA in 2019

Product	Approval Date	Approval Recipient	Indications; Notes
Immune globulin, s.c [Cutaquig – Immune Globulin Subcutaneous (Human)]	12/26	Octapharma Pharmzeutika	primary humoral deficiency; could be considered a biobetter relative to other immune globulins
Calcitonin, rDNA [Ubrelvy - ubrogepant	12/23	Allergan USA (merging into Abbvie)	migraine; a 505[b][2] drug approval, equivalent to biosimilar approval
Her-2 mAb--deruxtecan conjugate, rDNA [Enhertu - fam-trastuzumab deruxtecan-nxki]	12/20	AstraZeneca and Daiichi Sankyo Co. Ltd.	breast cancer; an antibody-drug conjugate (ADC)
Ebola vaccine [Ervebo - Ebola Zaire Vaccine, Live; V920]	12/19	Merck & Co	prevention of Ebola disease from Zaire ebolavirus
Nectin-4 mAb--monomethyl auristatin E (MMAE), rDNA [enfortumab vedotin-ejfv - Padcev] approval granted to this antibody-drug conjugate (ADC) on 12/18/2019 to Seattle Genetics Inc. and Astellas	12/18	Seattle Genetics Inc. and Astellas Pharm Inc.	treatment of urothelial (bladder) cancer; an antibody-drug conjugate (ADC

Pharm Inc. for treatment of urothelial cancer (bladder cancer			
TNF mAb, rDNA [Avsola - infliximab-axxq; ABP 710]	12/5	Amgen	autoimmune disorders; biosimilar approval, Remicade is ref. product
P-selectin mAb, rDNA [crizanlizumab-tmca - Adakveo]	11/15	Novartis (from acquisition of Selexis)	sickle cell disease
TNF mAb, rDNA [adalimumab-afzb - Abrilada]	11/8	Pfizer	Humira's diverse indications; biosimilar approval, Humira is ref. product
activin receptor-IgG1 Fc fusion protein, rDNA [luspatercept-aamt - Reblozyl]	11/8	Celgene (being acquired by Bristol-Myers Squibb/BMS)	anemia in adults with beta thalassemia.
G-CSF, rDNA, PEG- [Ziextenzo - pegfilgrastim-bmez]	11/4	Sandoz/Novartis	neutropenia; biosimilar approval, Neulasta is ref. product; also, a biobetter relative to Neupogen
VEGF mAb, rDNA [Beovu - brolucizumab-dbll]	10/7	Novartis	neovascular (wet) age-related macular degeneration (AMD)
PTH (11-34), rDNA [Bonsity - teriparatide; parathyroid hormone; PF708]	10/4	Pfenex Inc.	a 505[b][2] drug approval, equivalent to biosimilar approval; Forteo is ref. product
Poxvirus vaccine [Jynneos - Smallpox and Monkeypox Vaccine, Live, Non-Replicating; MVA-BN; Modified Vaccinia Ankara - Bavarian Nordic]	9/24	Bavarian Nordic A/S	prevention of disease from smallpox and monkeypox infection
glucagon-like peptide-1, rDNA [Rybelsus - semaglutide; GLP-1] approval granted on 9/20/2019 to Novo Nordisk for treatment of type 2 diabetes	9/20	Novo Nordisk	type 2 diabetes
glucagon, rDNA [Gvoke HypoPen; Gvoke Ready-to-Use Injection - glucagon]	9/10	Xeris Pharmaceuticals	hypoglycemia in diabetic patients; NDA for new route of admin. (s.c. injection); considered a biobetter
TNF mAb, rDNA [Hadlima - adalimumab-bwwd]	7/23	Samsung Bioepis (j.v. of Samsung and Biogen), with US marketing by Merck & Co.,	Humira's diverse indications; biosimilar approval, Neulasta is ref. product
CD20 mAb, rDNA [Ruxience - rituximab-pvvr]	7/23	Pfizer	Rituxan's diverse indications; biosimilar approval, Rituxan is ref. product
insulin, rDNA [Myxredlin - Insulin Human in 0.9% Sodium Chloride Injection]	7/22	Baxter	Diabetes; a 505[b][2] drug approval, equivalent to biosimilar approval; a biobetter relative to regular insulin products
glucagon, rDNA [Baqsimi Nasal Powder - glucagon]	7/20	Eli Lilly & Co.	hypoglycemia in diabetic patients; new route of admin.; could be considered a biobetter relative to Glucagon Emergency Kit for Low Blood Sugar
immunoglobulin [Xembify - immune globulin subcutaneous, human- klhw]	7/3	Grifols	primary immunodeficiencies; a biobetter relative to Vivaglobin and/or Hizentra
VEGF mAb, rDNA [Zirabev - bevacizumab-bvzr]	6/20	Pfizer	Avastin's diverse indications; biosimilar approval, Avastin is ref. product
Her-2 mAb, rDNA [Kanjinti - trastuzumab-anns]	6/13	Amgen (along with Allergan)	Breast and gastric cancer; biosimilar approval, Herceptin is ref. product
CD79b mAb-PAL ADC, rDNA [Polivy - polatuzumab vedotin-piiq; DCDS4501A; RG7596; CD79b mAb--maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB) linker--MMAE toxin]	6/10	Genentech/Roche	diffuse large B-cell lymphoma; an antibody-drug conjugate (ADC)

survival motor neuron 1 (SMN1) gene therapy, rDNA [Zolgensma - onasemnogene abeparvovec-xioi]	5/24	AveXis, subsidiary of Novartis	Pediatric spinal muscular atrophy (SMA); an AAV9 vector gene therapy
Dengue virus vaccine, live [Dengvaxia - Dengue Tetravalent Vaccine, Live]	5/1	Sanofi Pasteur	prevention of dengue disease
TNFr-Fc fusion protein, rDNA [Enticovo - etanercept-ykro]	4/25	Samsung Bioepis (j.v. of Samsung and Biogen)	Enbrel's diverse indications; biosimilar approval, Enbrel is ref. product
IL-23 mAb, rDNA [Skyrizi - risankizumab-rzaa; interleukin-23 monoclonal antibody, recombinant]	4/23	Abbvie	plaque psoriasis
sclerostin mAb, rDNA [Evenity - romosozumab-aqqg; AMG 785]	4/9	Amgen	osteoporotic fracture
IVIG [Asceniv - Immune Globulin Intravenous,	4/1	ADMA Biologics, Inc.	primary humoral immunodeficiency disease; could be considered a biobetter relative to other IVIGs
Her receptor mAb, rDNA [Trazimera - trastuzumab-qyyp]	3/11	Pfizer	Breast and gastric cancer; biosimilar approval, Herceptin is ref. product
Factor VIII, PEG-, rDNA [Esperoct - turoctocog alfa pegol, N8-GP; antihemophilic factor (recombinant), glycopegylated-exei]	2/19	Novo Nordisk	Hemophilia; a biobetter relative to other Factor VIII products
Her mAb plus hyaluronidase, rDNA [Herceptin Hylecta - trastuzumab and hyaluronidase-oysk]	2/28	Genentech/Roche	Breast cancer; a biobetter version of Herceptin, new route of admin.
von Willebrand's Factor mAb. rDNA [Cablivi - caplacizumab-yhdp; VWF mAb]	2/6	Ablynx, with marketing by Sanofi	acquired thrombotic thrombocytopenic purpura (aTTP)
Botulinum toxin A [Jeuveau - prabotulinumtoxinA-xvfs; botulinum toxin type A]	2/1	Evolus, Inc.	Glabellar (frown) lines; a biobetter relative to BOTOX Cosmetic
Her receptor mAb, rDNA [Ontruzant - trastuzumab-dttb; SB3]	1/16	Samsung Biologics	Breast and gastric cancer; biosimilar approval, Herceptin is ref. product

Product-related FDA Records

- A total of 35 biopharmaceuticals received full (vs. supplemental) approvals. As is now the norm, the great majority of products, 28 (80%), have recombinantly manufactured active agents. Recombinant monoclonal antibodies (mAbs), including derived fragments, were the product class with the most approvals, 15 (43%). Seven (20%) non-mAb recombinant proteins received approval. One gene therapy and zero cellular therapies received approvals.
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- Product approval-related records set in 2019 include
- Follow-on approvals: A total of 22 (63%) follow-on-type products received approval. This includes biosimilar, 505(b)(2) generic drug approvals (considered equivalent to biosimilar approvals), and biobetters or upgraded versions of prior-approved products containing much the same active agent but with some other change clearly making this a 'new' product (2,3). Biosimilars here do not include vaccines or blood-derived products, the majority of which are essentially biosimilars of prior versions, often even interchangeable.

- Biosimilar-type approvals: A total of 12 products received formal biosimilar or comparable generic drug approval. Ten (29%) products received formal biosimilar BLA approvals. Two products (6%) received these 505(b)(2) NDA approvals, which are in the process of shifting to be regulated as biologics, including existing approvals converted to biosimilar BLAs.
- Biobetter-type approvals: A total of 10 (31%) of products can be considered biobetters, having active agents substantially identical or (bio)similar to 1 or more prior approved products, with a formulation or other change making this a new product, with changes in the route of administration common. In prior years, before biosimilar approvals, biobetters sometimes constituted up to 50% of approvals. The portion of biobetters has decreased most likely due to the major increase in biosimilar approvals.

Company-related Records

Company-related records set in 2019 include:

- Approvals received by a company: Novartis, including approvals granted to its Sandoz subsidiary, and Pfizer each received 4 approvals, with these setting records for biopharmaceutical approvals received by a single company.
- Approvals received by companies receiving multiple approvals: A majority, 18 (51%), of approvals were received by companies having received multiple approvals in 2019. Besides Novartis and Pfizer each receiving 4 (8 total), other recipients of multiple approvals were Amgen (3), Samsung (including Samsung Bioepis; 3), Genentech/Roche (2), Sanofi (2) and Novo Nordisk (2).
- Approvals granted to Big (Bio)Pharma companies: A total of 29 (83%) of approvals, a record number and percentage, at least in recent years, were granted to companies easily recognized as among the very largest international (bio)pharmaceutical companies. Where 2 companies shared approval, only the largest was considered. The other 6 approvals went to clearly much smaller companies.

In terms of the regions where recipient companies are based, 17 (49%) are based in the USA, 13 (37%) in Europe; and 3 (9%) in Asia (all involving Samsung in S. Korea), with this a fairly common, expected distribution. There were no approvals in 2019 granted to companies based in or the products manufactured in developing countries, including India and China. Note, 'country' was assigned based on the location of the owner company, e.g., Genentech, owned by Roche, was considered 'European.'

Is There a Problem with Innovative Approvals?

The record number of formal biosimilar and equivalent generic drug approvals of biopharmaceutical products can be viewed as positive for the biopharmaceutical industry and patients. These approvals clearly show that biosimilars 'have arrived' in the US and are on track to become a mainstream part of the (bio)pharmaceutical industry. This year's record number of biosimilar approvals was expected, with the timing of patent expirations having resulted in a

number of analyses showing an expected spike in biosimilars able to enter the US market in the later 2010s (4,5). The *Biosimilars/Biobetters Pipeline Database* (http://www.biosimilarspipeline.com) reports over 1,050 biosimilars and 550 biobetters in various stages of development worldwide (6). In 2019., all but 1 biosimilar-type approval involved clearly Big (Bio)Pharma-type companies, with only one to a smaller company, Pfenex. Based on the pipeline, future biosimilar approvals can be expected to include an increasing number from small- and mid-sized companies in the US and Europe and other companies based worldwide, with India and China expected to become major sources in coming years.

With more follow-ons entering the market, with this requiring related patents expiring, the biopharmaceutical sector is finally maturing and becoming more like the drugs market. This includes a significant number of generic-like products. This is clearly a positive trend for the health care system and patients seeing increased competition, increasingly even lower prices, with growing competition among a growing number of follow-ons and their original reference products. Biosimilars, and to a lesser extent biobetter approvals, are and will also increasingly bring new players, including from developing countries, into the U.S. biopharmaceutical market, with this further increasing competition. However, very few of the now dozens of FDA-approved biosimilars have yet to be launched. Ongoing patent disputes, related rulings against biosimilar developers, and increasingly patent dispute settlements between biosimilar and original product developers are significantly delaying the start of U.S. marketing of most of the FDA-approved biosimilars.

The record number of biobetter-type products is positive in the sense that, although generally 'lesser innovative' vs. clearly innovative or fully novel products, these are still innovative products often bringing significant improvements for patients, despite lacking novel active agents. Biobetters, as new versions or variations of existing products, as with biosimilars, also increase competition with this presumed to lower prices. However, biobetters clearly involve somewhat lesser innovation compared to fully novel products.

The high proportion of both biosimilar and biobetter-type approvals can also clearly be viewed as a developing negative trend, with these products inherently involving lesser innovation than fully original new products (with novel active agents). Innovative new therapeutics are particularly highly valued in the U.S., where there tends to be a bias for new(er) vs. old(er) products. This year, the percentage and number of follow-ons is the highest to date, and the percentage of fully innovative/new products is the lowest. Perhaps indicative of a trend for smaller percentages of fully innovative products, this year 14 (40%), a minority, are considered New Biological Entities (NBEs) – products with active agents that are fully novel, generally in terms of primary structure. We report NBEs much as FDA annually reports drug (CDER) approvals involving New Molecular Entities (NMEs).

To some, the high percentage of follow-on approvals this year may be a concern, particularly in the context of many expecting or hoping for a larger number and percentage of innovative products. This includes many who perceive much higher value from innovative vs. more me-too therapeutics entering the market, or simply expect more innovative products from increased

R&D investments. The 2019 biologics approvals clearly do not yet reflect the pharmaceutical industry, led by the Big (Bio)Pharma companies, increasingly shifting its R&D and development pipelines to biopharmaceuticals vs. small molecule drugs. It is now commonly reported that the pharmaceutical industry is devoting 40% or more of its R&D to biopharmaceuticals vs. drugs. For example, "Whereas biotech accounted for just 15% of the pipeline back in 1995, by 2019 this has reached 39.7%. That means that fully four in every 10 drugs under development are now biotech-derived....this realignment is not over yet (7)." But this shift in R&D, by now likely collectively involving 100s of $millions or even $billions, has clearly not yet resulted in a significant increase in the number and, particularly, the percentage of innovative biopharmaceutical approvals.

Although 2019 findings show a lower percentage of innovative product approvals vs. prior years, with a further increase in follow-on, we consider it too early to make conclusions regarding the extent, if any, of any actual trend for decreasing number and percentage of fully innovative biopharmaceutical products entering the U.S. market. Rather, we expect coming waves of novel product approvals, much as starting to be seen this year with biosimilars, including:

- Cellular and gene therapies, including likely 10 or more gene therapy approvals/year starting soon
- Live microbes as therapeutics
- Other novel product classes, and
- More novel recombinant antibodies and other proteins.

These approvals will increase the number and percentage of innovative vs. lesser innovative product approvals in coming years, even though even many more biosimilar approvals are also expected. Only the future can tell whether recent and ongoing increased investments in biopharmaceutical vs. small molecule and other drugs R&D will result in proportionately more innovative biopharmaceuticals coming to market, or whether the portion of lesser-innovative follow-ons will remain high or even increase.

References:

1) Rader, R.A., "(Re)Defining Biopharmaceutical" *Nature Biotechnology*, July 2008, 26(7), p. 743-751.
2) Rader, R.A., "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part 1: Introduction and Basic Paradigms," *BioProcess International*, March 2007.
3) Rader, R.A., "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic? Part 2: Information, Nomenclature, Perceptions, and the Market," *BioProcess International*, May 2007, p. 20-28.
4) Rader, R.A., "Biosimilars Pipeline Shows Remarkable, Sustained Growth," *BioProcess Online* (and *Biosimilar Development*), Guest Column, March 7, 2019.
5) Rader, R.A., Biosimilars Pipeline Analysis: Many Products, More Competition Coming", *Biosimilar Development*, July 26, 2016
6) Rader, R.A., *Biosimilars/Biobetters Pipeline Database*, BioPlan Associates, at www.biosimilarspipeline.com

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