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Supplementary information

Investigating the origins of recent pharmaceutical innovation

In the format provided by the authors

Data sources and analysis

Given the long and multifactorial drug discovery and development process, analysis of the origin of innovative drugs is complex. For this article, an innovative drug is defined as a product that is new to the market and approved by the US Food and Drug Administration (FDA), and the origin of innovation is based on the legal entity that is mentioned in the patent application that claims the active pharmaceutical ingredient (API) of the FDA-approved drug.

To systematically analyse the origins of innovation, we combined (1) information published by the FDA on approved drugs (2015–2021) and (2) information available from patents/patent applications for the respective API. We focused our analysis on the prescription drug business of the top 20 biopharma companies by total sales 2020. Revenues from non-pharmaceutical sales were excluded. This affected the following business units: Roche Diagnostics; Johnson & Johnson Consumer Health and Medical Devices; Merck & Co. Animal Health; AbbVie Aesthetics, Eye Care and Women's Health; Sanofi Consumer Healthcare; GlaxoSmithKline Consumer Health Care; and Bayer Consumer Health and Crop Science. Companies and/or segments (Sandoz, Teva, Viatris) involved in the generic drug business were excluded. The latest 2020 revenue figures were collected via the Bloomberg database and automatically converted into US$. Revenues were manually adjusted for non-pharmaceutical sales using information from the annual financial reports.

Data on new molecular entities (NMEs) and new therapeutic biologics (NTBs) filed with the Center for Drug Evaluation and Research (CDER) and approved for the top 20 biopharma companies (1 Jan 2015 to 31 Dec 2021) were compiled from the official FDA website. Applications filed with the Center for Biologics Evaluation and Research (CBER) of the FDA, such as gene therapies, were not considered. For the 138 FDA-approved NMEs/NTBs in our analysis, we identified the respective substance (API) patent/patent application by using the following publicly available databases: https://go.drugbank.com, https://www.guidetopharmacology.org, and https://www.drugpatentwatch.com. For each drug, we used the international non-proprietary names (INN) of the active ingredients as a search term. Patent information (patent number, inventors, applicant/proprietor, priority, filing date, and date of grant) was extracted from ESPACENET of the European Patent Office (EPO).

The origin of an NME/NTB was defined as the legal entity that could first be associated with the underlying basic invention of the API — in most cases this was the proprietor mentioned of the (granted) patent. If the applicant and the proprietor differed, the applicant was defined as the originator of the respective NME/NTB. In addition, we reviewed whether the inventors were in fact employed by the applicant or proprietor by cross-checking with information from LinkedIn. Moreover, the origins of the drugs were verified with the help of AdisInsight.

Based on the collected data, we categorized each FDA approved drug (2015-2021) according to two dimensions: (1) 'applicant', and (2) 'foundation'. The term 'applicant' refers to the question of who (legal entity) filed the patent application claiming the API. Possible originating entity categories are pharmaceutical companies, biotech companies, universities, other academic institutions, or other entities. The term 'foundation' refers to the question of where the innovation was invented; that is, internally, externally, or in collaboration. And if invented externally, how did the top 20 biopharma company access the intellectual property (IP)?

With respect to 'applicant', the following definitions were used to categorize the FDA-approved drugs under evaluation:

- 'Pharmaceutical company' is a legal entity that was founded before 1976 (the date of Genentech's incorporation).
- 'Biotech company' is a legal entity that was founded after 1976, based on Drakeman[1]. Note that this classification does not take the temporal evolution of individual companies into account. Based on this definition, Amgen, Biogen and Gilead were classified as biotech companies in our analysis, although their current business models are similar to established pharmaceutical companies. This limits some of the conclusions of our analysis with respect to these three companies.
- 'Collaboration' refers to situation in which the origins of an FDA-approved drug lie in more than one legal entity. Both organizations are mentioned as applicants in the patent application, and both organizations are not from the same category (biopharma, biotech, university, other academic, other).
- 'University' refers to a situation in which the applicant for the API-claiming patent application is a university or an institute associated with a university.
- 'Other academic' refers to the situation that the origins of the FDA-approved drug lie either in non-profit research, such as the Scripps Research Institute, or governmental research institutes, such as the Walter Reed Army Institute of Research.
- A drug was categorized as 'other' if it originated outside the pharma, biotech, university, or other academic.

With respect to 'foundation', the following definitions were used to categorize the evaluated FDA-approved drugs:

- A drug was categorized as discovered 'internally' if the applicant, the proprietor, and the company receiving FDA approval are of the same legal entity and the inventors of the API worked in this organization. In case of an acquisition, the drug is categorized as 'internally' discovered if the acquiring legal entity is mentioned as an applicant in the patent application.
- A drug was categorized as discovered 'in collaboration' if the patent application claiming the API lists two or more legal entities as applicants and one of those legal entities received the FDA approval.
- A drug was categorized as discovered 'externally – licensing', if the proprietor of the patent and the company holding the FDA approval are not the same legal entity and a licensing deal is in place.
- A drug was categorized as discovered 'externally – acquisition', if the proprietor of the patent and the company holding the FDA approval are not the same legal entity and a transfer of IP rights took place.

Reference

1. Drakeman, D. Benchmarking biotech and pharmaceutical product development. *Nat Biotechnol* **32**, 621–625 (2014). https://doi.org/10.1038/nbt.2947

Supplementary Table 1 | Number of FDA-approved drugs (2015–2021) of top 20 biopharma companies*

No.	**Company**	**NMEs and NTBs**	**New drugs/ year**	**No.**	**Company**	**NMEs and NTBs**	**New drugs/ year**
1.	Novartis	15	2.14	11.	Gilead Science	6	0.86
2.	Roche	11	1.57	12.	Bristol-Myers Squibb	6	0.86
3.	AstraZeneca	11	1.57	13.	Takeda	6	0.86
4.	AbbVie	11	1.57	14.	Bayer	5	0.71
5.	Merck & Co.	9	1.28	15.	Amgen	5	0.71
6.	Eli Lilly	9	1.28	16.	Novo Nordisk	4	0.57
7.	Pfizer	8	1.14	17.	Daiichi Sankyo	3	0.43
8.	Johnson & Johnson	8	1.14	18.	Astellas	3	0.43
9.	Sanofi	7	1	19.	Biogen	3	0.43
10.	GlaxoSmithKline	7	1	20.	Boehringer Ingelheim	1	0.14
					Total	138	

NME, new molecular entity; NTB, new therapeutic biologic. *By total sales 2020.

Supplementary Table 2 | Organizational origins of drugs marketed by the top 20 companies between 2015–2021

Company	Internal	Collaboration	External: in-licensing	External: acquisition	External: other
Novartis	Cosentyx, Piqray, Entresto, Mayzent, Scemblix	Rydapt, Kisqali	Tabrecta, Leqvio	Netspot, Lutathera, Xiidra, Beovu, Adakveo	Egaten
Roche	Alecensa, Hemlibra, Enspryng	Evrysdi	Cotellic, Xofluza, Gavreto	Tecentriq, Ocrevus, Polivy, Rozlytrek,	
AstraZeneca	Tagrisso, Imfinzi		Koselugo, Tezspire	Strensiq, Kanuma, Calquence, Fasenra, Lokelma, Ultomiris, Saphnelo	
AbbVie	Rinvoq	Venclexta	Mavyret, Orilissa, Skyrizi	Avycaz, Kybella, Viberzi, Vraylar, Ubrelvy, Qulipta	
Merck & Co.	Zepatier, Pifeltro, Recarbrio		Zinplava, Prevymis, Steglatro, Verquvo	Bridion, Welireg	
Eli Lilly & Co.	Taltz, Verzenio, Emgality, Revvow		Olumiant	Portrazza, Lartruvo, Retevmo, Tauvid	
Pfizer	Vizimpro, Lorbrena, Daurismo			Ibrance, Eucrisa, Besponsa, Talzenna, Vyndaqel	
Johnson & Johnson			Yondelis, Darzalex, Tremfya, Erleada, Balversa, Rybrevant	Uptravi, Ponvory	
Sanofi			Praluent, Adlyxin, Kevzara, Sarclisa	Cablivi, Fexinidazole, Nexviazyme	
GSK	Nucala, Blenrep			Zejula, Rukobia, Jemperli	Krintafel, Cabenuva
Gilead Sciences	Genvoya, Biktarvy, Veklury			Epclusa, Vosevi, Trodelvy	
Bristol Myers Squibb	Daklinza		Empliciti	Idhifa, Inrebic, Reblozyl, Zeposia	
Takeda				Ninlaro, Alunbrig, Takhzyro, Motegrity, Exkivity, Livtencity	
Bayer	Aliqopa, Lampit, Kerendia		Vitrakvi, Nubeqa		
Amgen	Repatha, Aimovig	Evenity, Lumakras	Corlanor		
Novo Nordisk	Tresiba, Ozempic, Sogrova		Macrilen		
Daiichi Sankyo	Savaysa, Enhertu			Turalio	
Astellas		Xospata	Cresemba	Padcev	
Biogen			Zinbryta, Spinraza, Aduhelm		
Boehringer Ingelheim	Praxbind				

Only approvals from the FDA's Center for Drug Evaluation and Research are included. Additional information on the approved drugs, including the dates of approval, therapeutic area and partner companies, if applicable, is provided in Supplementary Fig. 1.

Colour code for organization type

Green = originated in pharma companies (53 drugs, 38%)

Yellow = originated in biotech companies (65 drugs, 47%)

Grey = originated as part of a collaboration of two entities of different categories (8 drugs, 6%)

Blue = originated in university (4 drugs, 3%)

Red = originated in other academic organizations (5 drugs, 4%)

Pink = originated in other organizations (3 drugs, 2%)

Supplementary Table 3 | Originators of new drugs (2015–2021) approved for top 20 biopharma companies

Originator	**Number of NMEs**	(%)	**Number of NTBs**	(%)	**Total**	(%)
Pharmaceutical companies	40	44	13	27	53	38
Biotech companies	35	39	30	63	65	47
Collaboration	5	6	3	6	8	6
Other academic	4	4	1	2	5	4
Universities	3	3	1	2	4	3
Other entities	3	3	-	-	3	2
Internally	24	27	14	29	38	28
Collaborative	6	7	1	2	7	5
Externally	57	63	33	69	90	65
Other	3	3	-	-	3	2
Total	90	100	48	100	138	100

NME, new molecular entity; NTB, new therapeutic biologic.

Supplementary Table 4 | Sources of new drugs (2015—2021) approved for top 20 biopharma companies

Origin of innovation	**NMEs and NTBs**	%
Externally – M&A	56	41
Internally	38	28
Externally – licensing	34	25
Collaboration	7	5
Other	3	2
Total	138	100

NME, new molecular entity; NTB, new therapeutic biologic.

Supplementary Table 5 | Origins of innovation for top 20 biopharmaceutical companies (2015–2021)

Company	NMEs/NTBs	Internally invented NMEs/NTBs		Collaborative NMEs/NTBs		Externally invented NMEs/NTBs		NME/NTBs sourced by licensing		NME/NTBs sourced by M&A		Other sources	
Novartis	15	5	(33%)	2	(13%)	8	(53%)	2	(13%)	5	(33%)	1	(7%)
Roche	11	3	(27%)	1	(9%)	7	(64%)	3	(27%)	4	(36%)	0	(0%)
AstraZeneca	11	2	(18%)	0	(0%)	9	(82%)	2	(18%)	7	(64%)	0	(0%)
AbbVie	11	1	(9%)	1	(9%)	9	(82%)	3	(27%)	6	(55%)	0	(0%)
Merck & Co.	9	3	(33%)	0	(0%)	6	(67%)	4	(44%)	2	(22%)	0	(0%)
Eli Lilly	9	4	(44%)	0	(0%)	5	(56%)	1	(11%)	4	(44%)	0	(0%)
Pfizer	8	3	(38%)	0	(0%)	5	(63%)	0	(0%)	5	(63%)	0	(0%)
Johnson & Johnson	8	0	(0%)	0	(0%)	8	(100%)	6	(75%)	2	(25%)	0	(0%)
Sanofi	7	0	(0%)	0	(0%)	7	(100%)	4	(57%)	3	(43%)	0	(0%)
GlaxoSmithKline	7	2	(29%)	0	(0%)	5	(71%)	0	(0%)	3	(43%)	2	(29%)
Gilead Science	6	3	(50%)	0	(0%)	3	(50%)	0	(0%)	3	(50%)	0	(0%)
Bristol-Myers Squibb	6	1	(17%)	0	(0%)	5	(83%)	1	(17%)	4	(67%)	0	(0%)
Takeda	6	0	(0%)	0	(0%)	6	(100%)	0	(0%)	6	(100%)	0	(0%)
Bayer	5	3	(60%)	0	(0%)	2	(40%)	2	(40%)	0	(0%)	0	(0%)
Amgen	5	2	(40%)	2	(40%)	1	(20%)	1	(20%)	0	(0%)	0	(0%)
Novo Nordisk	4	3	(75%)	0	(0%)	1	(25%)	1	(25%)	0	(0%)	0	(0%)
Daiichi Sankyo	3	2	(67%)	0	(0%)	1	(33%)	0	(0%)	1	(33%)	0	(0%)
Astellas	3	0	(0%)	1	(33%)	2	(67%)	1	(33%)	1	(33%)	0	(0%)
Biogen	3	0	(0%)	0	(0%)	3	(100%)	3	(100%)	0	(0%)	0	(0%)
Boehringer Ingelheim	1	1	(100%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)

NME, new molecular entity; NTB, new therapeutic biologic.