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Publication Date

2025-03-01

DOI

10.1016/j.jcpo.2024.100533

Journal of Cancer Policy 43 (2025) 100533

Contents lists available at ScienceDirect

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

Trend of sales revenue by year for top selling cancer drugs in the US and the effect of loss of market exclusivity

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ARTICLE INFO

Keywords:
Oncology drugs
Market exclusivity
Generic drugs
Biosimilar
Sales revenue
Pharmaceutical company

ABSTRACT

Biosimilars and generics have led to reduced cancer drug prices. The effect of biosimilar or generic drug competition on drug manufacturer revenue has not been previously described. In this study, the majority of top selling cancer drugs had a greater than 50 % decline in sales revenue within 2 years of generic or biosimilar market entry, reflecting both the decline in market share and reduction in unit drug price. This results in important drug manufacturer incentives, which may shape clinical trial agendas. The market structure incentives are unique for pharmaceutical companies due to the relatively short and limited duration of profitability. Policy changes such as patent reform leading to shorter duration of exclusivity may lead to greater incentive to expand low value indications in oncology.

1. Introduction

The generic and biosimilar drug market is of interest in cancer therapeutics because of the effect on drug cost [1–3]. Several cancer drugs developed more than 20 years ago continue to be widely used as standard of care, and there are several generic and biosimilar drugs that have become available following the original drug's patent expiration. Herceptin (generic name: trastuzumab) was first approved in 1998. Biosimilars entered the market in 2019 and there are currently 5 biosimilars available in the US. Rituxan (generic name: rituximab) was first approved in 1997, and biosimilars have available in the US since 2019, with 3 approved biologic drugs as of January 2024.

Faster uptake of biosimilars is observed in oncology compared to other specialties. The biosimilar uptake in the US for trastuzumab and rituximab at 3 years following biosimilar market entry was greater than 50 %, being 84 % and 73 %, respectively, in the third quarter of 2023. This compares to Lantus (generic name: insulin glargine) that maintains a 54 % market share for the brand product in 2023 following entry of biosimilars in 2015 [4]. Oral cancer drugs have also faced generic competition. Gleevec (generic name: imatinib) and Zytiga (generic name: abiraterone) were first approved in 2001 and 2011, and generic drugs have been available since 2016 and 2018, respectively. Imatinib and abiraterone are now also available at direct-to-consumer pharmacies, with predictable and transparent costs to patients.

The introduction of biosimilars has led to the reduction in drug prices that affect manufacturers. Biosimilars for trastuzumab have an up to 90 % reduced average sales price (ASP) in the US compared to the reference product Herceptin. The ASP in the first quarter of 2024 was $3188 for Herceptin and $310 for Kanjinti, which is the trastuzumab biosimilar with the highest market share (35 %) in 2023 compared to Herceptin (16 %) [5]. ASP is the weighted average of all manufacturer sales prices and includes all rebates and discounts. Data are collected by the manufacturer and submitted to Medicare.

Worldwide data based on wholesaler and distributers prices (IQVIA MIDAS) also show decrease in prices of reference products and biosimilar products in both middle-income and high-income countries. The average price of a biologic, including both reference drug and biosimilar, was reduced by 24.7 % for bevacizumab and 27.7 % for trastuzumab in the same year of market entry of biosimilar [6].

In this study, we describe the trend of worldwide sales revenue for top selling cancer drugs starting from year of initial drug approval. For drugs that have biosimilar or generic competition, we analyze the impact of generic or biosimilar market entry on annual sales revenue and discuss the structural causes and the resulting incentives for drug manufacturers.

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https://doi.org/10.1016/j.jcpo.2024.100533
Received 27 September 2024; Received in revised form 3 December 2024; Accepted 5 December 2024
Available online 9 December 2024

2. Methods

2.1. Data set creation

News articles of top selling cancer drugs were identified using a general search engine (Google) with search term "top selling cancer drug" and "bestselling cancer drug". Articles reporting top selling drugs based on sales revenue for any year between 2015 and 2021 were selected. A list of drugs with at least $500 million sales per reported year was compiled with removal of duplicate drugs. Drugs or vaccines for cancer prevention or supportive care were excluded. Drugs with high sales revenue in more recent years were not included as the purpose of this study is to observe the change in sales revenue following generic or biosimilar market entry.

2.2. Annual sales revenue

The yearly net sales amount for each drug was compiled from year of drug approval to year 2022. Data were collected from publicly available annual reports (10-K) of the pharmaceutical company available on Securities and Exchange Commission (SEC) website [7]. If the net sales data were not available on the 10-K report, quarterly reports (10-Q) were reviewed. For non-US companies, the 20-F report was reviewed if available. For companies that did not file reports to the SEC, the financial report was downloaded from the company website. Gross sales data were collected if net sales data were not available. If sales figures were reported in a foreign currency, they were converted to US dollars using the historic exchange rate on the last day of the year. The dollar amount was then adjusted for inflation to 2022 prices using the consumer price index for all urban consumers (CPI–U). Drugs with missing data in greater than 10 % of years were excluded. For years with missing data, the sales figure was imputed as the average value of the preceding and following years. Data for the years of change in ownership of the drug due to merger and acquisition were removed and imputed. The year of generic or biosimilar market entry in US and Europe was collected as described in the pharmaceutical company financial report.

2.3. Statistical analysis

Descriptive statistics were performed using Microsoft Excel. The yearly and cumulative sales revenue was plotted. The change in sales revenue from year of peak sales and from year of generic or biosimilar market entry was described as a percentage change from reference year. Our study involved publicly available data and did not involve individual patient data; thus, it was not submitted for institutional review board, in accordance with 45 CFR §46.102(f).

3. Results

Articles reporting top selling drug lists for years 2015, 2017, 2019 and 2021 were identified [8-11]. Fifteen drugs were included in the list, with year of market entry ranging from 1997 to 2015. Three drugs (Ibrance, Velcade, Sandostatin) were excluded due to greater than 10 % missing financial data for years the drug has been on market. One drug (Jakafi) was excluded as only non-US sales data were available. Data were collected for the remaining 11 drugs that are Avastin (bevacizumab), Darzalex (daratumumab), Gleevec (imatinib), Herceptin (trastuzumab), Imbruvica (ibrutinib), Revlimid (lenalidomide), Rituxan (rituximab), Zytiga (abiraterone), Tasigna (nilotinib), Opdivo (nivolumab), and Keytruda (pembrolizumab). Characteristics of these drugs, including cumulative sales, are presented in the Table.

These 11 drugs are used in a variety of malignant conditions. Six drugs (55 %) target hematologic malignancies, 3 (27 %) drugs for solid tumors, and 2 (9 %) drugs for both hematologic malignancies and solid tumors. Six (55 %) drugs were administered by intravenous or subcutaneous route, and 5 drugs (45 %) were administered orally. Net product sales were reported for 6 drugs and total sales revenue was reported for 5 drugs. Six drugs had generic or biosimilar market entry in both the US and Europe. These drugs were Avastin (bevacizumab), Gleevec (imatinib), Herceptin (trastuzumab), Revlimid (lenalidomide), Rituxan (rituximab), and Zytiga (abiraterone). (Table 1)

The median number of years from initial drug approval to generic or biosimilar market entry in the US was 16 years (IQR 16–20 years). All drugs with generic or biosimilar competition had a decline in net sales or total sales from peak. (Fig. 1) The interval between generic or biosimilar market entry and decline in annual sales to less than 50 % of peak was 2 years (IQR 2–2 years). For drugs reporting net sales, the decline was seen after 1–2 years. For drugs where only total sales data were available, the decline was seen after 2–4 years.

The median cumulative sales revenue prior to generic or biosimilar approval was $90.15 billion (IQR 69.9–99 billion) when adjusted to 2022 dollars. The median total cumulative sales revenue from approval to 2022 was $105.6 billion (IQR 53.1–120.0 billion) for drugs with generic or biosimilar market entry and $76.5 billion (IQR 27.2–108.7 billion) for all drugs. (Fig. 3) The median number of years of generic or biosimilar competition until 2022 was 4 years (IQR 3.25–5.5 years). Approval of a generic or biosimilar was associated with a reduction of, on average, 51.8 % in yearly sales revenue in the subsequent 2 years compared to sales at the time of biosimilar or generic introduction. (Fig. 2)

4. Discussion

Biosimilars and generics have led to reduced cancer drug prices. The change in drug price or market share of reference drugs over time following a biosimilar or generic drug market entry is well documented [12–15]. However, the effect of biosimilar or generic drug competition on drug manufacturer revenue has not been previously described. Here we observe a greater than 50 % decrease from peak annual revenue after a median of 2 years after a biosimilar or generic drug becomes available.

For drugs that report net product sales, which is the total revenue, excluding returns, allowances, and discounts, this decline is more pronounced with a greater than 50 % decline seen after 1 or 2 years following biosimilar or generic drug entry. This is likely explained by the fact that greater discounts or rebates may be offered after a generic or biosimilar drug becomes available, which is not reflected in the total revenue of drug. The effect on the manufacturer's sales revenue is not fully captured by considering either the reduction in manufacturer unit sales price (e.g. ASP) or decline in market share, individually [16]. Rather, it is the combined effect of unit sales price and market share that is reflected in drug sales revenue.

The competitive landscape for reference drugs goes beyond generic or biosimilar market entry for certain cancer drugs. While trastuzumab and rituximab do not have alternative treatments for many indications, imatinib faces competition from second generation tyrosine kinase inhibitors (e.g. dasatinib) in first-line treatment of chronic myeloid leukemia (CML), which is the most common indication for use. Ibrutinib also has both within class competition from second generation Bruton's tyrosine kinase inhibitors (e.g. acalabrutinib) and other class competition from venetoclax in first line chronic lymphocytic leukemia (CLL). In fact, ibrutinib has seen decline in sales revenue despite of not having generic competition.

Despite the complex market structure of the pharmaceutical drug industry, this study demonstrates an abrupt and steep decline in sales revenue after generic or biosimilar drug entry for top selling drugs. This incentivizes drug manufacturers to maximize revenue during the period of market exclusivity, and leads to greater focus on the expansion of drug indications, including approvals in other cancer types and settings for drugs previously approved in metastatic disease (e.g., adjuvant). Expanding the portfolio of cancer drug trials and indications outside of initial FDA indications has been seen for regorafenib, lenvatinib, sunitinib, cabozantinib [17–19].

Table 1
Cumulative and yearly sales revenue of top cancer drugs from approval to 2022.

	Generic name	Drug approval in US (year)	Pharmaceutical company	Generic or biosimilar entry (year)		Peak sales (year)	Peak sales revenue (2022 billion US$)
				US	Europe		
Rituxan†	Rituximab	1997	Roche	2019	2017	2012	9.59
Herceptin	Trastuzumab	1998	Roche	2019	2018	2014	8.62
Gleevec	Imatinib	2001	Novartis	2016	2016	2011	6.13
Avastin	Bevacizumab	2004	Roche	2019	2020	2014	8.82
Revlimid	Lenalidomide	2005	BMS	2022	2022	2020	13.8
Tasigna†	Nilotinib	2007	Novartis	-	-	2020	2.23
Zytiga	Abiraterone	2011	J&J	2018	2022	2018	4.13
Imbruvica†	Ibrutinib	2013	J&J	-	-	2020	4.70
Opdivo	Nivolumab	2014	BMS	-	-	2019	8.32
Keytruda†	Pembrolizumab	2014	Merck	-	-	-	
Darzalex†	Daratumumab	2015	J&J	-	-	-	

J&J: Johnson & Johnson, BMS: Bristol Myers Squibb
† Gross sales revenue available in financial report

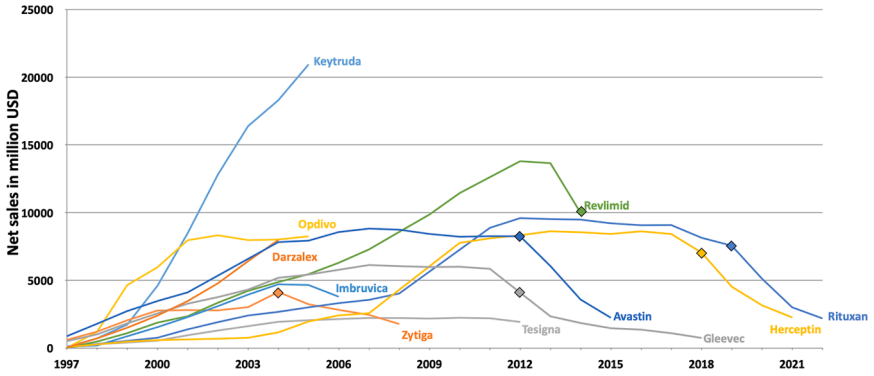

Fig. 1. Trend of yearly sales revenue of top brand name drugs from year of initial drug approval to 2022, The yearly sales revenue is in 2022 US dollars. The ⋄ point denotes the year of generic or biosimilar approval in the US.

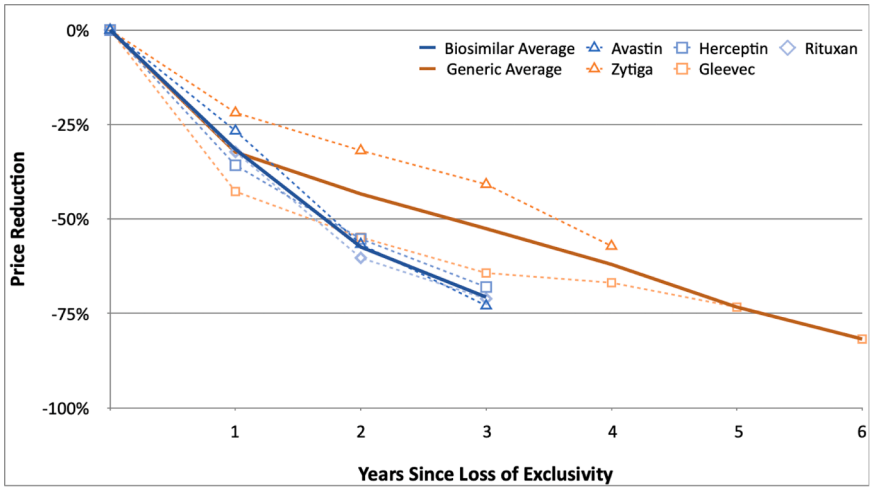

Fig. 2. Percentage decrease in yearly sales revenue from loss of exclusivity in the US, The average decrease for drugs with biosimilar entry and drugs with generic entry is in bold lines.

The incentive for profit is the primary motivation for innovation in drug development. Recognizing the market structure incentives for drug companies is important in formulating policy that promotes cost-effective high value care and addresses rising health care cost. This study demonstrates that pharmaceutical companies operate under a different market structure compared to other consumer products due to the relatively short lifespan of profitability. Reducing period of exclusivity may seem to lower healthcare costs, however paradoxically may lead to expansion of low value indications shortly after drug approval leading to increase in overall increase in healthcare cost that is unnecessary. There is increased scrutiny on the number of types of patents, or patent thicket density, that protects top selling brand drugs [20]. However, understanding the tradeoff between shorter exclusivity and greater incentive to expand low value indications in oncology is important in any proposed patent reform.

The profound decline in market share after biosimilar market entry is

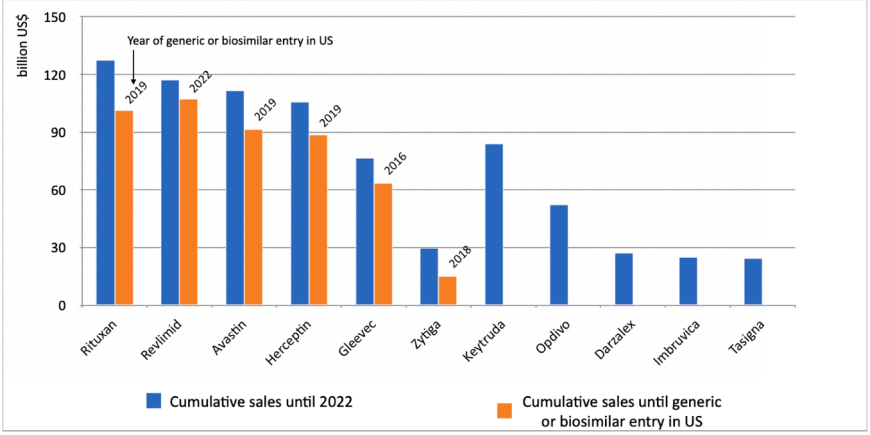

Fig. 3. Cumulative sales revenue of drugs from market entry to 2022 and cumulative sales of drugs until US biosimilar or generic market entry, Cumulative sales revenue is in 2022 US dollars. Year of generic or biosimilar availability and loss of exclusivity is noted for drugs with market competition.

unique to oncology drugs compared to other drug classes. Biosimilars gained 78 % and 82 % of market share 3 years from initial biosimilar launch of trastuzumab and bevacizumab while the biosimilar market share was 9 % for insulin glargine biosimilar at 3 years from initial biosimilar launch [4]. This difference may reflect the competitive market for oncology drugs. Patient preference for brand name drugs may also have a greater effect for self-administered medications such as insulin due to familiarity and ease of use.

5. Limitations

There are several limitations to this study. The data were limited to a small number of drugs selected because they earn the highest revenue. Yet, a strength of this approach was to focus on drugs with larger market impact. Nevertheless, market dynamics may be different for drugs with lower total revenue. The change in yearly sales was reported for worldwide sales revenue, while the dates of generic or biosimilar drug availability were based on the US market. The discrepancy in dates of US and non-US countries may affect the change in net sales revenue and generic or biosimilar market entry. Yet, the US is well known to the be the largest purchaser of drugs and the single largest source of global revenue, hence our focus on these dates.

6. Conclusion

The majority of top selling cancer drugs have a greater than 50 % decline in sales revenue within 2 years of generic or biosimilar market entry, reflecting both the decline in market share and reduction in unit drug price.

Policy impact statement

Due to the limited duration of profitability, shorter exclusivity periods lead to greater incentive to expand low value indications in oncology. Such tradeoffs should be recognized in discussing patent reform.

Disclosure

V.P. receives research funding from Arnold Ventures through a grant made to UCSF, and royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press. He declares consultancy roles with UnitedHealthcare and OptumRX; He hosts the podcasts, Plenary Session, VPZD, Sensible Medicine, writes the newsletters, Sensible Medicine, the Drug Development Letter and VP's Observations and Thoughts, and runs the YouTube channel Vinay Prasad MD MPH, which collectively earn revenue on the platforms: Patreon, YouTube and Substack. Disclosures of other authors

Funding

Arnold Ventures

CRediT authorship contribution statement

Alyson Haslam: Writing – review & editing, Formal analysis. **Myung Sun Kim:** Writing – original draft, Formal analysis, Conceptualization. **Vinay Prasad:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vinay Prasad reports financial support was provided by Arnold Ventures LLC. Vinay Prasad reports a relationship with United Healthcare that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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