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SUPPLEMENTARY INFORMATION

In format as provided by the authors

Developing blockbuster drugs: both nature and nurture

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Supplementary Box 1 | Dataset and analysis methods

Analysis on the nature of blockbusters
Products for this analysis were selected based on sales data retrieved from Evaluate Pharma® database, in October 2018. Four subsets of products were defined as follows:

- Blockbuster drugs with >US$2 billion peak-year sales (PYS) between 2016–2024 (*n* = 39)
- Blockbuster drugs with >US$1 billion PYS (but PYS < US$2 billion) between 2016–2024 (*n* = 33)
- Non-blockbuster controls: drugs with US$0.2–0.5 billion PYS between 2016–2024 (*n* = 38)
- Historic blockbusters: drugs with >US$2 billion sales in 2012, regardless of launch date (*n* = 61)

Additionally, the first three subsets were limited to products launched between 2010–2016 to ensure proper coverage for clinical trials data (avoiding incompleteness of clinical trial data before the mid-2000s) as well as sufficient sales forecasts coverage for products launched more recently.

Product characteristics for the selected drugs depicted in Figure 1, such as market segments (primary care, hospital, and so on) (Fig. 1a), therapeutic area (Fig. 1b), accelerated approval designations (such as breakthrough therapy status) (Fig. 1c) were retrieved from Evaluate Pharma®.

As the FDA's breakthrough therapy designation only came into play from July 9th, 2012 onwards, this specific analysis only included product with launch dates from 2014 onwards.

More granular information on the distribution of therapeutic areas within the defined drug subsets is shown in Table S1. Table S2 shows the median number of indications pursued by oncology drugs within the different drug subsets, as well as the share of oncology drugs within that subset to pursue 10 or more indications. Table S3 shows the distribution of technologies the drugs in each subset are based on (such as small molecule, monoclonal antibody, etc.). Of note, post-launch development activity was excluded from the analysis. For that purpose, clinical trials started after the launch date of a product were excluded from the sample.

Table S1 | Therapeutic category per drug group (% of drug group)

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster	Historic blockbuster
Therapeutic category	Blood	9%	3%	5%	11%
	Cardiovascular	9%	5%	0%	16%
	Central nervous system	12%	8%	11%	18%
	Dermatology	0%	5%	0%	0%
	Endocrine	6%	10%	11%	11%
	Gastro-intestinal	3%	3%	5%	2%
	Genito-urinary	3%	0%	3%	3%
	Immunomodulators	0%	0%	3%	2%
	Musculoskeletal	3%	8%	5%	8%
	Oncology	21%	41%	29%	11%
	Respiratory	15%	3%	5%	5%
	Sensory organs	0%	3%	0%	2%
	Systemic anti-infectives	18%	13%	16%	10%
	Various	0%	0%	8%	0%

Table S2 | Number of indications per oncology drug per drug group

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster	Historic blockbuster
Indications pursued	Median number of indications per drug	4	12	3	11
	% of drugs with > 10 indications	14%	56%	0%	57%

Table S3 | Technology per drug group (% of drug group)

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster	Historic blockbuster
Technology	Bioengineered vaccine	3%	0%	8%	5%
	Chiral chemistry	0%	0%	3%	0%
	Monoclonal antibody	15%	26%	3%	13%
	Monoclonal antibody (conjugated)	3%	3%	0%	0%
	Protein extract	3%	0%	3%	5%
	Recombinant product	6%	8%	16%	23%
	Small molecule chemistry	70%	64%	68%	52%
	Vaccine	0%	0%	0%	2%

Analysis on the nurture of blockbusters

Clinical trials data for the investigated products were extracted from ClinicalTrials.gov database and curated using proprietary McKinsey Clinical trials analytics tool (database download as of February 2019). We limited the clinical trials sample to industry-sponsored, interventional trials. Trials were matched to products based on a keyword search (leveraging drug names and relevant synonyms) across trial description and intervention fields of ClinicalTrials.gov dataset, and subsequently manually curated. To ensure a consistent analysis of the pre-launch period for evaluated products, we excluded all trials with start date after the first launch date of the respective product (date as provided by Evaluate Pharma®).

The standard clinical trial characteristics (such as phase, enrolment, trial duration etc.) derive directly from the ClinicalTrials.gov database. Indirect complexity measures (e.g., number of arms, sites, countries etc.) were calculated with McKinsey Clinical trials analytics tool. Recruitment length information was extracted from ClinicalTrials.gov archive databases on timing of trial status changes. Combination trials were identified via keyword search (combo, combination, combined, etc.) in the intervention field of protocol data provided in ClinicalTrials.gov and manually corrected to avoid artefacts.

We divided our analysis into three distinct areas: program strategy, trial design, and trial execution. Tables S4– S6 provide detailed comparison of metrics we analysed across those areas for the two blockbuster drug groups (blockbusters with >$1 billion but <$2 billion in peak-year sales (n = 39); blockbusters with >$2 billion in peak-year sales (n = 33)), and 'non-blockbusters' drug group ($200–500 million peak-year sales (n = 38)).

For the majority of the presented comparisons, we focused on late-phase trials (i.e. phase II and/or phase III) as these provide the best resolution for our metrics and limit the bias generated from comparing healthy volunteer trials versus patient trials.

The results indicate that clinical program strategies, individual trial designs and trial execution characteristics differ significantly between blockbuster and non-blockbuster products. Furthermore, the calculated values show correlation with potential market value of the products, meaning that values for blockbusters with >$1 billion but <$2 billion in peak-year sales (typically fall in-between the values calculate for non-blockbusters, and blockbusters with >$2 billion in peak-year sales.

Table S4 | Program strategy: number of trials started before launch per product; number of trials started before phase III per product

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster
Average number of trials per product prior to launch	All trials	23.2	31.4	15.4
	Oncology	24	29.7	17.5
	Non-oncology	23	32.5	14.4
	Phase I	8.3	11.2	6.2
	Phase II	7.1	8.7	6.2
	Phase III	8.9	10.6	5.1
Early-stage trials volume per product	Average number of trials before start of phase III	6.6	7.4	4.5

Table S5 | Trial design: average size of late phase trials; share of oncology trials with early-stage adaptive design; geographical footprint of trials; combination trials

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster
Trial size	Average number of patients per phase III trial	946.0	1026.6	589.4
	Average number of experimental arms per phase IIII trial	2	2.2	1.7
Adaptive design	Share of phase I/II Oncology trials	11.4%	10.5%	5.2%
Trial footprint	Average number of facilities per phase III trial	108.6	132.1	71.0
	Average number of countries per phase III trial	11.8	12.9	8.9
Combination trials	Share of combination trials in oncology	37%	44%	29%

Table S6 | Trial execution: recruitment rate per month and per month and site; share of terminated trials, main reasons for trial termination

		Blockbuster <$2 billion PYS	Blockbuster >$2 billion PYS	Non-blockbuster
Recruitment rate	Average number of patients recruited per month for phase III trials	60.3	75.2	53.7
	Average number of patients recruited per month per facility for phase III trials	1.57	1.12	3.2
Trial termination frequency	% of terminated, withdrawn or suspended phase II trials	3.5%	6.8%	15.0%
Trial termination reasons	Strategic decision	47%	33%	20%
	Lack of efficacy	24%	30%	32%
	Low enrolment	29%	21%	28%
	Safety	0%	9%	16%