Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: May 31, 2023

Citation: Evens RP, 2023. Biotechnology Commitment by Pharma Industry and its evolution vs Biotech Companies in Healthcare, Drug Development, and Business, Past & Present [2001-2022], Medical Research Archives, [online] 11(5). https://doi.org/10.18103/mra.v11i5.3876

DOI
https://doi.org/10.18103/mra.v11i5.3876

ISSN: 2375-1924

RESEARCH ARTICLE

Biotechnology Commitment by Pharma Industry and its evolution vs Biotech Companies in Healthcare, Drug Development, and Business, Past & Present [2001-2022]

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ABSTRACT:
What is the commitment of the pharma industry to biotechnology in its research, products, and business practices? Five issues demonstrate the pharma companies' extensive engagement with and embrace of biotechnology as a primary focus in their business practices (marketing, sales, acquisitions) and research over the timeframe of 2000 through 2022. Overall trends for biotechnology [1980 to 2000 to 2022] are explored for context and display the overall extent of biotech impact on products approved (number and types), their breadth of indications, and extent of utilization/sales. Discovery of biotech molecules addresses pharma versus biotech companies' results, significantly favoring biotech companies. The top 100 biotech products and drugs are discussed for 2001 versus 2011 versus 2021, especially changes over time, with pharma growth exceeding biotech companies. The top pharma & biotech companies are examined for marketing of biotech products, again showing dramatic expansion of pharma engagement. Mergers and acquisitions of biotech companies by pharma companies is presented, especially the extensive investments and breadth and depth of pharma companies engaged. All these parameters (products, companies, research, sales, company acquisitions) well documents the movement of pharma companies collectively to substantially incorporate biotech products into their research pipelines and product portfolios.

Introduction:

The biotechnology industry is considered to have started in the 1970s as evidenced by these 20 founding companies created in those early years of 1970s to especially early 1980s, such as, *Agouron*, Amgen, Biogen, *Centocor*, *Cetus*, *Chiron*, *Genentech*, *Genetics Institute, Genzyme*, *Imclone*, ImmunoGen, *Immunomedics*, *Immunex, MedImmune, Millenium,* Sarepta*, Scios, Sequus, Sicor*, and *Zymogenetics* in the United States [Italic print shows 16 of these 20 companies were acquired]. Leading biotech product companies in Europe were *Celltech*, Grifols, Ipsen, Novo Nordisk, *Serono*, and SOBI/KabiVitrum. The initial and cornerstone biotech technologies for product development were and are twofold, recombinant DNA and monoclonal antibody technologies, which account for 68.9% of all products approved in the United States through 2021. The first product officially recognized as produced through biotechnology, via recombinant DNA work, was the peptide, insulin, in 1982 at Genentech. In the 1980s and 1990s, only seven pharma companies were significantly and consistently engaged in biotechnology, Eli Lilly, Johnson & Johnson, Novo Nordisk, Roche, Schering AG, Schering-Plough, and Wyeth, mostly through product and company acquisitions. Over the 22 years from 2000 to 2021, all pharma worldwide companies became engaged in biotechnology substantially. Roche represents a company converting from pharma status before 1990 to the leading biotechnology company in product development and marketing. Worldwide biotech product sales reached $459.2 billion in 2021, which was 32% of worldwide all drug and product sales ($1,433.5 billion worldwide). In 2021, 576 biotech products were marketed in United States, European Union, Japan, and China worldwide by 175 companies, including #33 pharma and #73 biotech companies, along with 33 privately held companies, 15 biosimilar focused companies, and 23 others (e.g., generic, device). Co-marketing of biotech products by a pharma and biotech company is commonplace. Hundreds of biotech companies were acquired over 40 years from 1980 to 2021 by pharma companies totaling an investment of over $1 trillion dollars. Also, in-licensing of biotech products by pharma companies has been a common vehicle for biotechnology involvement. Research pipelines filled with biotech products are a predominant feature of pharma companies research, ensuring that many future biotech products are being developed by and then marketed by the pharma industry. In this publication, a biotechnology product includes eight product categories; recombinant proteins, monoclonal antibodies (including conjugates and fragments), peptides (recombinant and molecularly engineered), vaccines (recombinant and molecularly engineered), liposomal products, oligonucleotides (gene therapies and RNA inhibitory products), cell therapies, and tissue therapies. Proteins include blood factors, cytokines, enzymes, fusion proteins, growth factors, hormones, and toxin proteins. Plasma derived products, traditional vaccines, and extracts from nature are biological but are not considered emanating from biotechnology and are not included.

Materials & Methods:

This biotechnology review manuscript presents data summaries and calculations from the author's biotechnology records and files. The author has biotechnology databases (#45), that have been collected, maintained, tabulated, and summarized over the past 25 years on an annual basis from 2000 up to current times. Six categories of biotech-related data and information are maintained; 1. Marketed products in United States, Europe, Japan, China and rest of the world, including all categories of biotech products, indications, and their features [manufacturing and structural], 2. Companies (pharma and biotech) engaged in marketing and research of biotech products (products, companies, sales, research), 3. Mergers and acquisitions of biotechnology companies by pharma and biotech companies, 4. Research and development (molecules and research budgets), 5. Regulatory activity with biotech products (marketing and research activities and special designations) in United States and European Union, and 6. Sales of biotech products [worldwide] by individual products, by product categories, by company, by diseases (annually and over time). This publication abstracts data from these databases focused on pharma company engagement with biotechnology from 2000 to 2021. The information and data sources for these databases are quite extensive and include especially company annual reports and their news reports (over 200 companies annually), newsletters (e.g., FierceBiotech, FiercePharma, FierceVaccines, DIA Digest, BioWorld, FDA), technical and business reports (e.g., CenterWatch, EvaluatePharma, IQVIA, Statistica, BioWorld, Reuters), pharmaceutical organizations (BIO, PhRMA), government (FDA and EMA), and journals (e.g., Nature Biotechnology, Nature Reviews Drug Discovery, Genetic Engineering & Biotechnology News). All the data in the tables, graphs and narrative in this manuscript originates from and are

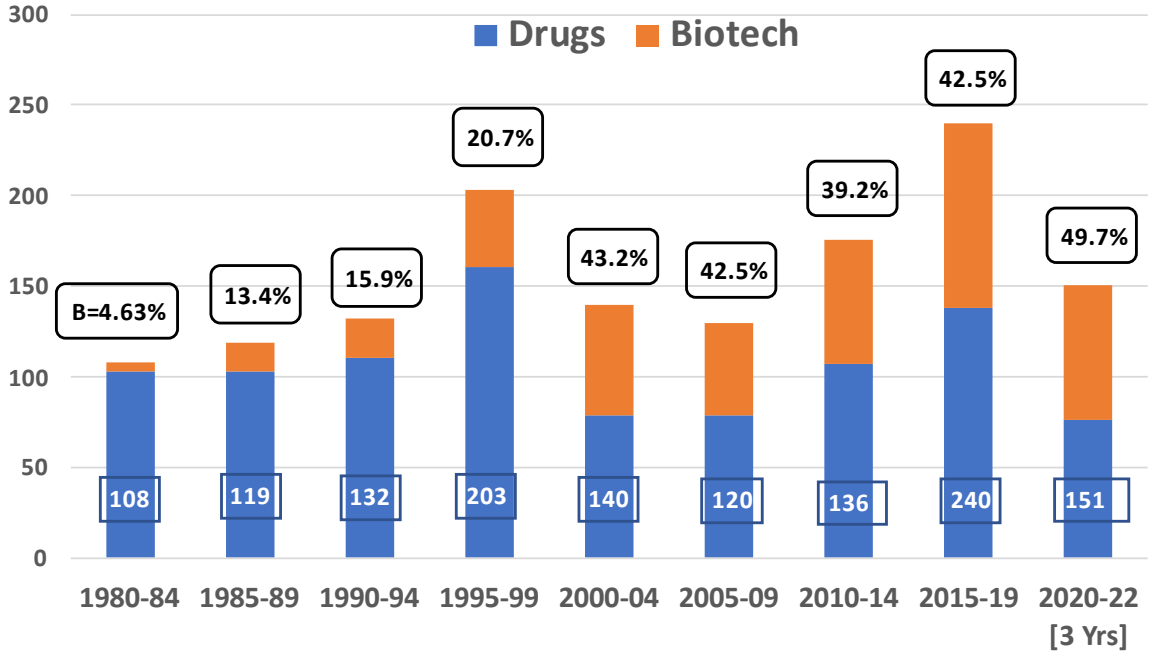
extracted from these biotech databases by the author, Ronald P Evens, B.S. Pharm., Pharm.D., FCCP, Research Professor, Center for the study of Drug Development, School of Medicine, Tufts University, Boston, Massachusetts and President of M.A.P.S. Biotech Inc, Napa, California. The biotechnology data tabulated and summarized here-in are targeted at the question of the commitment of the pharma industry to principally incorporating biotechnology into their research, product developments and marketing, and business practices.

Results:

Overall Trends for Biotechnology [1980 to 2000 to 2022]:

Regarding biotech products approvals in the United States (USA) by the Food & Drug Administration (FDA), **graph #1** displays the growing role of biotech in both the number of products per 5-year windows of time and the percentage of biotech products approved as well. From 1980 to 1999, biotech was the designation for 5% to 21% of approvals versus 39% to 49% from 2000 to 2020. Novel drugs and products include new molecular entities, new biological entities, as well as novel biotech products from molecular engineering that are blood proteins, peptides, cell therapies, gene therapies, RNA therapies, tissue therapies, liposomes, and vaccine.

Graph 1. Novel Drugs & Novel Biologic Products Approvals by FDA Over Time



Footnotes:

1.Y-axis is the number of products approved by Food & Drug Administration. X-axis is the 5-year time periods.

2. The numbers inside the blue bars indicate the total novel drugs AND novel biotech products approved by the FDA in that time-period.

3. The percentages in the boxes above the bars are the percentages of biotech products out of the total products and drugs approved in the time-period.

4. Biotech products include recombinant molecules and novel molecularly engineered products that are fusion proteins, coagulation proteins, peptides, oligonucleotides, vaccines, cell therapies, tissues therapies, and liposomes.

Furthermore, every decade displays [**see table 1**] a growing number of approvals in United States for pharma, biotech and other companies collectively. The number of companies engaged in new product approvals also increased significantly over time. Additionally, the number of indications grew substantially as well. These three overall biotech trends displayed in table one demonstrate the consistent, substantial, and dramatic growth in biotechnology from 1980 through 2022, culminating in 558 products, 512 indications and 207 separate companies. The number of indications

in 2010 and onward ballooned dependent on many new products for previously poorly treated diseases and especially on the expanded diagnostic parameters employed, including disease stages, first to up to 4th lines of treatments, hormonal designations (particularly in oncology), especially genetic subcategorization of diseases, and multiple drug combinations for a single disease. The breadth of indications for biotech products is expansive as demonstrated in **Table 2** for 17 disease areas being addressed with oncology by far the largest category. The number of products impacting each disease area is also noted. Another perspective on the usage areas for biotech is evidenced in **table 3** presenting the sales totals for the disease categories for top 100 products, along with the number of products in top 100 used for that usage area. Although oncology is usually the top area of use for biotech, infectious disease was the number one usage area based on 2021 sales, but this year was especially influenced by the height of the covid-19 epidemic and only five products costing $74 .1 billion. The most commonly treated specific diseases with biotech products are presented in **table 4**, ranking based on number of products employed to manage the specific indications. In the ranking of diseases, 10 specific conditions have 15 to 27 biotech products being utilized.

Worldwide biotech product sales reached $459.2 billion in 2021, which was 32% of worldwide all drug and product sales ($1,433.5 billion worldwide). In 2021 worldwide, 176 total companies marketed 578 biotech products in United States, European Union, Japan, and China, including #33 pharma and #72 biotech companies, along with 33 privately held companies, 15 biosimilar focused companies, and 22 other companies (e.g., generic, device). In United States and Europe, biotech companies marketed 38.5% of biotech products versus 52.8% by pharma companies, as well as 5.9% by biosimilar companies and 8.0% by private companies.

Table 1. Biotechnology – Number of Indications, Products & Companies Over Time in United States

Dates:	New Indications:	New Products:	No. Biotech Companies:	No. Pharma Companies:
Before 1980:	9	4	0	4
1980 to 1989:	18	25	17	15
1990 to 1999:	80	79	47	20
2000 to 2009:	78	113	69	20
2010 to 2019:	203	237	113	22
2020 to 2022:	123 **[3 Yrs]**	100	47	19
TOTALS over Time	**511**	**558**	**156**	**47**

Footnotes: 1. A company in any one decade can also market a product in another decade. 2. The totals for the number of companies represent how many individual different companies have originally marketed the products.

Table 2. Indications of Biotech Products – Disease Areas* & Over Time* [511]

	Disease Area	# Indications	# Products		Disease Area	# Indications	# Products
1	Oncology	183	175	**10**	Gynecology	15	86
2	Hematology	44	86	**11**	Rheumatology	13	48
3	Infectious Disease	41	87	**12**	Gastroenterology	13	49
4	Endocrinology	33	86	**13**	Nephrology	12	36
5	Neurology	26	42	**14**	Pulmonary	12	28
6	Dermatology	25	70	**15**	Surgery	12	23
7	Cardiovascular	24	42	**16**	Orthopedics	10	19
8	Ophthalmology	21	23	**17**	Other	10	10
9	Genetic Disease	15	31	**18**	Urology	4	25

Indications Over Time:	**<1980** - #9	**1980-89** - #18 2.4/Yr.	**1990-99** - #80 8/Yr.	**2000-09** - #78 7.8/Yr.	**2010-19** - #203 20.3/Yr.	**2020-22** - #122 40/Yr.

Table #3 Usage Areas & their Ranking for Top 100 Biotech Products by Sales in 2021 [TOTAL = $349.3 B +]

1. **Infectious Diseases** - $94.2 B – 27% - #15 2. **Oncology** - $75.7 - 21.7% - #22 3. **Dermatology** - $34.2 - 9.79% - #11,

4. **Endocrinology** - $33.9 – 9.71% - #17 5. **Rheumatology** - $28.4 – 8.13% - #10 6. **Ophthalmology** - $18.1 – 5.18% - #3,

7. **Neurology** - $17.5 – 5.01% - #8 8. **GastroEnterology** - $17.4 - #6 9. **Hematology** - $11.6 – 3.32% - #7,

10. **Pulmonary** - $8.1 - $2.32% - #4 11. **Gynecology** - $6.8 – 1.95% - #6 12. **Genetic Diseases** - $3.4 - 0.97% - #3

1st number is total product sales for usage area, 2nd number in percentage of total sales, 3ed number is number of products.

Table #4. Top 25 Specific Diseases based on Number of Approved Products in USA [12.31.2022]

Rank	Indications/Diseases	Products	Rank	Indications/Diseases	Products
1	Diabetes mellitus type 1	#27	**14**	Diabetes mellitus type 2	#11
1	Rheumatoid arthritis	#27	**14**	Gastric cancer	#11
1	Psoriasis, plaque	#27	**14**	Gastroesophageal junction cancer	#11
4	Psoriatic arthritis	#21	**17**	Colorectal cancer	#10
5	Ankylosing arthritis	#19	**18**	Melanoma	#9
6	Breast cancer	#18	**18**	Multiple myeloma	#9
7	Ulcerative colitis	#16	**20**	Neutropenia	#8
7	Crohn's disease	#16	**20**	Renal cell cancer	#8
9	Hemophilia Type A	#15	**22**	Prostate cancer	#7
9	Multiple sclerosis	#15	**22**	Osteoporosis	#7
11	Non-small cell lung cancer	#13	**22**	Hepatitis B	#7
11	Growth Deficiency	#13	**22**	Lymphocytic leukemia	#7
11	Non-Hodgkin's lymphoma	#13	**26**	Asthma	#6
#6 of top 10 = Inflammatory diseases & #11 of top 25 = Cancers					

Discovery of Biotech Molecules - Pharma versus Biotech

Discovery of a biotech molecule involves basic molecule creation and preclinical research efforts [e.g., biochemistry, molecular biology, molecular engineering, pharmacokinetics, pharmacology, toxicology]. For marketed biotech products, **table 5a** displays the predominance of biotech companies in discovery of eventually marketed biotech products, 81.1% of products for biotech versus 18.9% for pharma companies. In another perspective based on the number of companies engaged in discovery, again biotech companies predominate with 84.1% versus pharma 15.9%, as observed in **Table 5b.**

Table 5a. Discovery of Biotech Molecules Leading to Marketed Products – Biotech vs Pharma:

	Number:	**Percentages:**
Biotech Molecules to Products Originated from Pharma Co:	85 Molecules	% Pharma = 18.9
Biotech Molecules to Products Originated from Biotech Co.:	365 Molecules	% Biotech = 81.1

Table 5b. Type of Company - Biotech vs. Pharma in Discovery / Early Development:

	Number:	**Percentages:**
Number of Companies that Discovered Molecules – Pharma:	34 Companies	Pharma = 15.1%
Number of Companies that Discovered Molecules – Biotech:	191 Companies	Biotech = 84.9%

Currently (March 2022}, the number of biotech molecules and products is above 900 in late-stage clinical trials [investigational molecules plus marketed products for new indications] by over 400 companies, especially monoclonal antibodies [371 – 40.9%]. However, all product categories of biotechnology are well represented [proteins = 150, vaccines – 109, peptides – 82, cell therapies – 53, gene therapies – 49, RNAi – 44, liposomes – 13]. The top 24 companies with at least 6 molecules or products being studied in late-stage trials is found in **table 6,** demonstrating leadership by pharma who have larger R&D operations and budgets to support the very costly and extensive work of late-stage trials. Letter B next to company name indicates a biotech company focus (13 companies). Summarizing these data, 306 total molecules/products are found for the top 24 companies performing phase 2b/3 clinical trials. Biotech companies [#13] are studying 83 novel

molecules [31.4%, 6.3 molecules/company] versus 11 pharma companies evaluating 177 novel molecules [57.8%, 10.6 molecules/company], plus biosimilar companies [#5] researching 33 biosimilar molecules [10.8%]. From the full list of late-stage molecules/products (900 plus), 35 pharma companies are studying 248 molecules (6.5/company) versus 351 biotech companies are studying 699 molecules (2/company). Plus, 40% of the pharma companies are studying at least 5 molecules versus 4% of the biotech companies for these late-stage trials.

Table #6. Biotech Molecules in Late-Stage Clinical Trials by Top 24 Pharma & Biotech Companies, Feb. 2022

Company	All Products	Invest. Molecules	Company	All Products	Invest. Molecules
AbbVie	9	5	Innovent Biologic – **B**	9	6+3 bsm
Amgen – **B**	19	5+6 bsm	Ionis – **B**	9	8
AstraZeneca	20	9	Johnson & Johnson	16	8
Biocon – **B**	9	4+5 bsm	Merck	16	13
Biogen – **B**	8	7	Morphosys – **B**	6	5
Biothera – **B**	7	1+7 bsm	Novartis	25	14
Bristol Myers Squibb	12	3	Novo Nordisk – **B**	6	4
Celltrion – **B** Bsm	9	1+8 bsm	Pfizer	27	21
Eli Lilly	10	5	Regeneron – **B**	13	9
Gilead – **B**	8	6	Roche – **B**	27	11
GlaxoSmithKline	15	8	Sanofi	18	12
Henlius – **B**	8	2+6 bsm	Takeda	9	5

Footnotes:
B – Biotech Company. Bsm – Biosimilar molecules. All Products = marketed products for new indications plus investigational molecules.

In the discovery of the 435 marketed biotech products (novel molecules) in United States and Europe in 2021, drug discovery was executed by 201 biotech companies for 296 products and 28 pharma companies for 83 products, and 56 products by private and other small companies over the 1980s to 2021. However, the marketing of the biotech products has been and is dominated by pharma companies. For the top 25 companies, 243 biotech products are marketed by 14 pharma companies (17.4 per company) and 152 biotech products are marketed by 11 biotech companies (13.8 per company). Ten or more products are being researched (late-stage trials) by nine pharma companies and only three biotech companies.

Top 100 Marketed Biotech Products and Drugs in 2001 vs 2011 vs 2021, Pharma vs Biotech Companies

We now are examining and comparing drug sales of the top 100 drugs and biotech in three ways, biotech products versus drugs, at time-points a decade apart [2001, 2011, 2021], and for biotech versus pharma companies, which is presented in **table 7**. All biotech sales [row 1 of graph] versus drug sales [row five of graph] increased dramatically for biotech and much less for drugs over time from $27.1 billion – biotech / $77.8 billion - drugs [2001] to $112.7 / $141.9 billion [2011] to $285.8 / $150.7 billion [2021]. Biotech percentage of all sales rose well over time to be 25.8% in 2001 to 44.4% in 2011 up to 65.5% in 2021 [row 7 of the table 7]. For the top 100 drugs and biotech, total biotech sales rose over time much more than drug sales up to $285.8 billion [65.5% of all sales] for biotech versus up to $150.7 billion [34.5%] for drugs. Pharma companies sales in biotech accelerated much more than biotech companies [pharma comp.; $14.4 billion in 2001 to $62.9 in 2011 up to $200.6 in 2021] versus [Biotech comp.: $12.6 in 2001 to $49.9 in 2011 to $85.2 up to 2021], as shown in rows 2 and 3 of table 7.

For 2021, the top 50 biotech products only with worldwide sales of at least $2 billion are provided in **table 8** along with their marketing company, usage area, and sales. Pharma companies market 32 products [80%] achieving $187.3 billion [67.3%] in sales versus biotech companies with 22 products [55%] reaching $90.9 billion in sales [32.7%]. Six products are co-marketed by a pharma and biotech company. Pharma companies dominate biotech sales for these top 50 products.

Table #7. Top 100 Both Drugs & Biotech Sales – Biotech & Pharma Companies – 2001 & 2011 & 2021

Top 100 Drug & Biotech SALES	2001 Top 100	2011 Top 100	2021 Top 100
1.Total Biotech Sales: Biotech + Pharma	$ 27.06 B	$ 112.74 B	$ 285.75 B
2. Biotech Product Sales by Biotech Comp.	$ 12.64 B [#14]	$ 49.89 B [#20]	$ 85.20 B [#25]
3. Biotech Product Sales by Pharma Comp.	$ 14.42 B [#14]	$ 62.85 B [#27]	$ 200.55 B [#39]
4. Pharma Comp. % of Biotech	53.3%	55.7%	70.2%
5. Total Drugs Sales by Pharma Co.	$ 77.75 B [#72]	$ 141.85 B [#57]	$ 150.68 B [#42]
6. Drugs + Biotech Total Sales	$ 104.81 B	$ 254.59 B	$ 436.43 B
7. Biotech as % of All Sales	25.8%	44.3%	65.5%
8. Drugs by Pharma % of All Sales	74.2%	55.7%	34.5%

Footnotes:
Abbreviations; B – Billions of U. S. Dollars, Comp. – Companies,
Number in brackets is number of products. All sales includes both drugs and biotech products.

Table 8. Top 50 Biotech Product WW Sales [at least $2B USD] & Companies with Usage Areas in 2021

RNK	Products	Uses	Sales	Company	RNK	Products	Uses	Sales	Company
1	Comirnaty	ID	42.4	Pfizer/**BioNTech**	**26**	Lucentis	Oph	3.68	**Roche**/Novartis
2	Humira	D/GE/R	21.2	AbbVie	**27**	Hemlibra	H	3.66	**Roche**
3	Spikevax	ID	17.5	**Moderna**	**28**	Prolia	Gyn	3.59	**Amgen**
4	Keytruda	Onc	17.2	Merck	**29**	Orencia	R	3.51	Bristol Myers S.
5	Eylea	Oph	12.8	Bayer/**Regen.**	**30**	Rituxan	Onc	3.50	**Roche/Biogen**
6	Stelara	D/R	9.60	Johnson & Jhn	**31**	Simponi	R	3.49	Johnson & Jhn
7	Opdivo	Onc	8.51	Bristol Myers S.	**32**	Avastin	Onc	3.32	**Roche**
8	Regen-Cov	ID	7.94	**Regeneron**	**33**	Xolair	P	3.29	**Roche**/Novartis
9	Trulicity	End	6.60	Eli Lilly	**34**	Lantus	End	2.95	Sanofi
10	Ocrevus	N	6.48	**Roche/Biogen**	**35**	Herceptin	Onc	2.93	**Roche**
11	Dupixent	D/P	6.03	Sanofi	**36**	Skyrizi	D	2.94	AbbVie
12	Darzalex	Onc	5.67	Johnson & Jhn	**37**	NovoRapid	End	2.52	**Novo Nordisk**
13	Gardasil	ID	5.67	Merck	**38**	Humalog	End	2.45	Eli Lilly
14	Enbrel	D/R	5.64	**Amgen**/Pfizer	**39**	Imfinzi	Onc	2.41	AstraZeneca
15	Ozempic	E	5.33	**Novo Nordisk**	**40**	Victoza	End	2.38	**Novo Nordisk**
16	Prevnar	ID	5.27	Pfizer	**41**	Shingrix	ID	2.34	Sanofi
17	Entyvio	GE	4.74	Takeda	**42**	Cimzia	GE/R	2.28	UCB
18	Cosentyx	D/R	4.72	Novartis	**43**	Xgeva	Onc	2.26	**Amgen**
19	Botox	D&N	4.68	AbbVie	**44**	Bam&Est-mab	ID	2.24	Eli Lilly
20	Perjeta	Onc	4.59	**Roche**	**45**	Taltz	D	2.21	Eli Lilly
21	Tecentriq	Onc	4.17	**Roche**	**46**	Kadcyla	Onc	2.15	**Roche**
22	Soliris	H/Ne	4.00	AstraZeneca	**47**	Tremfya	D	2.13	Johnson & Jhsn
23	Vaxzevria	ID	3.98	AstraZeneca	**48**	Padcev	Onc	2.12	**Seagen**/Astellas
24	Actemra	R	3.86	**Roche**	**49**	Tysabri	N	2.06	**Biogen**
25	Remicade	D/GE/R	3.86	Jhnsn&Jn/Merck	**50**	Yervoy	Onc	2.03	Bristol Myers S.
Top 10 Usage Areas: Onc=13 products, D=10, R=9, ID=8, E=6, GE=4, N=3, H=2, Oph=2, P=2; **Ph.Co=34, Bio Co.=23**									

Footnotes:
Abbreviations: B – Billions, D -Dermatology, End – Endocrinology, GE – Gastroenterology, Gen – Genetic diseases, Gyn – Gynecology, H – Hematology, ID – Infectious Disease, Jhn – Johnson, N – Neurology, Ne – Nephrology, Onc – Oncology, Oph – Ophthalmology, P – Pulmonary, R – Rheumatology, Rnk-Rank S. – Squibb, USD – United States dollars, WW – Worldwide, # - Bold print indicates a biotech company.

Top Pharma & Biotech Companies and Marketing of Biotech Products

For the top 100 biotech products, there are 30 companies marketing products as listed in **table 9.** Biotech companies include 13 with 50 products [$124 billion in sales] and pharma companies number 17 with 66 products [$227 billion]. Sixteen products are co-marketed. Over time (2001 to 2011 to 2021) as observed in **table 10** for the top 25 companies, both the pharma and biotech company sales in biotech increased substantially, along with the number of marketed products. Pharma percentage of the biotech products and their sales increased much more than biotech,

changing from 45.1% to 54.0% to 65.0% at these 3 time-points. Over time we can also compare, the top 15 companies in the number of biotech products marketed per company. **Table 11** tabulates the total marketed products in five-year time–points and ranks the top 15 companies. In the early time of 2001, many biotech companies were leaders in products available, six of the fifteen companies. Seven companies were acquired and shown in italics in the table. Through many product and especially company acquisitions, the top companies were mostly and consistently pharma from 2006 to 2021 [for example, Eli Lilly, Merck, Pfizer, and Sanofi], except for Roche and Amgen]. A summary for the number of products for all these 15 leading companies collectively is found in **table 12** and compares pharma versus biotech companies over time. Pharma companies have marketed the majority of products, above 60% for 2001 to 2021, achieving 70% by 2021. Yet another comparison of pharma and biotech companies over time presents the top 10 companies based on sales totals of biotech products over time in **table 13.** Again, the data demonstrates the growing predominance for the major biotech products by pharma companies, 41.1% in 2001, 53.8% in 2011 and 62.2% in 2021. Of course, both the number of products and sales totals form biotech companies are still substantial over the full 20-year timeframe.

Table #9. Companies - Biotech vs Pharma Companies for Top 100 Biotech Products in 2021:
Biotech: 13 Companies
[Amgen, Biogen, BioNTech, CSL, Gilead, Horizon, Ipsen, Moderna, Novo Nordisk, Regeneron, Roche, Seagen]
- 50 products - $124 billion [35.5%]
Pharma: 17 Companies
[AbbVie, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Ironwood, Johnson & Johnson, Merck, Merck KGaA, Novartis, Pfizer, Sanofi, Teva, UCB]
- 66 products - $227 billion [64.5%]

Table #10. Top 25 Companies in Biotech Sales Over Time – 2001 vs 2011 vs 2021

Top 25 Companies	2001	2011	2021
Number Biotech Products	52	162	388
Total Biotech Sales in $B USD	$33.7	$134.1	385.8
Number Pharma Companies	12	14	15
Pharma Co. Biotech Sales $B USD	$15.2 [45.1%]	$72.6 [54.0%]	$250.7 [65.0%]
Number Biotech Products by Pharma Co.	26	84	277
Number Biotech Companies	13	11	10
Biotech Co. Biotech Sales $B USD	$18.5 [54.9%]	$62.0 [46.0%]	$135.0 [35.0%]
Number Biotech Products by Biotech Co.	31	80	131

Footnotes: Abbreviations: B – Billions; Co. – Company; USD – United States dollars

Table 11. Top 15 Companies - Number of Marketed Biotech Products Over Time

Rank	2001	2006	2011	2016	2021
1	11 Roche*^	14 Pfizer	15 Sanofi	19 Pfizer	39 Sanofi
2	10 *Genentech*^	13 Roche*	15 Pfizer	18 Roche*	32 Novartis
3	7 Johnson & Jn	12 Amgen*	14 Roche*	18 Sanofi	31 Roche*
4	7 Novo Nord.*	11 Novartis^	13 Merck	18 Novartis	30 Pfizer
5	7 *Wyeth*	11 Merck	12 Amgen*	16 Merck	22 Amgen*
6	6 Amgen*	9 Eli Lilly	11 Novartis	15 Amgen*	22 Novo Nord.*
7	6 *Serono**	9 Merck KGaA	9 Merck KGaA	15 Novo Nord.*	22 Eli Lilly
8	5 Eli Lilly	9 Novo Nord.*	9 Novo Nord.*	14 Eli Lilly	20 Takeda
9	5 Novartis	8 *Genzyme**	9 Eli Lilly	14 *Shire**	18 Merck
10	4 Bayer	8 Sanofi	8 *Genzyme**	9 Biogen*	17 AstraZeneca
11	4 *Genzyme**	7 Johnson & Jn	7 GlaxoSmithKl.	9 GlaxoSmithKl.	12 GlaxoSmithKl.
12	4 *Schering Plgh.*	6 GlaxoSmithKl.	7 Johnson & Jn	9 Merck KGaA	12 Johnson & Jn
13	4 Merck	5 Biogen*	6 Bristol M. Sq.	8 Bristol M. Sq.	11 Bristol M. Sq.
14	3 GlaxoSmithKl.	5 Bayer	5 Biogen*	8 Johnson & Jn.	11 AbbVie
15	3 Sanofi	4 Bristol M. Sq.	5 Bayer	6 SOBI*	10 Biogen* & SOBI*

Footnotes:
1. Abbreviations: Biot. – Biotech, Comp. – Company, Jn – Johnson, Kl – Kline, M. – Myers, Nord. – Nordisk, Ph – Pharma, Plgh – Plough, Prod. – Products, Sq. – Squibb
2. * Asterisk designates biotech companies.

3. ^ Genentech & Roche co-marketed all 10 Genentech products in 2001.
4. Italic print indicates a company that was later acquired.

Table #12. Top 15 Companies - Totals for Marketed Biotech Products - Pharma vs Biotech Companies

	2001	2006	2011	2016	2021
Ph. Comp. # Biot. Prod.	53	84	97	119	221
# Biot. Prod.	33	47	48	77	92
% Pharma Biot. Prod.	61.6%	64.1%	66.9%	61.0%	70.6%

Table #13. Top 10 Companies in Biotech Sales Over Time – 2001 vs 2011 vs 2021

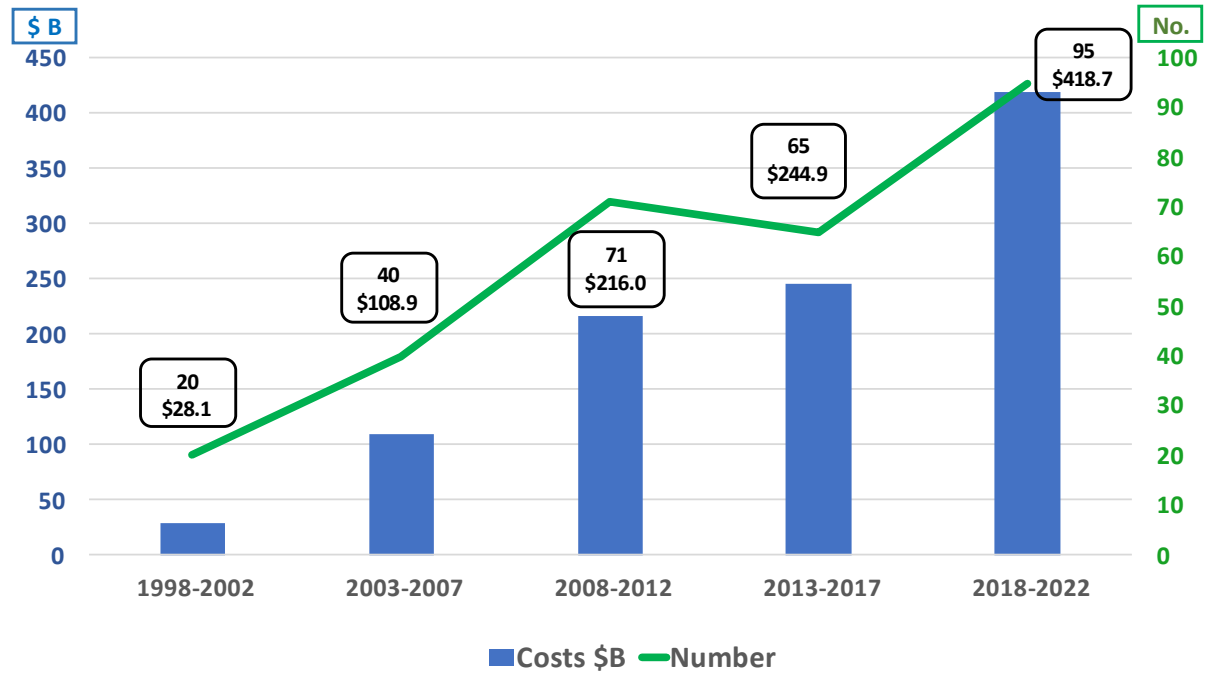
Rank	2001 [Co./# products/Sales $B]	2011 [Co./# Products/ Sales $B	2021 [Comp./# Products/Sales $B
1	Johnson & Jhnsn / 2 / $4.07	**Roche** / 19 / $26.6	Pfizer / 34 / $49.7
2	**Roche** / 8 / $4.06	**Amgen** / 9 / $15.0	**Roche** / 31 / $41.3
3	**Amgen** / 3 / $3.50	Sanofi / 21 / $10.9	AbbVie / 11 / $30.1
4	***Serono*** / 6 / $2.80	Pfizer / 13 / $10.8	Johnson & Jhnsn / 12 / $25.6
5	*Schering Plough* / 5 / $2.52	**Novo Nordisk** / 8 / $9.99	Merck / 18 / $25.3
6	**Novo Nordisk** / 6 / $2.36	AbbVie / 3 / $9.39	**Novo Nordisk** / 24 / $21.9
7	*Wyeth* / 5 / $2.20	Johnson & Jhnsn / 9 / $8.66	**Amgen** / 22 / $21.9
8	Novartis / 2 / $1.60	Eli Lilly / 7 / $5.84	Eli Lilly / 22 / $19.5
9	**Biogen** / 1 / $.972	Merck / 12 / $5.60	Sanofi / 39 / $18.4
10	***Immunex*** / 1 / $.762	Novartis / 17 / $5.78	**Moderna** / 1 / $17.5
B/Ph	Companies = 6 Biot. vs 4 Ph	Companies = 3 Biot. vs 7 Ph	Companies = 4 Biot. vs 6 Ph
B/Ph	Sales B = $14.5 B vs Ph $10.1 B	Sales B = $51.6 B vs Ph = $60.0 B	Sales B = $102.6 B vs Ph = $168.6 B
Ph % Bio	Total Pharma Comp. Sales of Biotech = 41.1%	Total Pharma Comp. Sales of Biotech = 53.8%	Total Pharma Comp. Sales of Biotech = 62.2%

Footnotes:
1.Abbreviations: **B** in bold print - Billions U.S. dollars; B – Biotech, Biot. – Biotech company; Co. - Company; Comp. – Company; Jhnsn – Johnson; # - Number; Ph - Pharma
2. Bold print – designates a biotech company & no bold print is a pharma company.
3. Italics – designates company that was acquired in later years.

Mergers & Acquisitions by Pharma Companies of Biotech Companies

The acquisitions of biotech companies have been quite substantial in total and over time by pharma companies in order to obtain biotech products and technologies. A massive expenditure of $1.02 trillion for 284 acquisitions has been invested over 22 years (1998 to 2022) by pharma companies (**Graph #2**). Expenditures were low in 1998 to 2002, but as the products proved to be major medical breakthroughs with very good profitability, a dramatic increase in numbers and costs followed. The graph shows for each time-period the number of acquisition deals and the total costs, reaching $419 billion for 95 acquisitions in last five years, 2018-2022. The mega acquisitions (at or over $5 billion) are provided in **table 14**, 191 deals from 1998 to 2022 displaying the pair of companies [pharma and biotech] with purchase prices. The top 10 pharma companies in acquisitions are provided also at bottom of **table 14** led by Pfizer. Additionally, biotech companies made similar acquisitions of other biotech companies to expand their research pipelines and marketed products (**Table 15**). The table displays the 20 top companies, which acquired 194 companies for $318.8 billion, in addition to Roche Laboratories. Before 1990, Roche was a pharma company, but through its collaboration and acquisition of Genentech through the 1990s, acquiring about 20 biotech products originally developed by Genentech, it transformed into a biotech company. Also, Shire evolved from a pharma to a biotech company through acquisitions of biotech companies.

Graph #2. Biotech Company Acquisitions by Pharma - 1998 to 2022 [Total = $1.02 Trillions]



Footnotes: 1. 5-Year intervals of time. **2.** Bars = US dollars. Line – Number of acquisitions **3.** Roche is a biotech company after 2000

Table #14. Mega Acquisitions of Biotech Companies By Pharma Companies [$5 to $74 B]

2018-2022: AbbVie – Allergan [$63], AstraZeneca – Alexion [$39], Bristol Myers Squibb – Celgene [$74], Celgene – Juno [$9] & Impact Bio [$7], Gilead – Immunomedics [$21], Johnson & Johnson – Momenta [$6.5], Merck – Acceleron {$11.5], Novartis – AxeVis {$8.7] & TMC [$9.7], Pfizer – Global Blood [$5.4], Sanofi – Bioverativ [$11.6], Takeda – Nimbus [$6] & Shire [$64]
2013-2017: AbbVie – Pharmacyclics [$31] & Stemcentx [$9.4], AstraZeneca – Synageva [$8.4], Gilead – Kite [$11.9] & Pharmasset [$11], GlaxoSmithKline – Novartis vaccines [$5.25], Perrigo – Elan [$8.6], Merck – Cubist [$5.9], Pfizer – Medivation [$14], Shire – Baxalta [$32] & NPS [$5.2] & Dyax [$6.5], Takeda – Ariad [$5.2]
2008-2012: Bristol Myers Squibb – Amylin [$5.3], Eli Lilly – ImClone [$6.1], Merck – Schering Plough [$41], Pfizer – Wyeth [$68], Sanofi – Genzyme [$20.1], Takeda – Millennium [$8.8], Teva – Cephalon [$6.8] & Ratiograstim [$5]
2003-2007: AstraZeneca – MedImmune [$15.6], Merck KGaA – Serono [$13.3], Bayer – Schering AG [$21.5], Novartis – Chiron [$5.4], Schering Plough – Organon [$14.4]
1998-2002: Johnson & Johnson – Alza [$10.5]
Top 10 Company Ranking 1. Pfizer - $138 Billion – 35 deals, **2**. Merck - $92.2 - 25, **3**. BMS - $89.9 - 13, **4**. Takeda - $80.2 - 12, **5**. Roche - $75.8 - 27, **6**. AstraZeneca - $60.4 - 15, **7**. -Sanofi - $55.7 -23, **8**. Novartis – $51.2 - 21, **9**. – AbbVie – $31.0 - 7, **10**. JnJ - $29.9 – 13. [Cost $704.3 B for 191 deals]

Table #15. Biotech Acquisitions by Biotech Companies 1990 to 2022

	Company	Costs	#	Blockbuster Deals >4 $B		Company	Costs	#	Blockbuster Deals
1	Amgen	76.3	19	Horizon, Immunex, Onyx	**11**	Grifols	4.5	5	
2	Roche	73 51	27	Genentech, Intermune, Spark	**12**	Horizon	3.7	4	
3	Gilead	56.8	19	Immunomedics, Kite, Pharmasset, 47 Therap.	**13**	Biocon	3.3	1	Viatris biosims
4	Celgene	28.8	9	Abraxis, Juno, Pharmion	**14**	Vertex	3.2	5	
5	*Genzyme*	19.7	28		**15**	Chiron	2.6	7	
6	CSL	13.2	5	Vifor Pharma	**16**	Samsung	2.3	1	
7	Alexion	13.0	6	Synageva	**17**	Genentech	2.2	2	
8	Biogen	12.0	7	IDEC	**18**	Morphosys	1.83	4	
9	Allergan	7.5	7		**19**	Ipsen	1.77	5	
10	Novo Nordisk	6.7	8	Dicerna	**20**	Emergent	1.23	3	
Biotech Totals [Top 20 Co.]: $318.8 B USD - #194 Companies.									

Conclusions & Discussion:

Pharma companies now depend significantly on biotech products to sustain their new product development challenges for novel products and for new expanded indications, plus fulfill financial expectations. Whether you examine the products in development, annual product approvals, novel products based on types of molecules and disease targets, number of products and sales of the top products, or mergers and acquisition, they all point to the same conclusion that biotechnology has become a cornerstone in pharma company success. The leading companies in biotechnology are now Sanofi, Bristol Myers Squibb, Merck, Novartis, Pfizer, and Takeda, along with the early collaborations from Eli Lilly and Johnson & Johnson, and of course the biotech company leadership from Amgen, Novo Nordisk, and Roche. Additionally, we constantly observe new successes with new companies entering the biotech marketplace; 176 companies market biotech products in 2022 in United States and Europe. Besides the targeting of many new indications for previously poorly managed diseases, the types of molecules have expanded into new areas, such as gene therapies and cell therapies, plus novel molecularly engineered monoclonal antibodies and fusion proteins.