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Recent trends in brand-name and generic drug competition

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Abstract

Objective:

To provide evidence on recent trends in: (1) market exclusivity periods (MEPs, the time between ___ ___new molecul___ ___s under Paragrap___

Methods

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Results:

For drugs experiencing initial generic entry in 2011–2012, the MEP was 12.6 years for drugs with sales greater than $100 million (in 2008 dollars) in the year prior to generic entry, 12.9 years overall. After generic entry, the brand rapidly lost sales, with average brand unit share of 16% at 1 year; 11% for NMEs with pre-generic entry sales of at least $250 million (in 2008 dollars). Over 80% of NMEs experiencing 2011–2012 initial generic entry had faced at least one Paragraph IV challenge from a generic manufacturer. These challenges were filed relatively early in the brand-name drug life cycle: within 7 years after brand launch, on average.

Limitations:

Analyses, including Paragraph IV calculations, were restricted to NMEs where generic entry had occurred.

Conclusion:

Pharmaceutical competition continues to evolve; while the average MEP below 13 years for 2011–2012 remains consistent with prior research, Paragraph IV challenges are increasingly frequent and occur earlier, and generic share erosion has intensified.

Introd

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protecting brand-name drugs, and generic drugs tend to rapidly supplant sales of the corresponding brand-name drug following generic entry.

The Hatch-Waxman Act included a number of provisions aimed at facilitating approval of generic drugs by the Food and Drug Administration (FDA) and encouraging generic entry (and other provisions encouraging innovation described later below). One of the primary provisions of the Act established an Abbreviated New Drug Application (ANDA) process, which greatly reduced the cost of completing an FDA application for approval of a generic drug. Prior to the Hatch-Waxman Act, generic manufacturers were required to submit original safety and efficacy data on their products to gain market approval by the FDA. To meet this requirement, the generic manufacturer generally had to duplicate many of the brand-name manufacturer's trials[1]. Under the ANDA process, generic manufacturers need only demonstrate that their products have the same active ingredients as and are 'bioequivalent' to their brand-name counterparts. Generic manufacturers also received a research exemption for bioequivalence studies, allowing them to begin research on the innovator's drug prior to patent expiration, without running afoul of patent law.

The Hatch-Waxman Act also created incentives for generic manufacturers to challenge brand-name patents before they expired. For example, under a so-called Paragraph IV challenge, the generic manufacturer files a Paragraph IV ANDA, notifying the FDA that it claims its generic product does not infringe on a listed patent on the brand-name drug, or that a patent held on the brand-name drug is not valid. If the brand-name drug manufacturer files a patent infringement action against the generic company within 45 days of r___ ___ ot approve the gene___ ___ settlement, or until a___ ___ entive for generic ___ ___ manufacturer (or manu___ ___ approval of its appli___ ___-day period of ex___ ___ generic version ___ ___ dosage form or ___ ___ ed by the day of fi___ ___ s if they file on the s___ ___ es only to the dos___ ___ to file a

The 180-day period of exclusivity generally is very profitable to a generic manufacturer because the generic manufacturer tends to drop price only modestly below the brand price during this period, generic share increases rapidly, and generic sales are enjoyed by a single manufacturer (or a few first-filing manufacturers). This provides substantial incentives for being the first to file a Paragraph IV challenge, or being among the first-filers.

In an effort to balance these provisions aimed at encouraging more generic competition for brand-name drugs, the Hatch-Waxman Act also established new incentives for innovation for brand-name drug manufacturers. For example, innovators can receive an additional period of patent protection through so-called patent term restoration. This provision extends the life of a patent on a drug by up to 5 years, with the aim of compensating for time that the innovator company spent conducting human clinical trials on the drug before it applied to the FDA for approval of the drug through a New Drug Application (NDA) and also for a portion of the time the NDA is under FDA review. Under patent term restoration, the life of the patent cannot be extended by more than 5 years, and the remaining patent term after FDA approval cannot exceed 14 years, including the extension.

In addition to patent term restoration, innovative brand-name drugs are also protected from early ANDA filings through a data exclusivity provision in the Hatch-Waxman Act. Data exclusivity runs concurrently with patent protection and restricts the FDA from receiving a generic application that relies on a brand-name drug's safety and efficacy data for 5 years following that drug's approval (unless there is a Paragraph IV challeng

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that the prescription must be 'dispensed as written'. As a result, generic products' share of total prescriptions in the US increased from 36% in 1994 to 84% in 2012[4].

The impact of Hatch-Waxman on incentives to innovate has received somewhat less attention. A 1998 report by the Congressional Budget Office estimated that generic competition reduces by 12% the net present value of the total stream of future profits expected from the average brand-name drug. In particular, the Congressional Budget Office found that, for brand-name drugs, the negative effects on returns from generic competition probably outweighed the positive effects of patent term restoration, described above[5].

The objective of this study was to provide evidence on recent trends in three factors that have a potentially substantial influence on the balance of cost savings and incentives for continued innovation in the form of new drugs: (1) MEPs for new brand-name drugs; (2) the likelihood and timing of Paragraph IV patent challenges under the Hatch-Waxman Act, through which generic manufacturers challenge the validity or applicability of patents protecting brand-name drugs; and (3) the rate and extent of generic drug penetration following initial generic entry.

The findings presented extend and expand upon research originally conducted by Grabowski and Kyle[6] and updated in Grabowski et al.[7], which evaluated data on MEPs for all new molecular entities (NMEs) experiencing initial generic entry between 1995 and 2008. Here, we further extend those prior analyses to include data on all NMEs experiencing initial generic entry through September 2012, allowing for evaluation of trends over a long period of time for key features of generic competition. We collected and ana   rroboration of the 2   ling the time period c

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merged with similar data for the time period 1995–2006. The data set used in the analysis contained information about all 460 drugs experiencing first generic entry during this period, including 257 NMEs, and 203 new formulations of older drugs. New formulations include changes in the form of administration—for example, changing from an injection to a topical application—but not new strengths or new indications. We excluded several products from the analysis based on the following criteria: one product was excluded because generic versions of it were subsequently withdrawn as a result of litigation following initial entry; and seven products were excluded because the original brand FDA approval pre-dated October 1962 and the requirements for safety and efficacy data introduced at that time. Our analysis focused on NMEs and we present data only on the 257 NMEs experiencing initial generic entry between January 1995 and September 2012 because regulations for generic entry differ if the brand-name product is a new formulation.

In addition to providing the information necessary to calculate MEPs, the data also included information on drug characteristics, such as mode of administration and number of generic entrants. All sales data are presented in 2008 dollars, adjusted using the US Department of Labor's Consumer Price Index for All Urban Consumers as the market deflator.

We supplemented the market exclusivity data with a detailed review of information from the FDA's website on Paragraph IV ANDA filings8. We also analyzed ANDA approval letters in the study period and searched other public information including company press releases, court documents, and industry trade reports, to identify all of the drugs in the da   the first
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of first generic entry, illustrating the increasing extent of brand-name drug erosion for drugs more recently experiencing first generic entry.

Methods

Consistent with prior research, we defined the MEP as the time between the launch of a brand-name drug and the launch of its first generic competitor. As noted, this definition reflects the often complex interaction among many technical, regulatory, and competitive factors, including: the timing of patent filings, the amount of patent term lost during product development, the duration of regulatory review before FDA approval, the eligibility for patent term restoration under the Hatch-Waxman Act, the likelihood and outcome of generic patent challenges (including the possibility of a stay on generic entry for up to 30 months pending court decisions on patent infringement suits), entry decisions by generic manufacturers, and the duration of FDA review of generics. Any one or a combination of these factors can affect the market exclusivity of a particular drug. The average MEP remains a key determinant of profitability and incentives for innovation.

The average number of generic entrants within 1 year of first generic entry was calculated by level of sales (i.e., less than $100 million, greater than or equal to $100 million and less than $250 million, greater than or equal to $250 million and less than $1 billion, $1 billion or larger), based on sales in the year prior to generic entry and inflation-adjusted to 2008 dollars using the US Department of Labor Consumer Price Index for All Urban Consumers, and by time period of initial generic entry (i.e., 1995–1998, 1999–2003, 2004–2008, 2009–2011).

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All figures presented are unweighted averages. Figures in parentheses following calculated averages are standard deviations. Figures for Paragraph IV filing frequency and timing (as presented in Exhibit 3) are 3-year moving averages.

Results

Average period of market exclusivity

Figure 1 shows the average length of the market exclusivity period for all new drugs, by year of first generic entry, and for those with annual sales greater than $100 million in the 12 months prior to generic entry (in 2008 dollars). Between 1995–2012, the average MEPs for all drugs experiencing first generic entry ranged between 12.2–13.7 years over the period.

Figure 1. Average market exclusivity period by year of first generic entry: new molecular entities.
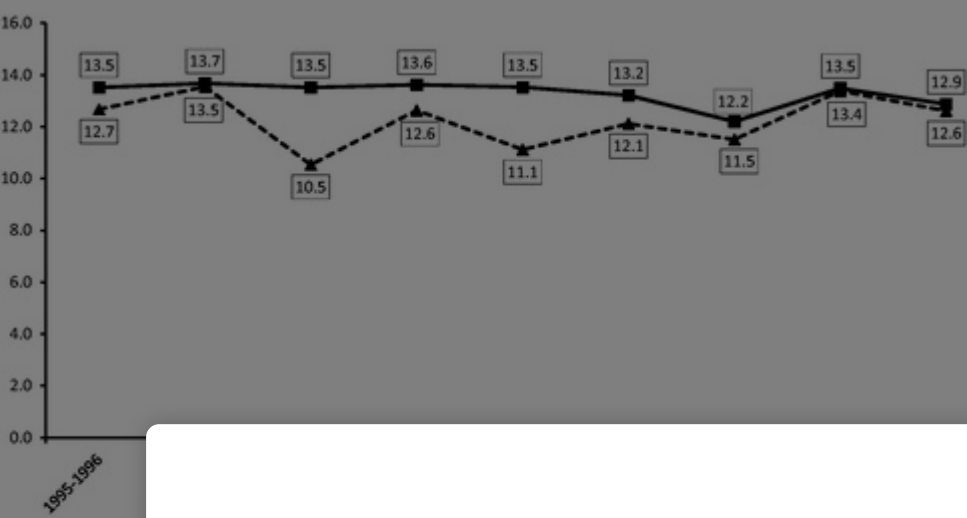
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initial period (1995–1996). Figures for each cohort of NMEs, as defined by year of first generic entry, are presented in Table 1.

Table 1. Average market exclusivity period by year of first generic entry.

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Average MEPs were similar whether we analyzed drugs with annual sales greater than $100 million, $250 million, or $1 billion (in 2008 dollars, data not shown).

Figure 2 summarizes the number of generic entrants observed for NMEs in the data. The exhibit shows the average number of a brand-name drug's generic competitors in the market 12 months after the first generic entry, segmented by level of sales and by time period. The number of generic entrants is higher for drugs with larger sales before the first generic entry and for drugs experiencing first generic entry after 1998. For example, one drug with over $1 billion in annual sales prior to generic entry experienced first generic competition in the period 1995–1998 and it faced six generic entrants after 1 year. The corresponding figures for drugs with over $1 billion in annual sales (in 2008 dollars) prior to generic entry were an average of between eight and nine generic entrants for the period 1999–2003, between 11 and 12 for 2004–2008, and between nine and 10 for 2009–2011. Similar trends in the number of generic entrants were experienced for drugs with under $1 billion in sales.

Figure 2. entry: new molecula

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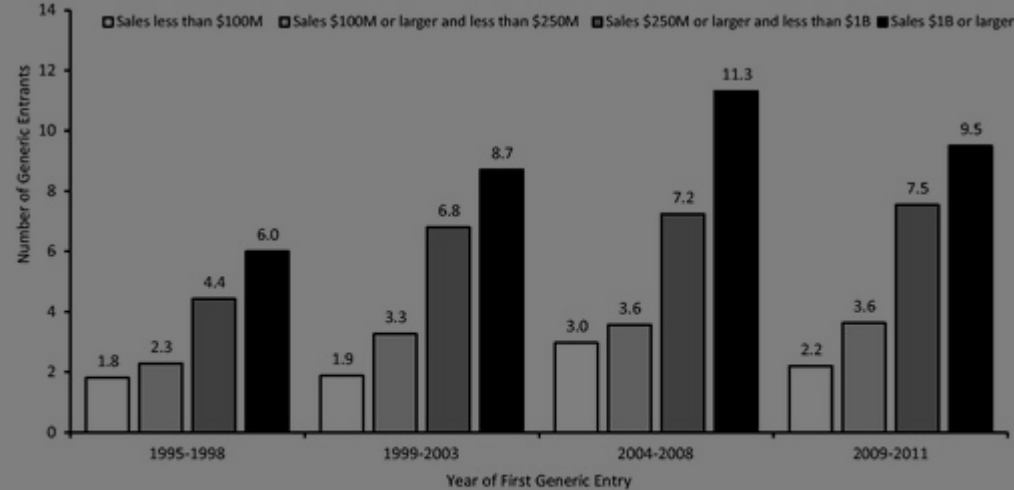
Source:
IMS Health data on all new drugs with initial generic entry in the period 1995 through September 2012.
Notes:
New molecules with sales in the year prior to generic entry, inflation-adjusted to 2008 dollars using the Consumer Price Index for All Urban Consumers.

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Paragraph IV challenges

The likelihood of a Paragraph IV challenge being filed has increased substantially in recent years (Figure 3). Only 9% of drugs experiencing first generic entry in 1995 had experienced a Paragraph IV challenge at any point prior to first generic launch. That share increased steadily to 81% by drugs experiencing first generic entry in 2012. Drugs with sales greater than $100 million the year before first generic entry (in 2008 dollars) faced an even higher probability of a Paragraph IV filing, increasing from 17% in 1995 to 84% in 2012 (data not shown).

Figure 3. Paragraph IV filing frequency and timing (3-year moving average).

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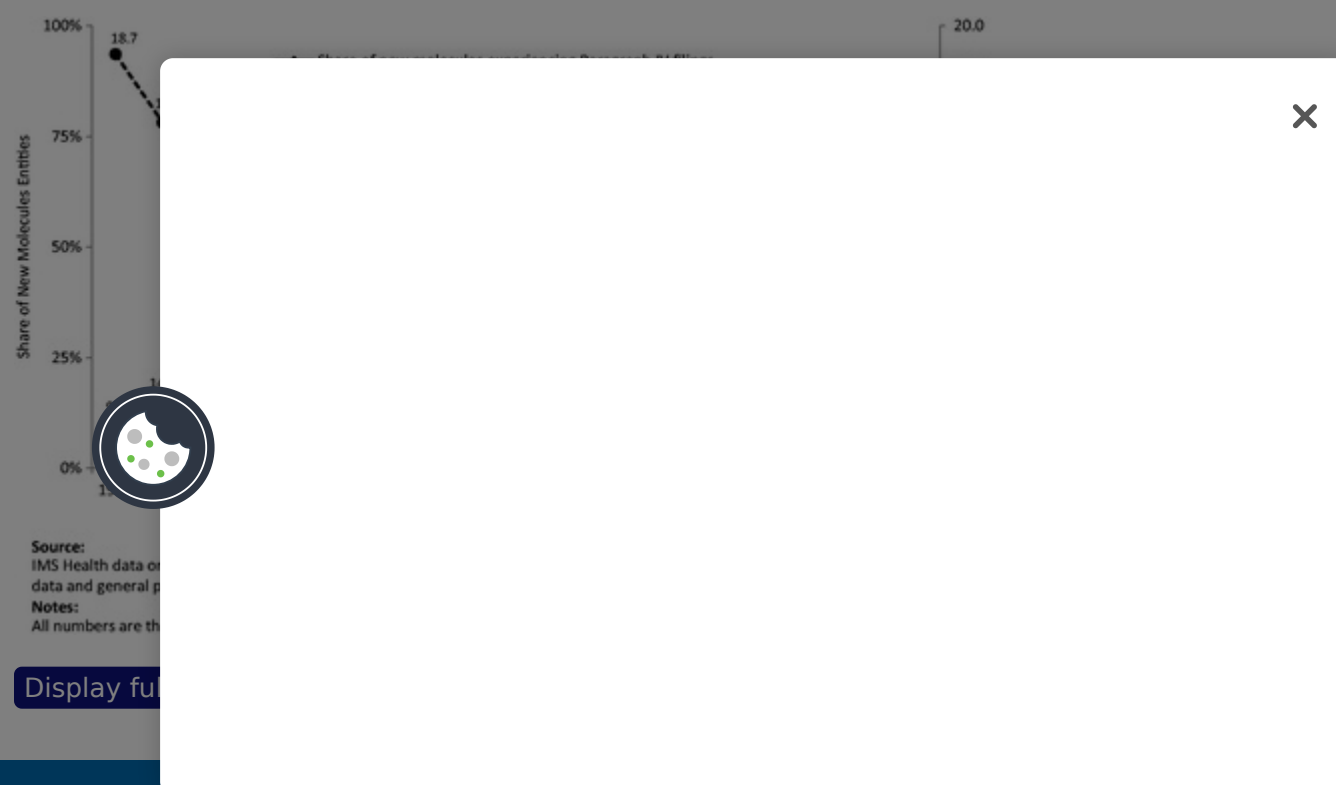
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Paragraph IV challenges also occur sooner following the launch of a brand-name drug (Figure 3). For drugs experiencing first generic entry in 1995 and also experiencing a Paragraph IV challenge, the average time between launch and the first Paragraph IV challenge was 18.7 years (6.2). That time fell to 6.9 years (3.4) for drugs experiencing first generic entry in 2012. For new drugs with sales greater than $100 million in the 12 months before first generic entry (in 2008 dollars), the time between brand launch and first Paragraph IV challenge fell from 14.3 years (one drug) in 1995 to 5.9 years (2.7) for 16 drugs in 2012 (data not shown). Paragraph IV challenge activity is even more aggressive for new drugs with sales greater than $250 million (in 2008 dollars). Of these drugs that experienced first generic entry in 2012, 92% also experienced a Paragraph IV challenge (13 of 14 drugs), and the average time from launch to first challenge was 6.3 years (3.0).

The calculations reflected in Figure 3 reflect averages across all new drug introductions associated with first generic entry in a given year. They may vary according to factors such as the drug's sales prior to generic entry, the nature of the patents protecting the drug, and the ease with which generic manufacturers can imitate the drug to satisfy FDA regulations. In particular, for higher-revenue drugs, generic manufacturers may be less selective when filing challenges, as even a low likelihood of success in litigation can yield a large expected return on the investment necessary to challenge a patent. For instance, researchers have found that court decisions on Paragraph IV challenges filed prior to 2005 involved a disproportionate share of high-revenue drugs[9]. Others have calculated that, as brand-name drug revenue increases, the probability of success required to justify a patent challenge by a generic manufacturer diminishes to below 1%[10]. F   009, brand
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2008 dollars) prior to first generic entry, generic erosion was even more pronounced; the corresponding figure was only 11% (0.09) of units at 1 year.

Figure 4. Average monthly brand share of standard units of the molecule/form following first generic entry.
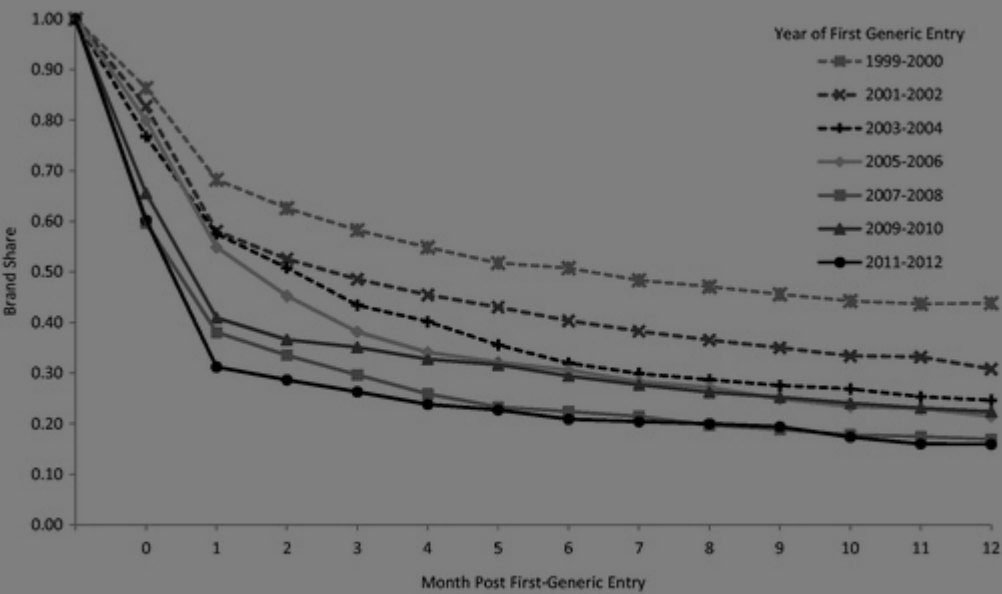
Source:
IMS Health data for all new molecular entities with first generic entry in the period 1999 through September 2012.
Note:
Initial generic entry occurs at some point during month "0". Month "1" is the first full month of generic competition.

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In comparison, drugs experiencing first generic entry in 1999–2000 maintained a share of 44% (0.28) of units at 1 year following first generic entry. Grouping drugs into 2-year periods by the date of first generic entry illustrates the steady increase in the rate and extent of generic penetration over the past decade.

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following initial generic entry. For NMEs experiencing initial generic entry in 2011–2012 and with pre-generic entry sales of at least $250 million (in 2008 dollars), average brand unit share had fallen to 11% at 1 year; for all NMEs with initial generic entry in 2011–2012, average brand unit share at 1 year had fallen to 16%.

While the average MEP for brand-name drugs has remained relatively constant over the past 10–15 years, generic manufacturers are challenging the patents protecting brand-name drugs more often and earlier, which may have a downward impact on future MEPs (we calculate MEPs only for those already experiencing generic entry). Over 80% of brand-name drugs experiencing initial generic entry in 2012 had faced at least one Paragraph IV patent challenge from a generic manufacturer, up from only 9% for drugs experiencing initial generic entry in 1995. These challenges are filed relatively early in the brand drug life cycle, on average within 7 years of brand launch.

Conclusions

Pharmaceutical competition continues to evolve since the passage of the Hatch-Waxman Act in 1984. While the average MEP for brand-name drugs, currently 12.6 years for NMEs with pre-generic entry sales of $100 million (in 2008 dollars) and 12.9 years for all drugs, has remained relatively constant, consistent with prior research, other factors have changed. Over the past decade, Paragraph IV challenges have become increasingly frequent and occur earlier, and generic share erosion has intensified.

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Related Research Data

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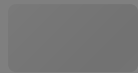
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