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## RESEARCH ARTICLE

# Biotechnology – A Continual Revolution in Product Development and Healthcare – 1<sup>st</sup> 20 Years versus 2nd 20 Years and Beyond.

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### ABSTRACT

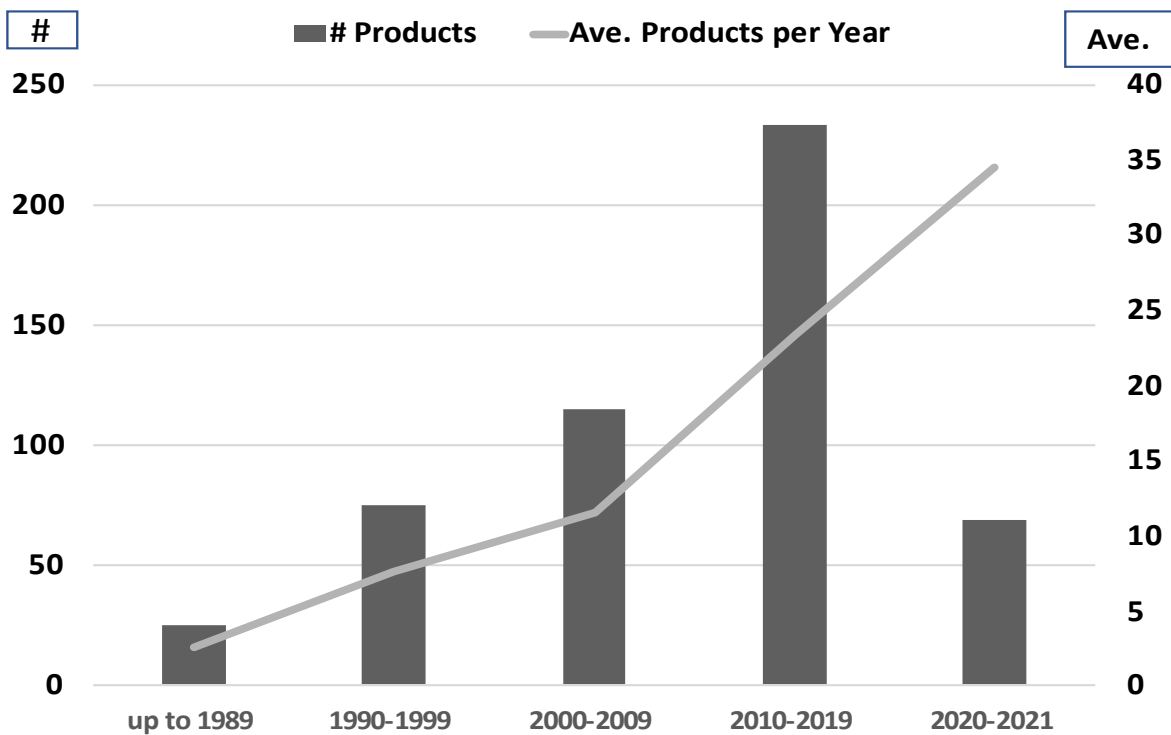
Biotechnology (the science and the business) has revolutionized product development and healthcare worldwide over the past 40 years with novel molecules, new companies, and major advances in disease mitigation. The revolution has continued and even accelerated as can be observed in comparing the last 20 years (2000-2019) versus first 20 years (1980-1999), and the recent years of 2020 and 2021 as well. This biotech review addresses the many product categories, indications, research, companies, business changes, and product sales, especially comparing these two time periods and demonstrating the substantial growth and impact of biotechnology and continuing the revolution through the last two years (2020-2021). Over 500 biotech products are available worldwide in 10 different categories of molecules for over 460 indications with over 160 biotech and pharma companies marketing the products. Biosimilar products (close duplicates of marketed products) have become commonplace in last 15 years. The top companies in biotech research and sales over these 40 years include Roche, Amgen, and Novo Nordisk, along with all the pharma companies becoming engaged. Twenty plus of the leading biotech companies have been acquired over these times. All of pharma is now dedicated to biotech molecule development independently and mostly in extensive collaboration with biotech companies. Clinical research has expanded with the top 90 biotech companies that spend at least \$100 million in one year totaling over \$50 billion in 2020, along with tens of billions from pharma companies for biotech research & development. Over 600 molecules are being studied in phase three clinical trials. Worldwide biotech sales grew to \$327 million in 2020 from \$35 billion in 2001 with biotech over 25% of all drug sales. The biotech revolution is alive and well and continuing with novel molecules from exiting and more new biotech and pharma companies for further advances in healthcare.

This treatise addresses the biotechnology revolution and its dramatic growth and expansion, covering the past 42 years from 1980 to 2021, where-in the author has been collecting data for the last 25 years and maintains 35 biotech databases, which are being reviewed in this publication, and are encompassed in his new database publication, Evens RP. Global Biotech Database e-Sourcebook 2021, Editor – Kenneth KI, Publisher - Tufts Center for the Study of Drug Development, Tufts University, Boston, MA 12/2021. The data sets, tables, and graphs all come from the database publication with data updates for 2021 as available. The definition of products in biotechnology in this publication encompasses nine product categories; recombinant proteins, monoclonal antibodies (also fragments and antibody-drug conjugates), peptides (recombinant and molecular engineered), vaccines (recombinant and molecular engineered), oligonucleotides (RNA inhibitory molecules and gene therapies), cell therapies, tissue therapies, liposomes, and polymers. Naturally occurring substances and extracts from nature or blood can be biologicals, but they are not biotech and are excluded, as well as diagnostic agents being excluded.

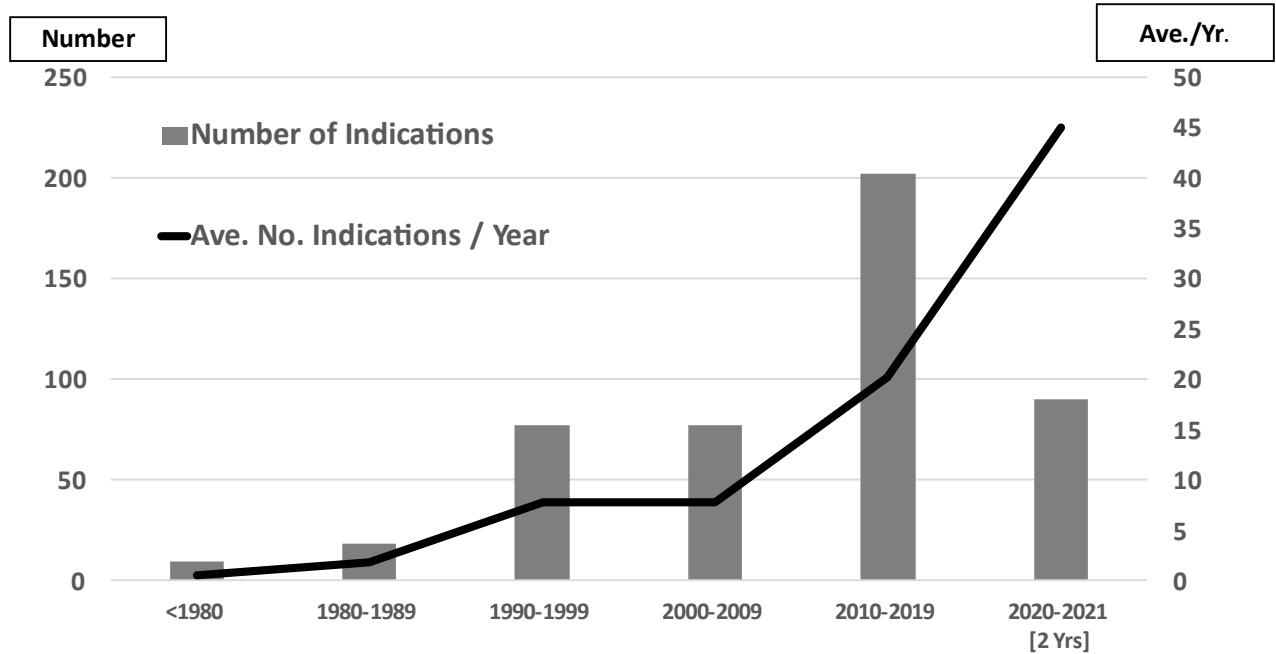
**Section 1. Introduction:** The 1960s and especially 1970s were the times for creating the core sciences of recombinant DNA technology and monoclonal antibodies that have and still do underpin biotechnology and also establishing the early biotechnology companies that produced the start of the biotechnology revolution in the 1980s. University based discoveries and innovations often have led to spin-out biotech companies. Success of the science and business of biotechnology in biopharma can be measured by the number and the variety of products, many indications with disease mitigations, companies (biotech and pharmaceutical), research & development, and product sales. In overview, biotechnology has demonstrated a substantial crescendo pattern of growth; first, with 518 products being marketed world-wide in United States (USA), Europe and Japan by December 2021 and 64 more products marketed in Europe and Japan; second, by 474 indications being approved by the USA Food & Drug Administration (FDA) and European Medicines Agency ; third, with 167 companies marketing products in United States (USA), Europe, and Japan in 2021; fourth, with over 420 companies conducting phase 3 clinical trials on 850

molecules for over 350 indications by 2021; and fifth, by \$327 million in worldwide sales occurring in 2020. From the first 20 years - 1980 to 1999 period, versus the second 20 years - 2000 to 2019 period, and then up to the recent 2 years of 2020 & 2021, we first can observe in USA a substantial product growth from 11.6 products per year versus 23.5 per year versus 35 per year (see Figure 1), respectively. Secondly and similarly dramatic growth occurred in the indications for biotech products in 10 year intervals from 1.8 per year versus 7.7 per year versus 20.2 per year versus 45 per year (see figure 2), respectively. Third, growth in companies (pharma and biotech) launching new biotech products increased from #51 companies in first 20 years versus #179 in second 20 years versus #72 (only 2 years, 2020 and 2021), respectively. In Figure 3. the evolution of the number of biotech FDA approved products is presented with steady and remarkable growth over time from 1980 to 2021 in 5-year intervals, along with added indications being approved for already marketed products. A promising stream of future products is quite likely with over 850 biotech products in phase 3 clinical trials for 350 plus indications by 425 pharma and biotech companies.

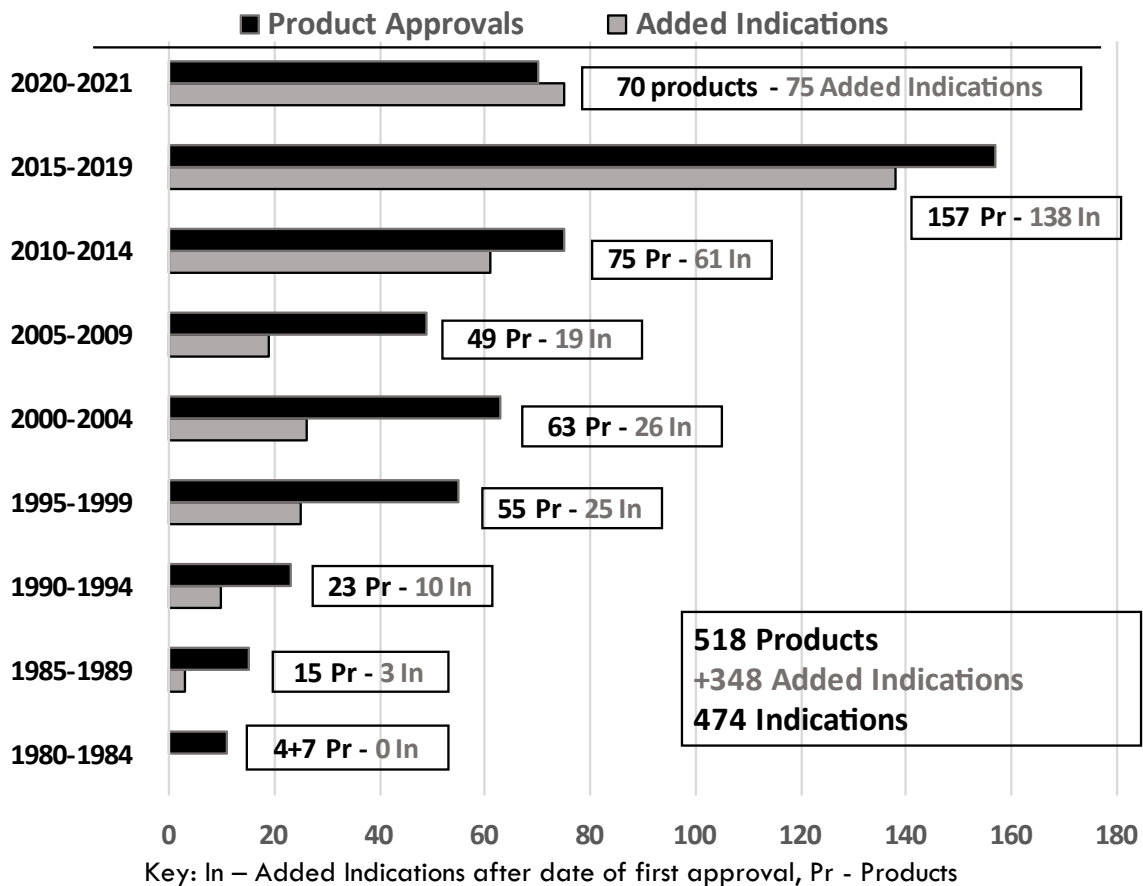
**Figure 1. Biotech Products – Number of FDA approvals Over Time [10-Year Time Intervals]**



**Figure 2.** Indications [First & Later Approvals] for Biotech Products Over Time [10-Year Time Intervals]



**Figure 3.** Biotech FDA Product Approvals from 1980 to 2021 [5-Year Time Intervals]



**Section 2. Products:** The categories of biotech molecules and products are tabulated for the USA FDA approvals up to December 31, 2021 in *Table 1*. The three largest categories of products are recombinant proteins, monoclonal antibodies, and peptides. Proteins (recombinant) comprise 152 products (126 molecules) in eight subcategories (coagulation, enzymes, fusion proteins, growth factors, hormones, interferons, interleukins, and toxins) addressing 150 indications. Second, monoclonal antibodies include 140 products (112 distinct molecules), addressing 178 indications. The third largest category of products is peptides (135 products) including both recombinant and molecular engineered molecules addressing 52 indications. Vaccines include recombinant molecules and molecular engineered products (especially conjugates and multi-serotypes), numbering 32 products and 22 indications. Five other categories include oligonucleotides (16 products, 12 indications), liposomes (13 & 14, respectively), cell therapies (13 & 15, respectively), tissues therapies (11 & 5, respectively), and polymers (5 & 7, respectively). The dramatic growth over time in types of

biotech products is presented in *Table 2*, elucidating substantial growth in 10-year windows of time from 26 products (1980-89) to 78 (1990-99) to 112 (2000-09) to 232 (2010-19) and to 70 (in only 2 years, 2020-2021). The type of biotech products developed have changed over time. The 10-year time period of 2000-2019 experienced quite large product growth, led by proteins with 96 products, monoclonal antibodies with 85, peptides at 68, vaccines at 19, oligonucleotides at 14, cell therapies at 14, and 19 others. These 232 products comprise 44.8% of all product approvals. Over time, monoclonal antibodies have increased to become the most common product approvals (114 in last 12 years) versus 68 peptides and 58 proteins. Earlier in the first 20 years, proteins accounted for 43 products versus peptides with 33 products, and monoclonal antibodies with only 8 products. Another couple prominent product developments in just recent years has been approvals of cell therapies and oligonucleotides, because of their technologies advanced to permit approvals of unique molecules with unique mechanisms of action for improved disease response rates.

**Table 1.** Biotechnology Products Approved by USA FDA by Categories [12.31.2021]

Product Categories:	# Molecules:	# Products:	# Indications:
<b>Antibodies (Mabs)</b>	113	140	180
<b>Proteins - Hormones</b>	13	26	32
<b>Proteins - Enzymes</b>	32	33	24
<b>Proteins - Growth Factors</b>	16	22	19
<b>Proteins - Interferons</b>	11	14	15
<b>Proteins - Interferons</b>	4	4	5
<b>Proteins - Coagulation</b>	28	31	10
<b>Fusion Proteins</b>	15 [+27] *	15 [+27] *	27
<b>Proteins - Toxins</b>	5	5	16
<b>Other Proteins</b>	2	2	2
<b>Vaccines (Recom. &amp; M.E.)</b>	32 [21 & 11] ^	32 [21 & 11] ^	22
<b>Liposomes</b>	11	13	14
<b>Cells</b>	13	13	14
<b>Tissues</b>	7	11	5
<b>Peptides (Recom &amp; M.E.)</b>	102 [40 & 62] ^	135 [48 & 87] ^	52
<b>Oligonucleotides</b>	16	16	15
<b>Polymers</b>	4 [+6]*	4 [+6]*	7 [+9]*
<b>Totals</b>	<b>424</b>	<b>518</b>	<b>473</b>

Footnote: M.E. – molecular engineered, Recom. – Recombinant, # - Number

\* The number in parens for fusion proteins & polymers designates additional products listed in other categories.

^ The numbers in parens for peptides and vaccines designates the number of molecules or products that are recombinant (1<sup>st</sup> number) and molecular engineered (2<sup>nd</sup> number).

**Table 2.** Types of Biotech Products [FDA Approvals] by Categories Over Time [10-Year Intervals]

Categories of Products	1980 - 1989*	1990 - 1999	2000 - 2009	2010 - 2019	2020 & 2021	Totals 1980-2021
<b>Hormones - Protein</b>	1	13	7	3	2	26
<b>Enzymes - Protein</b>	1	6	9	15	2	33
<b>Growth Factors – Protein</b>	2	3	8	8	1	22
<b>Cytokines – Protein</b>	2	8	4	2	1	17
<b>Blood Factors – Protein</b>	0	5	7	18	1	31
<b>Fusion Proteins<sup>^</sup></b>	0	1 [2]	4 [5]	8 [16]	2 [6]	15 [29]
<b>Toxins – Protein</b>	0	0	3	2	0	5
<b>Other Proteins</b>	1	0	0	0	1	2
<b>[All Proteins]</b>	<b>[7]</b>	<b>[36]</b>	<b>[42]</b>	<b>[56]</b>	<b>[10]</b>	<b>[149]</b>
<b>Peptides</b>	16	17	34	51	17	135
<b>Vaccines</b>	2	4	7	14	5	32
<b>Monoclonal Antibodies</b>	1	7	18	85	29	140
<b>Liposomes</b>	0	5	2	6	0	13
<b>Tissues</b>	0	3	6	4	1	14
<b>Cells</b>	0	2	1	6	4	13
<b>Polymers</b>	0	3	1	0	0	4
<b>Oligonucleotides</b>	0	1	1	10	4	16
<b>Decade Totals</b>	<b>26*</b>	<b>78</b>	<b>112</b>	<b>232</b>	<b>70</b>	<b>518</b>

Key: \* Prior to 1980, 4 peptides [molecular engineered] were FDA approved over 20 years and are included in the 1980-1989 tabulation. <sup>^</sup> Fusion proteins; the number in parens designates the fusion protein products also listed in other protein categories above. Total number of fusion proteins is the combination of the two numbers within & without parens.

Over these 40 plus years, 42 biotech products (8.1%) have been removed from the USA market mostly due to marketing changes (such as, new improved products, very low usage), and a few due to adverse effects. Another significant development addresses biosimilar biotech products, which are duplicates of previously approved recombinant products that have a separate and distinct approval process to establish similarity in quality, efficacy and safety. Biosimilars are a major development in last 15 years, starting in Europe in 2007 and USA in 2015 with 66 and 40 products, respectively, approved and marketed, involving 21 molecules (monoclonal antibodies - 6, proteins - 11, and peptides - 4). Worldwide, 36 companies market these 106 products in Europe and USA, plus nine companies in China are engaged as well. Providing the same patient care outcomes, biosimilars usually cost about 25% less or even more, offering possible cost-effectiveness to healthcare systems.

**Section 3. Indications:** Indications for biotech products numbered 474 as of 12.31.2021, which have grown quite dramatically in last 12 years (see figure 2); 1<sup>st</sup> 20 years equals 104 indications vs 344 indications in 2<sup>nd</sup> 20 years. The reasons for such growth are manifold; first, the discovery and marketing of many new products for previously untreated diseases of course. Second, the advances in diagnostics have created subcategories of disease that respond differently to products, especially in

oncology, such as, multiple genetic markers (positive or negative) in one disease, acute vs chronic disease, newly diagnosed vs advanced vs recurrent vs metastatic disease, tissue or cell location of disease (local vs invasive), multiple cell types in a tissue (e.g., squamous vs non-squamous, small cell vs non-small cell, 10-plus cell types in lymphoma). Third, multiple different treatment categories exist as well, such as induction vs maintenance, 1<sup>st</sup> - 2<sup>nd</sup> - 3<sup>rd</sup> - 4<sup>th</sup> lines of therapy, varied mechanisms of action vs same disease, and adverse event profiles. Biotech product indications are broad in the scope of diseases and can be represented by the number of indications per medical discipline, as demonstrated in table 3. Oncology presents by far the most indications [175], followed by infectious diseases [48], hematology [41], dermatology [34], and endocrinology [31], rounding out the top five medical disciplines. Biotech products dramatically overcame previously poorly and only symptomatic treatments to achieve pathophysiologic disease control, and also the first ever treatments for previously untreated diseases. A few examples follow; 1. Proteins, such as interferon-beta for multiple sclerosis, enzyme replacement therapy for incurable genetic diseases, such as, agalsidase beta for Fabry disease and elosulfase alfa for Morquio syndrome, darbepoetin for anemias in nephrology and oncology, factor eight recombinant proteins for Hemophilia A and B, etanercept for rheumatoid arthritis and psoriasis, aflibercept for acute macular degeneration, ovulatory

failure with follitropin alfa; 2. Peptides for osteoporosis with teriparatide, diabetes with liraglutide; 3. Oligonucleotides (RNA inhibition) such as nusinersen for spinal muscle atrophy and golodirsen for Duchenne's muscular dystrophy; 4. Vaccines for pneumococcal, herpes

zoster, meningitis, and Covid-19 infections; 5. Monoclonal antibodies (over 100) for manifold immune and oncologic diseases (170 plus), vastly improving patient responses and disease control.

**Table 3.** Indications for Biotech Products by Medical Discipline (1980 to 2021)

<u>Medical Discipline:</u>	<u>Number of Indications:</u>	<u>Medical Discipline:</u>	<u>Number of Indications:</u>
Cardiovascular	26	Neurology	26
Dermatology	34	Oncology	175
Endocrinology	31	Ophthalmology	20
Gastroenterology	12	Orthopedics	16
Genetic diseases	13	Pulmonary	11
Gynecology	16	Rheumatology	26
Hematology	41	Surgery	13
Infectious Disease	48	Urology	9
Nephrology	12		

Footnote: One indication fits and can be listed in more than one medical discipline.

**Section 4. Companies:** The companies engaged in biotechnology include the roles of research and development and / or sales and marketing. Overall, 222 companies from 1980s to 2021 were engaged in the discovery and early phase research (preclinical) of biotech molecules that resulted in the marketed products. The top 30 companies involved in R&D are presented in *table 4a*, in order of the number of molecules per company. The leading R&D companies for the most biotech molecule discoveries have been the companies which were fully focused on biotechnology (7 of top 10), that is, Genentech, Amgen, Novo Nordisk, Regeneron, Biogen, Genzyme, and PDL Pharma, along with three pharma companies, Novartis, Sanofi, and Eli Lilly. In the top 33 companies in biotech R&D,

biotech companies comprised 18 of them (55%). Of the companies creating biotech products (R&D), 11 of the top 33 were acquired mostly by pharma companies and also big biotech. The top 30 companies engaged in marketing and sales of biotech products, based on the number of marketed biotech products, are listed in *table 4b*. Nine of the top 10 companies in marketing (based on number of marketed biotech products) were pharma companies, because of three reasons, that is, company acquisitions, product acquisitions, and internal research programs. Amgen is the only biotech company in the top 10 marketing companies. Twenty of the top 35 marketing companies for marketed biotech products are pharma (57%).

Table 4a. Top 30 Companies in Biotech R&D: Molecule Discovery & Early Phase Research [1980-2021]
<b>Top 10 Companies in R&amp;D [Number of Molecules in Research in Brackets]:</b> <u>Genentech</u> [17], <u>Amgen</u> [16], <u>Novo Nordisk</u> [14], <u>Novartis</u> [14], <u>PDL Pharma</u> [11], <u>Sanofi</u> [11], <u>Regeneron</u> [9], <u>Biogen</u> [9], <u>Eli Lilly</u> [8], <u>Genzyme</u> [8]
<b>Next 12 Companies in R&amp;D:</b> <i>Enzon Pharma</i> [7], <i>GlaxoSmithKline</i> [7], <i>Merck</i> [7], <i>Chiron</i> [6], <i>Johnson &amp; Johnson</i> [6], <i>Roche</i> [6], <i>Serono</i> [6], <i>Cambridge Antibody Technology</i> [5], <i>Centocor</i> [5], <i>GenMab</i> [5], <i>Medarex</i> [5], <i>Nektar</i> [5]
<b>Next 9 Companies in R&amp;D [4 Molecules each]:</b> <i>AstraZeneca</i> , <i>Bayer</i> , <i>Genetics Institute</i> , <i>Halozyme</i> , <i>Ionis</i> , <i>MedImmune</i> , <i>Pfizer</i> , <i>Shire</i> , <i>Wyeth</i>
Table 4b. Top 30 Companies Marketing Biotech Products Worldwide [12.31.2021]
<b>Top 10 Companies in Marketing [Number of Products in Brackets]:</b> <u>Sanofi</u> [36], <u>Novartis</u> [32], <u>Takeda</u> [28], <u>AstraZeneca</u> [20], <u>Novo Nordisk</u> [23], <u>Eli Lilly</u> [23], <u>Amgen</u> [22], <u>Merck</u> [19], <u>Roche</u> [17], <u>Johnson &amp; Johnson</u> [17]
<b>Next 15 Companies in Marketing:</b> <u>Biogen</u> [13], <u>GlaxoSmithKline</u> [9], <u>Bristol Myers Squibb</u> [12], <u>SOBI</u> [11], <u>Viatrix</u> [11], <u>AbbVie</u> [10], <u>Regeneron</u> [10], <u>Ipsen</u> [9], <u>Kyowa Kirin</u> [9], <u>Merck KGaA</u> [9], <u>Organon</u> [9], <u>Samsung Bioepis</u> [9], <u>Astellas</u> [8], <u>Boehringer Ingelheim</u> [8], <u>Ferring</u> [8]
<b>Next 10 Companies in Marketing:</b> <u>BioMarin</u> [6], <u>JCR Pharma</u> [6], <u>Azurity</u> [5], <u>Bausch Health</u> [5], <u>Celltrion</u> [5], <u>CSL Behring</u> [5], <u>Eisai</u> [5], <u>Gilead</u> [5], <u>Jazz</u> [5], <u>Smith &amp; Nephew</u> [5]

Key: Underlined companies are or were biotech focused. Italic print indicates companies that were acquired by a pharma or big biotech company.

The top companies marketing biotech products based on biotech sales are addressed in table 5 over time (20 years) for years, 2001, 2005, 2010, 2015, and 2020 [see Table 5]. The top companies throughout these 20 years were Roche, Amgen, and Novo Nordisk, with AbbVie and Merck joining the top 5 in 2020. In 2001, 8 of the top 15 companies based on sales were biotech companies, and by

2010 and 2020, only 4 companies were biotech. By 2010, Roche transformed into a predominately biotech company with biotech sales comprising 70-80% of all product sales and their focus on biotech molecules in R&D. In table 5, the biotech companies are underlined, and the companies that were acquired are in italic print.

**Table 5.** Top Companies in Worldwide Biotech Sales for 2001 – 2005 - 2010 – 2015 - 2020

#	2001	\$ B	2005	\$ B	2010	\$ B	2015	\$ B	2020	\$ B
1	<u>Johnson/J</u>	4.15	<u>Amgen</u>	11.81	<u>Roche</u>	23.93	<u>Roche</u>	30.26	<u>Roche</u>	40.19
2	<u>Amgen</u>	3.59	<i>Roche</i>	11.15	<u>Amgen</u>	14.35	<u>Amgen</u>	19.53	<i>AbbVie</i>	25.34
3	<u>Novo Nord</u>	3.93	<u>Genentech</u>	7.98	<u>Novo Nord</u>	9.53	<i>AbbVie</i>	15.58	<u>Amgen</u>	21.57
4	<i>Eli Lilly</i>	2.64	<i>Johnson/J</i>	5.85	<i>Pfizer</i>	9.28	<u>Novo Nord</u>	15.19	<i>Merck</i>	20.20
5	<i>Roche</i>	2.59	<u>Novo Nord</u>	4.79	<i>Merck</i>	8.63	<i>Sanofi</i>	12.17	<u>Novo Nord</u>	19.29
6	<i>Novartis</i>	2.42	<i>Wyeth</i>	3.74	<i>Abbott</i>	8.10	<i>Pfizer</i>	12.13	<i>Johnson / J</i>	19.24
7	<u>Genentech</u>	2.21	<i>Eli Lilly</i>	3.51	<i>Sanofi</i>	8.03	<i>Johnson/J</i>	11.45	<i>Sanofi</i>	15.90
8	<u>Schering-P</u>	1.83	<u>Schering-P</u>	2.85	<i>Johnson/J</i>	7.48	<i>Eli Lilly</i>	7.11	<i>Eli Lilly</i>	15.57
9	<i>Wyeth</i>	1.51	<i>Sanofi-Av</i>	2.79	<i>Eli Lilly</i>	6.05	<i>Merck</i>	6.96	<i>Bristol MS.</i>	15.05
10	<u>Serono</u>	1.38	<i>Abbott</i>	2.31	<i>Merck K.</i>	4.56	<i>Novartis</i>	6.78	<i>Novartis</i>	14.13
11	<u>Biogen</u>	1.29	<i>Schering A</i>	2.27	<i>Novartis</i>	4.39	<u>Biogen</u>	6.72	<u>Regeneron</u>	13.33
12	<u>Chiron</u>	1.17	<u>Biogen</u>	2.52	<u>CSL Behr.</u>	4.01	<i>Shire</i>	5.83	<i>Takeda</i>	11.05
13	<i>Immunex</i>	0.76	<u>Serono</u>	2.16	<i>GlaxoSK.</i>	3.42	<i>Bristol MS</i>	4.54	<i>Pfizer</i>	10.78
14	<u>Genzyme</u>	0.69	<i>Novartis</i>	1.85	<i>Teva</i>	3.31	<i>Merck K.</i>	3.78	<u>Biogen</u>	9.92
15	<u>Schering A</u>	0.61	<u>Genzyme</u>	1.68	<u>Biogen</u>	3.15	<i>Bayer</i>	3.52	<i>GlaxoSK.</i>	7.73
	Tot. \$30.68		Tt. \$67.26		T. \$118.22		T. \$161.54		T. \$259.21	

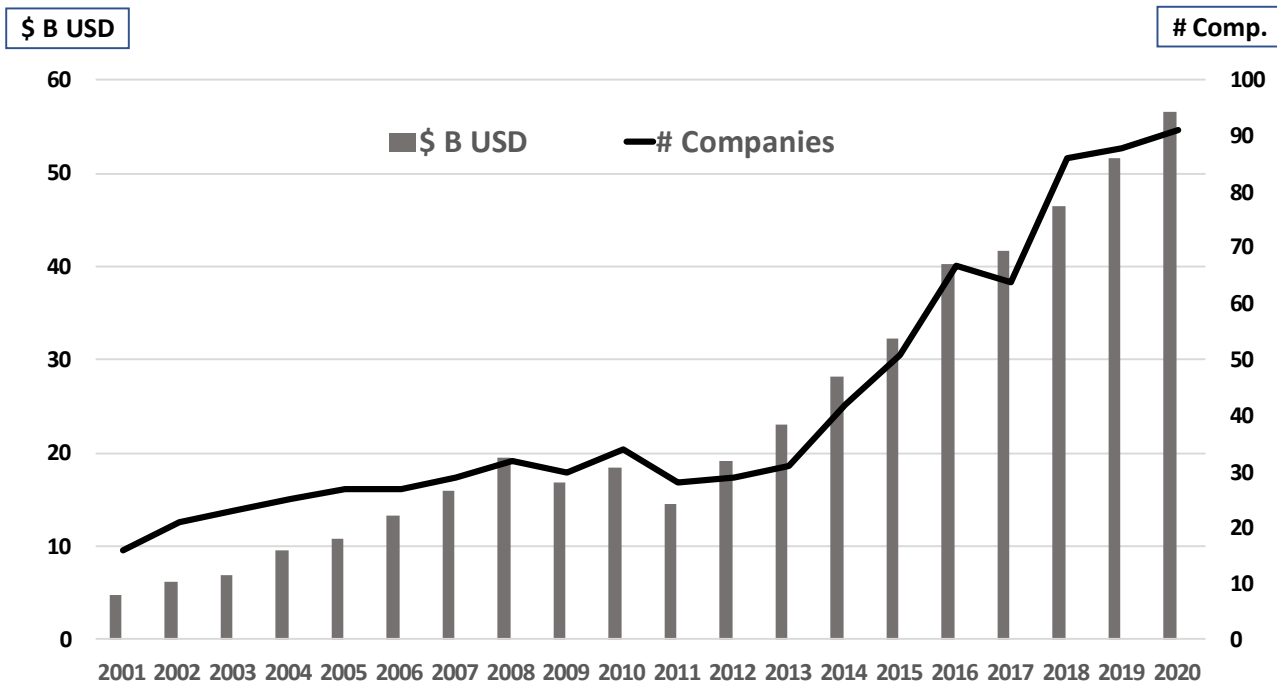
Key: # - Rank order of companies, highest sales to lowest. \$ B - Billions of U.S. dollars. Tot. / Tt / T. - Total U.S. dollars. Italic print designates company that was acquired in later years. Underlining indicates a biotech focused company. Bristol MS. - Bristol Myers Squibb, CSL Behr. - CSL Behring, GlaxoSK. - GlaxoSmithKline, Johnson/J - Johnson & Johnson, Merck K. - Merck KGaA, Novo Nord - Novo Nordisk, Schering A - Schering AG, Schering PI - Schering Plough



**Section 5. Finances:** Financial considerations for biotech evolution are addressed in three areas; R & D financing for biotech, initial public offerings (IPOs) for biotech companies moving from private to public companies with major cash infusions, mergers and acquisitions of biotech by pharma companies, and recent immune-oncology R & D investments, all of which have grown substantially in dollar values and number of transactions over the full 40

plus years. R&D financing by biotech companies has experienced significant growth over these 40 years for the leading biotech companies, spending \$100 million of more on R & D in one year, from 16 companies spending \$4.8 billion in 2001, to 34 at \$18.5 billion in 2010, to 51 at \$32.4 billion, up to 91 at \$56.6 billion in 2020 (see Figure 4).

**Figure 4. R&D Financing of Biotech Companies Over Time [\$ Billions USD] [Companies Funding at or over \$100 million in one year]**

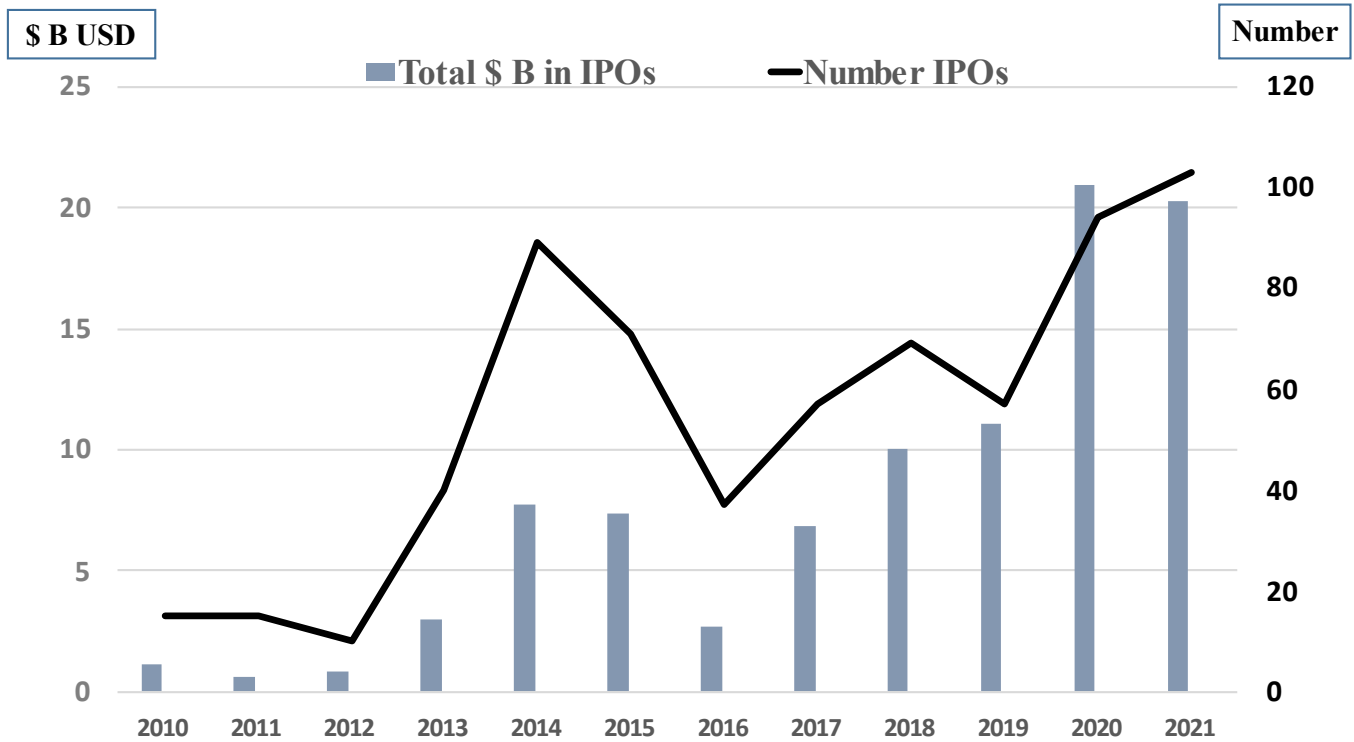


The financing of biotech companies also is found in initial public offerings (IPOs) when a company moves from private to public status, which is based mostly on their scientific advances and future financial opportunity, and also is found in the investments from pharma and big biotech through partnership funding with biotech companies. Figure 5 displays well the number and amounts of IPO investments and the dramatic growth committed; in 2010, \$1.12 billion for 15 IPOs, in 2015, \$7.39 billion for 71 and in 2020 \$20.05 billion for 91. Partnership funding from pharma companies to biotech can demonstrate as well the major financial investments within the biopharma industry for biotech R&D, \$6.0 billion in 2002, \$22.4 B in 2007, \$37.9

B in 2012, 68.7 B in 2017 and 109.4 B in 2020. Before and after IPOs are executed, research biotech companies often need infusions of cash at regular intervals in order to continue their research, which is accomplished with follow-on stock offerings, multiple venture capital rounds of funding, government grants, and especially partnership funding from pharma or big biotech companies, the latter of which usually amounts to 40-60% of all funds/investments in any one year for biotech companies; for example, \$6 billion out of \$10 B total in 2002, \$22.4 out of \$52.8 total in 2007, \$37.9 out of \$74.1 total in 2012, \$64.6 B out of \$137.4 B total in 2017.



**Figure 5.** Initial Public Offerings [IPOs] for Biotech Companies 2010 to 2020



A major financing development in the evolution of biotechnology for both R&D and S&M is the mergers and acquisitions of biotech companies mostly by pharma companies and some big biotech over these 42 years. *Table 6* summarizes the mergers and acquisition by pharma companies of their biotech counterparts from 1998 to 2021, spending over \$1 trillion on about 300 deals, increasing massively from \$28 billion in 1998-2003 to \$395 billion in 2018-2021. *Table 6* additionally lists the top 42 company pairs that were blockbusters deals (over \$1 billion up to \$60 plus billion). Furthermore in R&D funding, immuno-oncology area has become a major focus of the biopharma industry

in only the last decade with novel molecules, novel mechanisms of action maximizing immune stimulation, and substantial increases in cancer mitigation and response rates. In the timeframe of only 2013 to 2021, 669 companies have dedicated R&D to immune-oncology products, such as monoclonal antibodies, various cell therapies, vaccines, proteins, peptides, and small molecules and 13 products have been approved, mostly monoclonal antibodies and cell therapies so far. Over 2012 to 2021, the number of collaborative deals has been 418 by 285 different companies at investments (original payments and future long-term biobucks) of \$241.8 billion.

**Table 6.** Mergers & Acquisitions of Biotech Companies by Pharma Companies Over Time

Years	# Deals / # Dollars	Major Biotech Deals [Mega Blockbusters at or over \$5 B] [Acquirer & Acquired Company]
2018 – 2021 [4Yrs]	77 \$395 B	AbbVie – Allergan, AstraZeneca – Alexion, BMS – Celgene, Celgene – Juno & Impact Bio, Gilead – Immunomedics & Forty-Seven & Kite Pharma, Johnson & Johnson – Momenta, Merck – Acceleron, Novartis – AxeVis & The Medicines Company, Roche – Spark, Sanofi – Bioverativ & Ablynx, Takeda -Shire
2017 - 2013	79 \$258 B	AbbVie – Pharmacyclics & Stemcentrx, Actavis – Allergan, Gilead – Pharmasset, Merck – Cubist, Perrigo – Elan, Pfizer – Medivation, Roche – Intermune, Shire – Baxalta & Dyax & NPS
2012 - 2008	80 \$268 B	BMS – Amylin, Eli Lilly – Imclone, Johnson & Johnson – Crucell, Pfizer – Wyeth, Roche – Genentech [49%], Sanofi – Genzyme, Takeda – Millenium, Teva – Cephalon & Ratiopharm

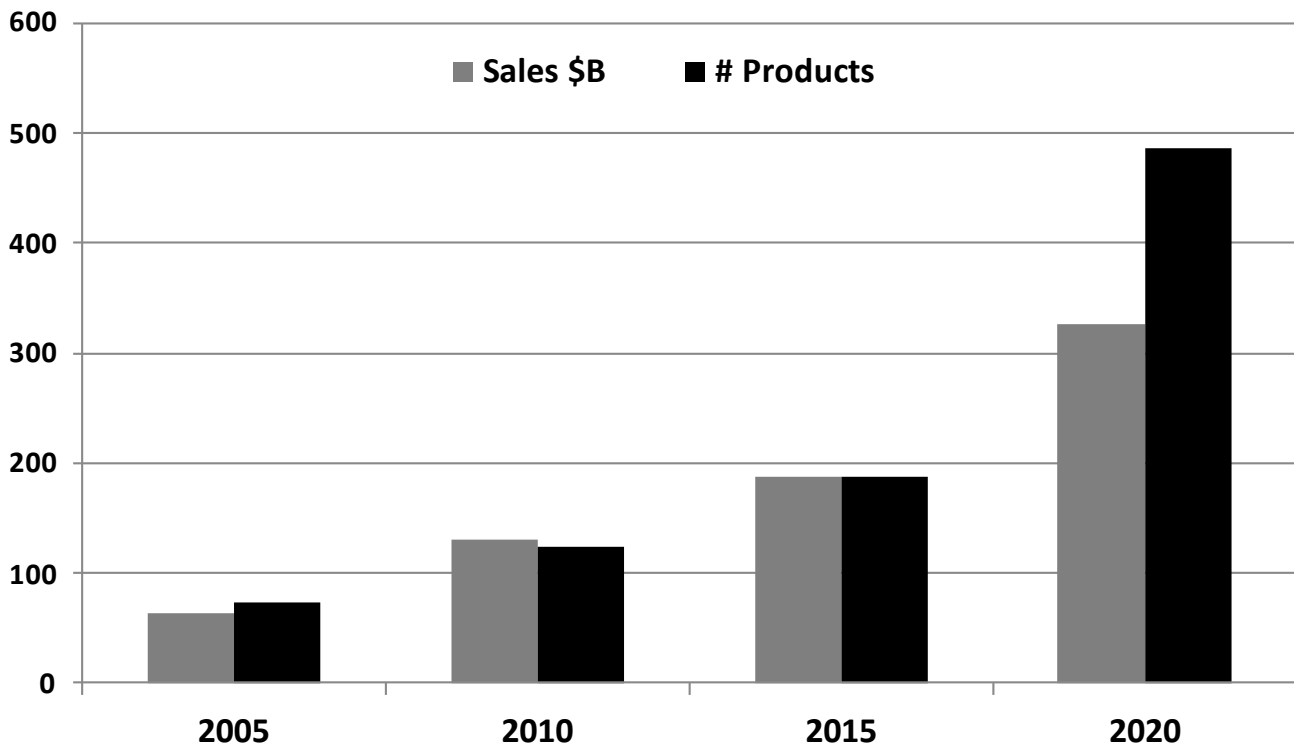
2007 - 2003	42 \$110 B	AstraZeneca – MedImmune, Merck – Organon (via Schering-Plough), Merck KGaA – Serono
2002 - 1998	20 \$28 B	Johnson & Johnson – Alza & Centocor, Pfizer – Genetics Institute, Roche – Genentech [51%]

Key: B – \$ Billions of U.S. Dollars, BMS – Bristol Myers Squibb

**Section 6. Sales:** Success of biotechnology can also be measured by the sales of biotech products, reaching \$327 billion worldwide for about 500 products in 2020, and exceeding about 25% of all drug sales. The growth in sales volume worldwide was from \$33.4 billion for 73 products reporting their sales up to the \$327 billion for 487 products where sales are reported for individual products (see Figure 6). Additionally, a comparison of the top 100 drugs and biotech products in 2020 displays the success of biotech further with biotech comprising 52 products at a cost of \$291 billion to drugs at 48 products at a cost of \$149 billion. The top 15 biotech products based on annual worldwide sales are listed in table 7. Total sales for these

top 15 products increased almost 6-fold from \$20 Billion in 2001 to \$113 billion in 2020. The type of products in these sales groupings changed over time in the predominance of proteins versus monoclonal antibodies (mabs); 2001 - 8 proteins vs 2 mabs; 2010 - 6 proteins vs 6 mabs; 2020 – 3 proteins vs 8 mabs. In table 7, the medical disciplines for the top 15 products are noted by a superscript, and, as can be observed, ten disciplines are engaged with these top 15 products; e -endocrinology, g – genetic disease, h-hematology, i -immune (dermatology, gastroenterology, rheumatology), id – infectious disease, n – neurology, ne – nephrology, o – oncology, op – ophthalmology, p – pulmonary, t – transplant.

Figure 6. Biotech Total Product Sales Over Time - 2005 to 2020



**Table 7.** Top Biotech Products in Worldwide Sales: 2001 - 2005 - 2010 - 2015 - 2020

#	2001	\$ B	2005	\$ B	2010	\$ B	2015	\$ B	2020	\$ B
1	Procrit <sup>ne/o</sup>	3.43	Rituxan <sup>o</sup>	5.57	Remicade <sup>i</sup>	8.37	Humira <sup>i</sup>	14.36	Humira <sup>i</sup>	20.24
2	Epogen <sup>ne/o</sup>	2.11	Enbrel <sup>i</sup>	3.66	Enbrel <sup>i</sup>	7.37	Remicade <sup>i</sup>	9.16	Keytruda <sup>o</sup>	14.38
3	Rituxan <sup>o</sup>	1.77	Remicade <sup>i</sup>	3.48	Rituxan <sup>o</sup>	7.11	Enbrel <sup>i</sup>	8.70	Eylea <sup>o</sup>	10.71
4	Novolin <sup>e</sup>	1.74	Procrit <sup>ne/o</sup>	3.32	Humira <sup>i</sup>	6.66	Rituxan <sup>o</sup>	8.28	Stelara <sup>i</sup>	8.01
5	Enbrel <sup>i</sup>	1.62	Aranesp <sup>ne/o</sup>	3.27	Avastin <sup>o</sup>	6.19	Avastin <sup>o</sup>	7.19	Opdivo <sup>o</sup>	7.92
6	Peg-Intron <sup>id</sup>	1.45	Copaxone <sup>n</sup>	3.00	Hercept. <sup>o</sup>	5.20	Lantus <sup>e</sup>	7.02	Enbrel <sup>i</sup>	6.35
7	Neupogen <sup>o</sup>	1.35	Epogen <sup>ne/o</sup>	2.46	Lantus <sup>e</sup>	4.65	Herceptin <sup>o</sup>	6.55	Rituxan <sup>o</sup>	6.23
8	Sandimmune <sup>i/t</sup>	1.20	Neulasta <sup>o</sup>	2.29	Copaxone	4.00	Prevnar <sup>id</sup>	6.25	Prevnar <sup>id</sup>	5.85
9	Humulin <sup>e</sup>	1.11	Bioclata <sup>h</sup>	2.20	Neulasta <sup>o</sup>	3.56	Copaxone <sup>n</sup>	4.93	Ocrevus <sup>n</sup>	5.48
10	Herceptin <sup>o</sup>	0.74	Herceptin <sup>o</sup>	2.11	Lucent. <sup>op</sup>	2.98	Neulasta <sup>o</sup>	4.80	Trulicity <sup>e</sup>	5/39
11	Zoladex <sup>o</sup>	0.73	Avastin <sup>o</sup>	1.97	Avonex <sup>n</sup>	2.55	Eylea <sup>op</sup>	4.03	Avastin <sup>o</sup>	5.34
12	Gonal-F <sup>e</sup>	0.73	Novolog <sup>e</sup>	1.91	Epogen <sup>ne/o</sup>	2.52	Lucentis <sup>op</sup>	3.59	Remicade <sup>i</sup>	4.50
13	Betaseron <sup>n</sup>	0.68	NovoRap. <sup>e</sup>	1.91	Aranesp <sup>ne</sup>	2.48	NovoRapid <sup>e</sup>	3.08	Darzalex <sup>o</sup>	4.19
14	Synagis <sup>id</sup>	0.52	NeoReco. <sup>ne</sup>	1.79	Prevnar <sup>id</sup>	2.42	Advate <sup>h</sup>	2.84	Perjeta <sup>o</sup>	4.16
15	Cerezyme <sup>g</sup>	0.50	Avonex <sup>n</sup>	1.54	Rebif <sup>n</sup>	2.20	Levemir <sup>e</sup>	2.72	Dupixent <sup>d/p</sup>	4.13
	<b>Total \$19.68</b>		<b>Tot. \$40.39</b>		<b>Tot \$68.27</b>		<b>Tot. \$93.50</b>		<b>Tot. \$112.88</b>	

Key: # Designates rank order of products from highest sales to lowest.

Designates more than one product lumped together by company; Darzalex – Darzalex/Darzalex Faspro, Novolog – Novolog/Novolog N, Prevnar – Prevnar 7/13, Procrit – Procrit/Epex, Rituxan – Rituxan/ Mabthera

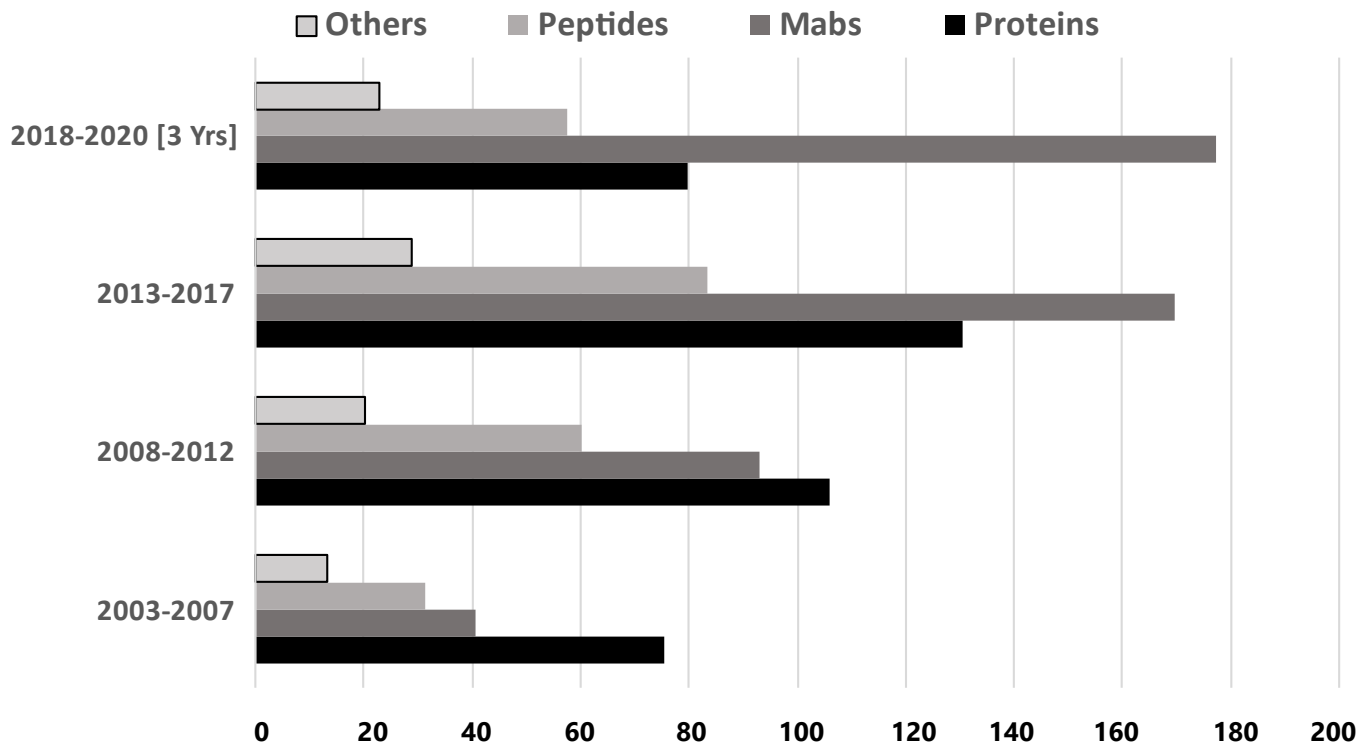
Abbreviations: B – Billions of U.S. dollars, Hercept – Herceptin, Lucent – Lucentis, NeoReco – NeoRecormon, NovoRap – NovoRapid, Tot. – Total sales for top 15 products.

Superscripts designate usage areas based on medical disciplines; d – dermatology, e – endocrinology, g – genetic diseases, h -hematology, i – immune diseases (in dermatology, gastroenterology, rheumatology), id – infectious disease, n – neurology, ne – nephrology, o – oncology, op – ophthalmology, p – pulmonary, t -transplant

We can observe in figure 7 that all worldwide biotech product sales are tabulated by the 3 main types of products; proteins, monoclonal antibodies, and peptides, along with an other category. Examining all biotech product sales from 2003 to 2020 (see figure 7), proteins are the most common product category in first 20 years based on total sales, and monoclonal antibodies are the most common in second 20 years. The two areas of oncology and the immune diseases (including medical disciplines of dermatology, gastroenterology, ophthalmology, pulmonary and rheumatology) predominate in the number of approved biotech products and products sales. In further examination, blockbuster products, as defined by sales of \$1 billion in one year, have increased extensively in the following 5-year intervals; #20 in 2003, #38 in 2008, #47 in 2013,

#64 in 2018, and #81 in 2020. For the 81 blockbuster products in 2020, the medical discipline of oncology ranked first in estimated sales at \$79.1 billion, followed by endocrinology at \$29.1 B (Diabetes mellitus 27.9 B), dermatology at \$27.8 B, rheumatology at 26.6 B, gastroenterology at \$15.7 B, infectious disease at \$15.0 B, ophthalmology at \$14.2 B, and neurology at \$13.7. The top 15 companies with biotech product sales are presented in Table 5 with Amgen, Novo Nordisk, Roche as lead companies from 2002 through 2020. However, the top 15 companies based on sales changes significantly over time, as both more companies have acquired biotech products and also other companies dedicated themselves to develop biotech internally, as well as product in-licensing.

**Figure 7.** Biotech Worldwide Product Sales by Types of Products [Proteins, Monoclonal Antibodies (Mabs), Peptides, Others] [in Billions USD]



**Summary:** This treatise describes the extensive and manifold roles biotech has played in developing the leading products, creating the leading companies, and advancing health care for hundreds of diseases. The growth in biotechnology has been consistent and dramatic in number of products, types and novelty of molecules; number, breadth and novelty of indications; breadth and extent of

research; extensive product sales; number and type of companies, all of which well establishes biotechnology as a revolution in both the biopharma industry and healthcare over these only 40 plus years. This growth and expansion is expected to continue well into this 21<sup>st</sup> century.

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