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Supplementary information

First-in-class versus best-in-class: an update for new market dynamics

In the format provided by the authors

Dataset and analysis methods

Scope. For this analysis, we assessed 29 classes of drugs with novel mechanisms inaugurated after 2010, composed of 104 products in total. We started from a set of 499 FDA-approved products (as of October 1, 2022), filtering down subsequently as follows:

- Novel (276 products passed this filter): Classes had to be newly created, with no existing marketed products utilizing the same mechanism launched prior to 2011. This allowed us to focus on the commercial dynamics of the last decade and avoid any overlap with the previous analysis.
- Significantly sized (229 products passed this filter): Classes had to have at least one product with greater than $300 million in confirmed or forecasted nominal sales from 2011–2028 that had launched in the United States.
- Competitive (136 products passed this filter): Classes had to have more than 1 product, all launched from 2011 to the time of this analysis.
- Market dynamics (104 products passed this filter): We excluded classes with unusual market dynamics, such as those covering conditions like HIV where the standard-of-care involves multiple combination therapies, classes where most of the products were launched by one company, and classes with other factors that confound competitive analysis.

Within the set of in-scope mechanistic classes, we also consolidated or split classes with the same mechanism of action but different modalities based on approval and/or development for overlapping indications. For example, we combined calcitonin gene-related peptide (CGRP) monoclonal antibodies and small-molecule antagonists into one class because of their similar mechanism in acting to block the binding of CGRP to its receptor and their usage to treat migraines. In contrast, we split Janus kinase (JAK) inhibitors into two separate classes based on their usage to treat myelofibrosis (a rare bone marrow cancer), separately from those used to treat inflammatory/auto-immune disorders like rheumatoid arthritis or atopic dermatitis. We also considered that many of the classes in-scope have highly active ongoing development, with multiple products in clinical trials and expected to launch in the future. We included products that have been filed for FDA approval or are expected to be shortly for which pivotal clinical trial data was available. This added 6 products, bringing the scope up to the final total of 104.

Methodology. We sought to replicate the approach used in the previous analysis (*Nat. Rev. Drug Discov.* **12**, 419–420; 2013). as much as possible in order to allow comparisons to be made. We assessed three variables for each product relative to other products within their class:

- Launch order: We used the rank-order of the date of each product's first approval by the US Food and Drug Administration (FDA) – regardless of indication and approval in other geographies.
- Therapeutic advantage: We used a three-point scale from 1 (worst) to 3 (best), comparing efficacy, safety, and usage/administration profiles across common indications as well as coverage of distinct indications, with more weight given to indications with larger patient populations. Products that receive the highest score (3) on the scale are clearly superior to others in their class and are unlikely to be clearly surpassed in the near future by yet-to-be launched products, while products receiving the lowest score (1) have clear shortcomings in safety and/or efficacy that following products have addressed or could address.
- Commercial success: We calculated the present value of global sales for each product from 2011 to 2028 based on historical data and consensus forecasts, using 2021 as the present year and using a 10% discount rate for past and future sales. Each product's level of commercial success was based on the

share of present value of sales that they captured within their class. Sales data and forecasts were taken from EvaluatePharma as of July 2022.

In dividing classes by those used to treat multiple indications, we chose to use the relatively higher-level indication definitions specified by EvaluatePharma.

Limitations. The analytical approach described above has some caveats that should be kept in mind when assessing the results. In terms of assessing therapeutic advantage, these products are often not directly compared in clinical trials, so comparisons were made based on data from separate trials, which may be confounded by differences in patient populations or clinical protocols. Furthermore, this analysis reflects the information available at time of writing – development timelines and product profiles may change over time, which could impact the accuracy of sales forecasts used as input to our quantification of commercial success. More broadly, our approach to quantifying commercial success gives an advantage to earlier launches based on the time-value of money (money in the present is more valuable than money of the same nominal value to be received later). We tested an approach using sales from a single year to quantify the level of commercial success – although the advantage of earlier launches was slightly diminished, the relative levels of success remained. In the capital-intensive biopharmaceutical industry where drug sales are used to fund development of future products, we believe that an approach that gives more value to revenue received earlier in time more accurately reflects economic reality.

There are also market factors, internal or external to the firms involved, that might affect these results. Commercial success is partially driven by the commercial capabilities of the companies distributing these products, which may result in differential sales independently of the therapeutic value of each drug. Events outside of the control of biopharmaceutical companies can also have a significant impact on the relative success or failure of particular products. For example, this analysis includes products that were launched immediately before or during the COVID-19 pandemic, which resulted in major disruptions to clinical and commercial operations across the industry and affected new diagnoses in a wide range of conditions, potentially affecting the normal commercial launch process and progression of sales.

Additional detail on overall results

Compared to third-to-launch and later products, the second-to-launch and best-in-class products are largely competing on the same ground as first-to-launch products, with all the disadvantages that a follower has. We also found that products launching fourth-or-later are on average capturing more commercial value than late products did in the 2013 analysis. This increased value for later entrants is driven by the overall increase in competition in mechanistic classes, leading to the development and launch of multiple “generations” of a class within a shorter timeframe, as well as biopharma companies pursuing alternative indications and innovative market access strategies in order to gain a foothold in the market.

Additional detail on market dynamics

Oncology favours first-to-launch products

- In many of these classes, the first product has benefitted from a long lead time over later entrants, such as the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (Imbruvica; Johnson & Johnson/AbbVie), which launched almost four years before any other products in its class and captured 77% of the total class value.
- In other situations, the first product managed to fend off fast-followers by demonstrating superior therapeutic value and/or a broader overall label – most famously, pembrolizumab, which has managed to outcompete nivolumab (Opdivo; Bristol Myers Squibb), approved just three months later, based on superior efficacy in most of the indications they share, particularly in first-line NSCLC where pembrolizumab showed efficacy as a monotherapy and nivolumab failed to do so.
- In a minority of cases, a superior follower is projected to outcompete the first entrant, such as ciltacabtagene autoleucel (Carvykti; Johnson & Johnson), a B-cell maturation antigen (BCMA)-targeting CAR-T cell therapy. Analysts predict that Carvykti's superior efficacy over the first entrant idecabtagene vicleucel (Abecma; Bristol Myers Squibb) will enable Carvykti to capture 55% of the value in the class, despite launching nearly a year later.

Outside of oncology, late entrants can capture more value

This is particularly well illustrated in the class of calcitonin gene-related peptide (CGRP) blockers (used as migraine treatments), in which eight products launched from 2018 to 2021, most of which have similar therapeutic value. Companies competing in this space have tried differentiating their assets by frequency of administration, route of administration and product pricing with varying levels of success. Companies playing in these types of classes need to think beyond therapeutic advantage and consider strong commercial differentiation as well.

Wide disease space gives an advantage to first entrants

First entrants without clear therapeutic superiority in classes with the potential for indication expansion have succeeded through:

- Getting a long head start over followers – For example, the guanylate cyclase type-C receptor agonist linaclotide (Linzess; AbbVie/Ironwood), used to treat irritable bowel syndrome and constipation, launched over 4 years before plecanatide (Trulance; Bausch), so despite having a less favourable side effect profile and more difficult administration, it took 92% of the commercial value of the class.
- Getting to line extensions faster than followers – For example, the anti-IL17 monoclonal antibody secukinumab (Cosentyx; Novartis), used to treat psoriasis, psoriatic arthritis and ankylosing spondylitis among other conditions, launched only about one year before a therapeutically superior product, ixekizumab (Taltz; Eli Lilly), but launched in all three of the above indications before ixekizumab had launched at all, compounded by ixekizumab's slow speed to matching those approvals. Thus, secukinumab is set to capture 63% of the commercial value of this class.

Highly competitive classes are claimed by first entrants or fast-followers

Fast-followers in classes with simultaneous development (where the first two entrants launch within two years of each other) can succeed with major efficacy improvements and/or addressing larger and more valuable patient populations. For example, tafamidis (Vyndaqel/Vyndamax; Pfizer), a small molecule transthyretin (TTR) stabilizer, failed to show enough benefit in treating polyneuropathy caused by TTR amyloidosis to gain FDA approval, but has shown significant benefit in treating

cardiomyopathy caused by that condition, which affects a substantially larger patient population. Thus, tafamidis is set to capture 65% of the commercial value of the class, compared to the 17% that the initial entrant, the RNA-interference-based patisiran (Onpattro; Alnylam), that launched nine months earlier. In some cases, alternative pricing schemes and more convenient or alternative dosing were successful – particularly in therapies for chronic conditions where access and ease of use can be key in differentiating between largely therapeutically undifferentiated treatments.

Future trends

Looking ahead, trends impacting R&D may continue to shift the balance of whether a first-in-class or best-in-class strategy should be pursued. For example, technological advancements such as AI-driven trials and *in silico* screening will likely accelerate development programs – companies that use these tools effectively can gain advantage in getting to market faster than their competitors. Novel modality development may open up new targets to treatments that were otherwise inaccessible and increase competition in those that are poorly addressed by existing therapies, and advances in personalized medicine may make late entry more feasible, with the ability to identify patients that are likely to respond to treatments. Finally, companies must consider the impact of policy reforms. Policies that seek to reduce the cost burden of the most expensive drugs, such as the provisions in the Inflation Reduction Act of 2022 that call for discounts based on time after approval, may raise the bar even further for followers to garner the same levels of pricing, thereby further advantaging first entrants. Companies also need to position themselves to take advantage of efforts by health authorities to promote the development of innovative new drugs, in the same way that accelerated approvals have made it possible to gain regulatory approval more quickly for products that are likely to be highly beneficial.

Supplementary Table 1 | Detailed listing of classes and products covered in this analysis

Therapeutic Area	MoA Class	Product	Generic name	Company	FDA approval year	Launch rank
Oncology	PD-1/PD-L1 mAbs	**Keytruda**	**pembrolizumab**	**Merck & Co**	**2014**	**1**
		Opdivo	nivolumab	BMS	2014	2
		Tecentriq	atezolizumab	Roche	2016	3
		Bavencio	avelumab	Merck KGaA	2017	4
		Imfinzi	durvalumab	AstraZeneca	2017	5
		Libtayo	cemiplimab	Sanofi	2018	6
		Jemperli	dostarlimab	GSK	2021	7
		Tyvyt	sintilimab	Eli Lilly	TBD	8
		Tislelizumab	Tislelizumab	BeiGene/Novartis	TBD	9
	BTK inhibitors	**Imbruvica**	**ibrutinib**	**J&J**	**2013**	**1**
		Calquence	acalabrutinib	AstraZeneca	2017	2
		Brukinsa	zanubrutinib	BeiGene	2019	3
		Velexbru	tirabrutinib	Ono	TBD	4
	CDK4 & CDK6 inhibitors	**Ibrance**	**palbociclib**	**Pfizer**	**2015**	**1**
		Kisqali	ribociclib	Novartis	2017	2
		Verzenio	abemaciclib	Eli Lilly	2017	3
		Cosela	trilaciclib	G1 Therapeutics	2021	4
	CD38 mABs	**Darzalex**	**daratumumab**	**J&J**	**2015**	**1**
		Sarclisa	Isatuximab	Sanofi	2020	2
	JAK inhibitors (oncology)	**Jakafi**	**ruxolitinib**	**Incyte**	**2011**	**1**
		Inrebic	fedratinib	BMS	2019	2
		Vonjo	pacritinib	CTI	2022	3
Oncology	PARP inhibitors	**Lynparza**	**olaparib**	**AstraZeneca**	**2014**	**1**
		Rubraca	rucaparib	Clovis Oncology	2016	2
		Zejula	niraparib	Tesaro	2017	3
		Talzenna	talazoparib	Pfizer	2018	4
		Pamiparib	pamiparib	BeiGene	TBD	5
	ALK inhibitors	**Xalkori**	**crizotinib**	**Pfizer**	**2011**	**1**
		Zykadia	ceritinib	Novartis	2014	2
		Alecensa	alectinib	Roche	2015	3
		Alunbrig	brigatinib	Takeda	2017	4
		Lorbrena	lorlatinib	Pfizer	2018	5
		Rozlytrek	entrectinib	Roche	2019	6
	CD19 bi-specific antibodies & CAR-T cell therapy	**Blincyto**	**blinatumomab**	**Amgen**	**2014**	**1**
		Kymriah	tisagenlecleucel-T	Novartis	2017	2
		Yescarta/ Tecartus	axicabtagene ciloleucel/ brexucabtagene autoleucel	Gilead	2017/ 2020	3
		Breyanzi	lisocabtagene maraleucel	BMS	2021	4
	B-Raf kinase inhibitors	**Zelboraf**	**vemurafenib**	**Roche**	**2011**	**1**
		Tafinlar	dabrafenib	GSK	2013	2
		Braftovi	encorafenib	Pfizer	2018	3
	BCMA CAR-T cell therapy	**Abecma**	**idecabtagene vicleucel**	**BMS**	2021	1
		Carvykti	ciltacabtagene autoleucel	Johnson & Johnson	2022	2
	c-Met kinase inhibitors	**Tabrecta**	**capmatinib**	**Novartis**	**2020**	**1**
		Tepmetko	tepotinib	Merck KGaA	2021	2
		Orpathys	savolitinib	AstraZeneca/HutchMed	TBD	3

Oncology	RET tyrosine kinase inhibitor	**Retevmo** Gavreto	**selpercatinib** pralsetinib	**Eli Lilly** Blueprint/Roche	**2020** 2020	**1** 2
	CD19 mAbs	**Monjuvi** Zynlonta	**tafasitamab** loncastuximab tesirine	**Incyte** ADC	**2020** 2021	**1** 2
	PDGFRa inhibitors	**Ayvakit** Qinlock	**avapritinib** ripretinib	**Blueprint** Deciphera	**2020** 2020	**1** 2
	FGFR inhibitors	**Balversa** Pemazyre Truseltiq Lytgobi	**erdafitinib** pemigatinib infigratinib futibatinib	**J&J** Incyte BridgeBio Taiho	**2019** 2020 2021 2022	**1** 2 3 4
Immunology	JAK inhibitors (oral)	**Xeljanz** Olumiant Rinvoq Opzelura Cibinqo Jyseleca	**tofacitinib** baracitinib upadacitinib ruxolitinib abrocitinib filgotinib	**Pfizer** Eli Lilly AbbVie Incyte Pfizer Galapagos/Gilead	**2012** 2018 2019 2021 2022 TBD	**1** 2 3 4 5 6
	IL-17 mAbs	**Cosentyx** Taltz Siliq Bimzelx	**secukinumab** ixekizumab brodalumab bimekizumab	**Novartis** Eli Lilly Bausch UCB	**2015** 2016 2017 TBD	**1** 2 3 4
	IL-23A mAbs	**Tremfya** Ilumya Skyrizi Mirikizumab	**guselkumab** tildrakizumab risankizumab mirikizumab	**J&J** Sun Pharma AbbVie Eli Lilly	**2017** 2018 2019 TBD	**1** 2 3 4
Immunology	IL-5 mAbs	**Nucala** Cinqair Fasenra	**mepolizumab** reslizumab benralizumab	**GSK** Teva AstraZeneca	**2015** 2016 2017	**1** 2 3
	Cortisol synthesis inhibitors	**Isturisa** Recorlev	osilodrostat levoketoconazole	**Recordati** Xeris	**2020** 2021	**1** 2
Cardiometabolic	SGLT2 inhibitors	**Invokana** Farxiga Jardiance Steglatro	**canagliflozin** dapagliflozin propanediol empagliflozin ertugliflozin	**J&J** BMS Boeringer Ingelheim Merck	**2013** 2014 2014 2018	**1** 2 3 4
	PCSK9 inhibitors	**Praluent** Repatha Leqvio	**alirocumab** evolocumab inclisiran	**Sanofi** Amgen Novartis	**2015** 2015 2021	**1** 2 3
	Beta 3 adrenoceptor agonists	**Myrbetriq** Gemtesa	**mirabegron** vibegron	**Astellas** Urovant/Kissei	**2012** 2020	**1** 2
Central Nervous System	SMA treatments	**Spinraza** Evrysdi	**nusinersen** risdiplam	**Biogen** Roche	**2016** 2020	**1** 2
	TTR modulators	**Onpattro** Tegsedi Vyndaqel Amvuttra	**patisiran** inotersen sodium tafamidis meglumine vutrisiran	**Alnylam** Ionis Pfizer Alnylam	**2018** 2018 2019 2022	**1** 2 3
Central Nervous System	CGRP blockers	**Aimovig** Ajovy Emgality Ubrelvy Vyepti Nurtec Qulipta Zavegepant	**erenumab** fremanezumab galcanezumab ubrogepant eptinezumab rimegepant sulfate atogepant zavegepant	**Amgen** Teva Eli Lilly AbbVie Lundbeck Biohaven AbbVie Biohaven	**2018** 2018 2018 2019 2020 2020 2021 TBD	**1** 2 3 4 5 6 7 8
	Dual orexin receptor antagonists	**Belsomra** Dayvigo Quviviq	**suvorexant** lemborexant daridorexant	**Merck** Eisai Idorsia	**2014** 2019 2022	**1** 2 3
Gastro-Intestinal	GUCY type-C receptor agonists	**Linzess** Trulance	**linaclotide** plecanatide	**Ironwood/AbbVie** Bausch	**2012** 2017	**1** 2
Musculo-skeletal	Dystrophin exon-skipping antisense (exon 53)	**Vyondys 53** Viltepso	**golodirsen** vitolarsen	**Sarepta** Nippon Shinyaku	**2019** 2020	**1** 2