MANAGERIAL AND DECISION ECONOMICS
Manage. Decis. Econ. **28:** 491–502 (2007)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/mde.1356

Generic Competition and Market Exclusivity Periods in Pharmaceuticals

Henry G. Grabowski[a,*] and Margaret Kyle[b]

[a] *Department of Economics, Duke University, Durham, NC 27708, USA*
[b] *Departments of Strategy and Economics, London Business School, London NW1 4SA*

In this paper we examine generic competition and market exclusivity periods for pharmaceuticals experiencing their initial generic entry between 1995 and 2005. We find that generic competition has increased over several dimensions. First, an increasing number of drugs are subject to generic entry, including drugs with relatively modest annual average sales. Second, drugs with larger sales attract more generic entrants and have shorter market exclusivity periods than smaller selling drugs. Third, blockbuster drugs with annual sales in excess of $1 billion have experienced significant decreases in their market exclusivity periods in recent years. We also find that Hatch-Waxman Act patent challenges have negatively affected market exclusivity periods over the 1995 to 2005 period. Copyright © 2007 John Wiley & Sons, Ltd.

INTRODUCTION

It has been asserted that pharmaceutical products have been enjoying increasing periods of freedom from generic competition. For example, some pharmaceutical industry critics suggest that the average 'patent life' of new drugs has increased, and in some cases 'doubled,' since the 1980s. (NIHCM Foundation, 2000). These arguments, however, are not an accurate way of determining the amount of time a brand name drug is on the market before generic competition. The more accurate approach is the market exclusivity period (MEP), or the amount of time the brand name pharmaceutical is on the market before generic competition.

This paper examines actual MEPs for new drugs experiencing first generic competition in the past decade. We find that generic competitors are challenging brand name pharmaceuticals at a variety of sales levels; and that after the first generic entry, there is still a market for additional generic competitors. In addition, we find that since 2002, there has been a large number of 'blockbuster' drugs exposed to generic competition for the first time, and their average market exclusivity has declined significantly compared to the blockbuster drugs that experienced entry prior to 2002.[1] A complementary analysis of drugs first launched in the 1980s did not reveal any MEPs from this period that had both large commercial sales and the absence of generic competition in 2005.

BACKGROUND AND DATA SAMPLES

Generic entry is regulated under the Hatch-Waxman Act (formally known as the Drug Price Competition and Patent Term Restoration Act of 1984). Title I of the Hatch-Waxman Act establishes the Abbreviated New Drug Application (ANDA) process for generic entry. Under the ANDA requirements, generic firms must demon-

*Correspondence to: Department of Economics, Duke University, Durham, NC 27708, USA. E-mail: grabow@econ.duke.edu

strate that their drug is bioequivalent, meaning that the rate and extent of availability of the drug at the site of action in the body is not significantly different from the innovator's product. Although generic firms have to demonstrate bioequivalence, they do not have to reproduce the safety and efficacy data submitted by the original NDA applicant. The Act also allows firms to do their bioequivalence testing and ANDA filings prior to patent expiration. These features allowed generics to enter the market much more quickly than was previously the case, usually within a few months of patent expiration (CBO, 1998) In the pre-Hatch-Waxman period, entry typically did not occur until three years or more after patent expiration and many commercially significant products did not experience any generic entry (CBO, 1998).

Title II of the Hatch-Waxman Act provided for partial restoration of the patent time lost during the regulatory review and clinical testing period. Since firms typically apply for patents prior to the beginning of human testing, much of the nominal 20-year patent term is lost during the lengthy pre-market development period for a new drug. (DiMasi *et al*., 2003) The Law provides a formula for restoring part of the lost time on one patent, but it also constrains extensions to a maximum effective patent life (EPL) of 14 years, and caps the length of restoration at 5 years (even if this yields a maximum EPL of less than 14 years).[2]

When filing an ANDA, generic firms must make one of four patent certifications. These are referred to as Paragraph I, II, III, and IV certifications. In particular; (1) that the drug has not been patented; or (2) that the patent has already expired; or (3) the date on which the patent will expire, and that the generic will not go on the market until that date passes; or (4) that the patent is not infringed or is invalid. (Mossinghoff, 1999) The Hatch-Waxman Act awards a 180-day exclusivity period to the first generic firm (or firms) that files, and maintains, a paragraph IV patent challenge. There is a data exclusion provision prohibiting generic firms from submitting an application for a generic drug that relies on innovator safety and efficacy for 5 years from approval of any innovator drug containing a new molecular entity. (The period shrinks to 4 years if the generic drug application is submitted with a Paragraph IV certification.) The Law also now provides for one stay of up to 30 months on the approval of an ANDA while legal proceedings with respect to patent infringement and validity, are ongoing at the trial court level. (Padden and Jenkins, 2004)[3] The number of patent suits associated with paragraph IV filings has grown dramatically in recent years (Grabowski, 2004).

While several studies have attempted to estimate MEPs based on the filings of the innovator's patents in the Orange Book, MEPs are determined by a complex interaction of technical, regulatory, and competitive factors. In particular, MEPs are influenced by the innovator's patent filings, its clinical and regulatory review time before FDA approval, the eligibility for patent term restoration, the ability of generic firms to circumvent or successfully challenge in court the innovator's patents, and the length of time that the generic firm incurs in obtaining its ANDA approval at the FDA.

In this paper, we undertake an analysis of MEPs for the drug products that have recently experienced generic competition. IMS provided us data that enabled us to calculate MEPs for all drug products first experiencing generic competition in the period 1995–2005. This included data for new molecular entities (NMEs) as well as data on new formulations (e.g. controlled release formulations and combination drugs. New dosage strengths are not treated as separate observations).

The objective of the analysis is to examine what variables affect MEP and how MEPs have been changing over time. To the extent that we are obtaining observations from a stable distribution over time, this analysis can give insights into what the distribution of MEPs is likely to be for NMEs experiencing generic competition in the next several years. However, it is appropriate to consider how various developments could affect future MEPs. In particular, the increasing number of Paragraph IV challenges may lead to shorter MEPs in future time periods. The big upsurge in patent challenges in recent years is concentrated at earlier stages in the lifecycle than previously was the case (Grabowski, 2004). Hence, this has the potential to significantly shorten MEPs in the future. These developments would not be fully reflected in the data examined here.

ANALYSIS OF DATA AND TRENDS

Sample characteristics

The sample consists of 251 drug products that experienced generic competition between January

DOI: 10.1002/mde

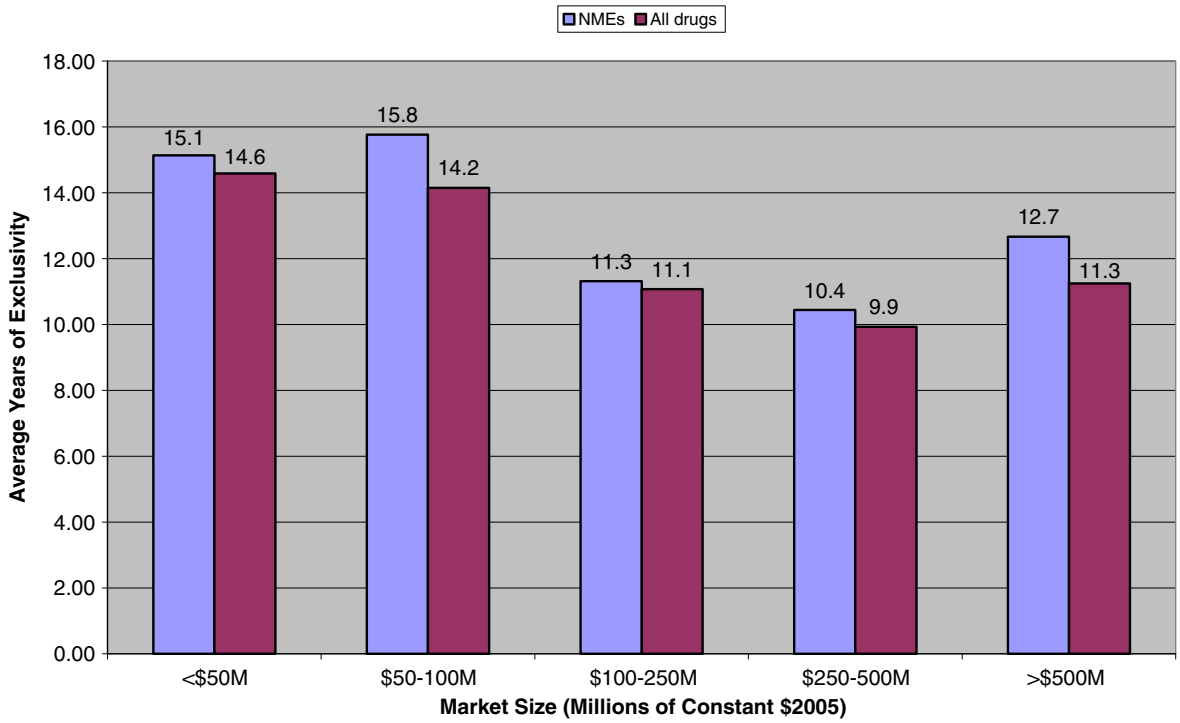


Figure 1. Market exclusivity by market size.

1995 and December 2005. The sample includes 147 NMEs and 104 new product formulations (e.g. combinations, controlled release delivery systems, injectibles, etc.).[4] A new formulation is treated as separate observation from the new molecular entity with the same active ingredient. This is based on both supply and demand side considerations. To gain market entry, new formulations typically must undergo additional clinical trials (although perhaps only comparative bioavailability studies) and a new FDA regulatory approval process. On the demand side of the market, managed care organizations also do a new review and often give different formulary status to a new formulation depending on their judgment of the extent of its therapeutic advance and the availability of close substitutes, including generic versions of alternative formulations with the same active ingredient.[5] In this section, the principal focus is on NMEs but results for all drug products are presented for comparison purposes.

MEPs by market size categories

In Figure 1 we display the MEPs by market size categories. We categorize drugs experiencing generic competition by their annual sales in the year prior to generic entry. The market size categories are less than \$50 million, \$50–\$100 million, \$100–\$250 million, \$250–\$500 million, and greater than \$500 million.[6] All sales are measured in constant 2005 dollars using the CPI −U as the market deflator.

There is an inverse relationship between market size and MEPs. The NMEs in the two smallest size categories have the longest MEPs with averages of approximately 15 years. By contrast, the average MEPs for market size categories above \$100 million are in the 10.5–12.5 year range. The results for all drugs are qualitatively similar but average MEPs are somewhat smaller in value than for the sample of only NMEs.

One finding that is surprising is the relatively large number of NMEs with small market sales experiencing initial generic competition during the 1995–2005 period. The results in Table 1 show that 54 of 147 NMEs experiencing initial generic entry had sales of less than \$50 million and more than half of the sample (77 NMEs) had sales of less than \$100 million. The large number of NMEs experiencing generic entry with small annual sales appears to reflect a broadening of the business

DOI: 10.1002/mde

model of generic firms. In particular, they are extending their focus beyond blockbuster and commercially significant entities to targeting NMEs in the niche sales category.

On economic grounds, generic firms have incentives to focus on being early entrants into markets with large revenues (Scott Morton, 1999; Grabowski and Vernon, 1992). One would expect entry into niche markets would occur as generic firms broaden their portfolio and this could occur well after the date of patent expiration. This is consistent with the observation that there are many outliers with very long MEPs in the case of the NMEs with sales below $100 million, but not those NMEs with larger sales (discussed further below). Hence, it would seem reasonable to hypothesize that the MEPs are larger for NMEs with small sales because of longer intervals between patent expiration and the onset of generic competition. We do not think it is because the EPL for these smaller selling drugs is longer.

Table 1. Number of drugs experiencing generic competition by market size

Market Size[a]	NMEs	All drugs
< $50 Mil	54	103
$50 Mil–$100 Mil	23	44
$100 Mil–$250 Mil	29	46
$250 Mil–$500 Mil	19	25
>$500 Mil	22	33
Total	147	251

[a] Market size is measured by sales revenues (in 2005$) in the 12 month period prior to first generic entrant.

In Figure 2 we present the average number of generic entrants after 1 year of generic competition for drugs of varying market sales. As expected, greater market sales draws more generic entrants within the first year of generic competition. In particular, markets with less than $50 million in market sales have less than two generic competitors after Year 1, whereas markets with sales greater than $500 million have more than seven generic competitors. However, even markets with sales of $50–100 million averaged between two and three generics within one year of generic entry. These results are consistent with several studies by economists that product sales are a key determinant of generic entry and competition (Grabowski and Vernon, 1992; Scott Morton, 1999; Reiffen and Ward, 2002).

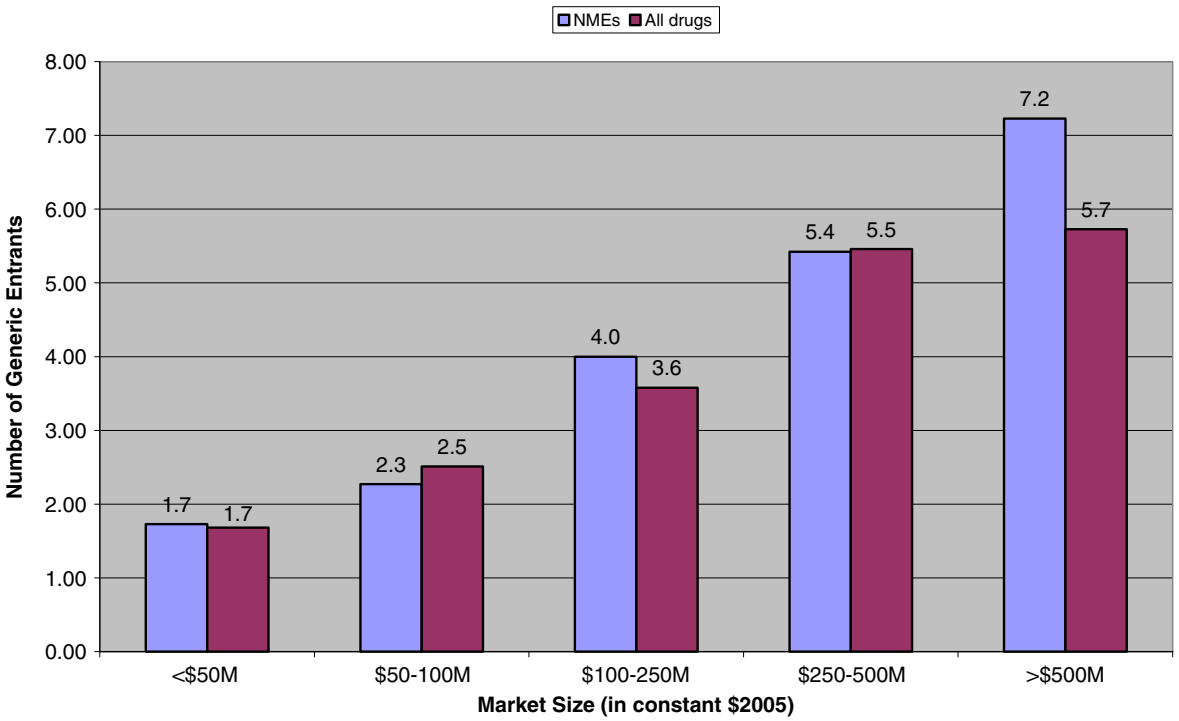
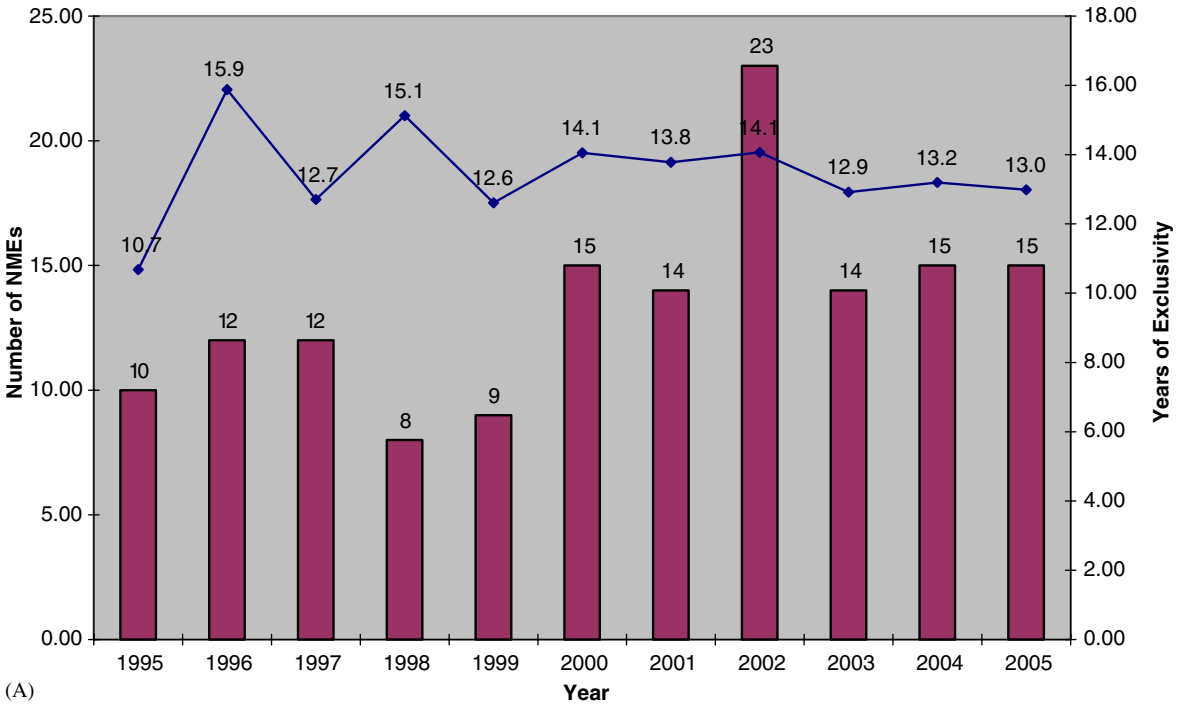
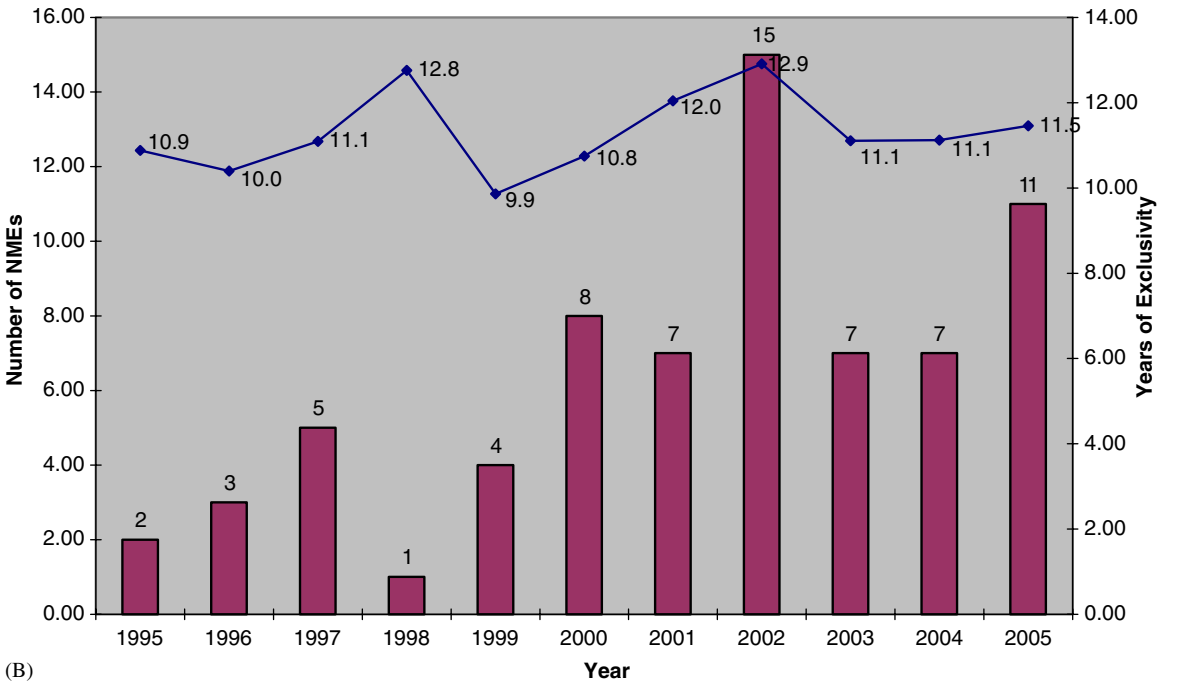


Figure 2. Average number of generic entrants within 1 year, by market size.

DOI: 10.1002/mde



(A)



(B)

Figure 3. (A) Number of NMEs experiencing generic entry and average exclusivity, by year; (B) Number of NMEs with sales > \$100 M experiencing generic entry and average exclusivity, by year.

Time Trends and Frequency Distributions

Figure 3(A) presents the average yearly MEP values for NMEs, categorized by year of first generic entry. The figure also shows the number of NMEs experiencing initial generic entry in each year for the 1995–2005 period. There is a strong upward trend in the annual number of

DOI: 10.1002/mde

NMEs subject to generic competition for the first time. The period 2000–2005 had an average of 16 NMEs subject to generic competition for the first time compared to 10 NMEs in the 1995–1999 period.

The average MEPs in Figure 3(A) fluctuate generally within a range of 12–15 years. There is no discernible trend in MEPs over the 1995–2005 period. However, given that the group of NMEs with relatively small sales comprise a large and expanding share of NMEs in our sample, it is also appropriate to consider various sub-samples of NMEs on this issue.

Figure 3(B) considers the category of NMEs with sales greater than $100 million. This reduces the sample size by roughly one-half. However, the NMEs with sales greater than $100 million account for more than 90% of the drug sales first exposed to generic competition over the 1995–2005 period. This reflects the skewed distribution of pharmaceutical sales. (Grabowski *et al.*, 2002; Grabowski, 2004).

Figure 3(B) shows the average annual MEPs for NMEs with sales greater than $100 million. The average MEPs for each year are generally lower than for the full sample of NMEs. For example, the average MEPs for the 2003–2005 period are approximately 11 years in Figure 3(B), compared to 13 years in Figure 3(A). There is also less variability in year-to-year fluctuations than in Figure 3(A). The frequency distributions for MEPs are considered below. They indicate a significant number of long-tail observations (MEPs greater than 20 years) for NMEs with less than $100 million in market sales. This is not the case for NMEs with sales above $100 million.

As in the case of the complete NME sample, there is a decided upward trend in the annual number of NMEs with sales greater than $100 million that are first exposed to generic competition. This is reflected in Figure 3(B) by the fact that the period 1995–1999 had an average of only three drugs experiencing initial generic competition. By comparison, the period 2000–2005 had an average of nine NMEs experiencing initial generic competition.

An analysis of the frequency distributions confirms the presence of several outliers for the sample of NMEs with sales less than $100 million. In particular, there are 17 NMEs with MEPs greater than 20 years. This is shown in Figure 4(A). By contrast there are only three such NMEs with an MEP greater than 20 years in the distribution of NMEs with sales greater than $100 million (Figure 4(B)). Furthermore, the latter distribution has a much higher percentage of the NMEs with relatively short MEPs. In particular, 30 of the 70 NMEs (43%) with sales greater than $100 million have 10 years or less of market exclusivity, compared to 17 of 77 NMEs (22%) with sales less than $100 million. The results are unchanged qualitatively if we include all drug products in the analysis rather than only NMEs.

The Blockbuster Sales Category of NMEs

Given the highly skewed distribution of returns for NMEs, it is also relevant to focus on drugs in the very high end of the sales distribution. In particular, Grabowski *et al.* (2002) have analyzed the distribution of returns to various cohorts of NMEs introduced between 1970 and 1994. They find that the top 10% of NMEs ranked by sales account for more than 50% of the total value for all NME introductions. These 'high value,' or blockbuster, NMEs are frequently first-in-class or best-in-class new product entrants in markets with many potential patients and unmet medical needs. (Grabowski *et al.,* 2002) In addition to the importance of these entities from a therapeutic standpoint, innovators are critically dependent on the revenues from these top decile compounds to earn a positive return on their overall portfolio. At the same time, health sector payors look to generic entry for these products to generate significant price competition and savings in their drug budgets. It is therefore appropriate to analyze the category of NMEs that have sales above industry benchmarks, for example, of a billion dollars or more in the year prior to generic entry, given the special importance of these entities to innovators, patients, and payors.

In Figure 5, the top panel shows the number of billion dollar NMEs experiencing first generic entry in two sub-periods of our sample. In particular, from 1995 to 2001, there were only two such NMEs first exposed to generic competition—Zantac in 1997 and Prozac in 2001. However, in the 4 year period since 2002, there have been eight of these billion dollar NMEs experiencing initial generic competition. Hence, there has been a several-fold increase in the number of blockbuster products recently exposed to generic competition.

DOI: 10.1002/mde

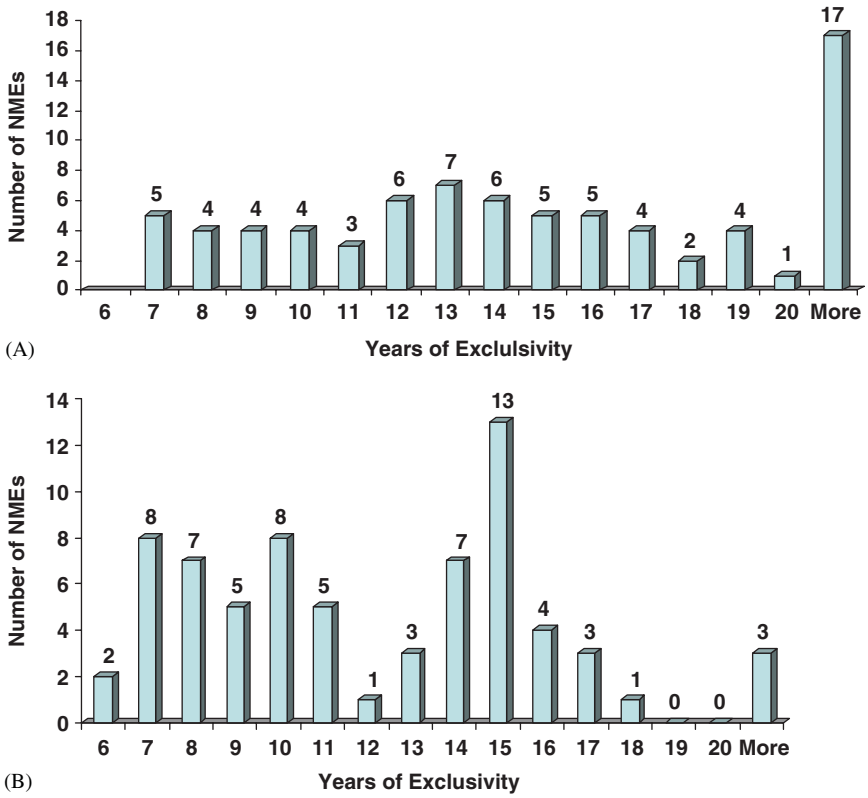


Figure 4. Market exclusivity periods distrubution for NMEs with market size: (A) $<\$100$ M; (B) $>\$100$ M.

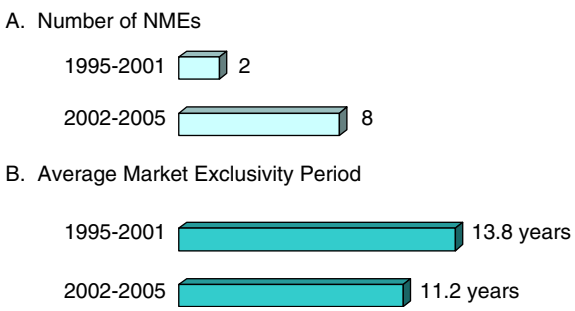


Figure 5. Billion dollar NMEs experiencing first generic entry for two time periods: (A) number of NMEs; (B) average market exclusivity period.

The lower panel in Figure 5 shows the mean MEP for the billion dollar products in the two periods. For the two products experiencing first generic competition prior to 2001, the MEP averaged just under 14.0 years. By comparison, the eight products experiencing first generic competition since 2002 had an average MEP of 11.2 years.[7] (Moreover, if one excludes the two antibiotic drugs from this calculation, the average MEP for the six remaining drugs is only 9.4 years.) These recent values for MEP represent relatively short product life cycle return periods for products that typically take more than a decade to develop and whose sales revenues are critical to the returns to R&D for the overall portfolio of new drug introductions.[8]

It is relevant to mention that all but a few of these billion dollar drugs over the 1995–2005 period have been subject to paragraph IV challenges by generic firms. The fact that these challenges are now occurring earlier in the product life cycle may be one of the significant factors explaining the tendency toward shorter MEPs in recent years. This is an important general topic for further research that is considered further in the next section.

REGRESSION ANALYSIS

In order to examine the specific effects on MEP of factors like market size or paragraph IV patent challenges, we estimated a multi-variable regression

DOI: 10.1002/mde

Table 2. Determinants of MEP for drugs experiencing first generic competition between 1995 and 2005

Variable	(1)	(2)	(3)
Constant[a]	19.36***	17.58***	15.84***
	(3.39)	(3.96)	(4.33)
Log of market size[b]	−0.69**	−0.71**	−0.70**
	(0.26)	(0.27)	(0.28)
Paragraph IV challenge	−1.53*	−1.60*	−1.22
	(0.93)	(0.96)	(0.98)
NME	1.12	1.27	1.66
	(1.72)	(1.74)	(1.18)
New formulation	−0.42	−0.35	0.47
	(1.76)	(1.79)	(2.28)
Injectible	1.87*	1.55	1.66
	(1.09)	(1.11)	(1.18)
Other administration	−0.28	−0.98	−1.19
	(1.26)	(1.30)	(1.42)
Year of first generic entry included	No	Yes	Yes
Therapeutic class indications included	No	No	Yes
R^2	0.08	0.11	0.16
F	3.28	1.80	1.68

***significant at 1%;**significant at 5%;*significant at 10%.

[a] The combination oral contraceptive group and oral dosage forms are omitted from these equations but are implicit in the constant term.

[b] Log of market size is defined as the logarithm of sales revenues in the twelve month period prior to initial generic entry.

model. The unit of observation is the 251 drug products in our sample that first experienced generic competition between 1995 and 2005. The results are presented in Table 2.

The key independent variables of interest in Table 2 are the sales of the product at the time of generic entry, and whether the product is subject to a paragraph IV challenge. In addition, control variables are also included for the type of product (i.e. NME, new formulation, or combination oral contraceptive) and its mode of administration (oral, injectible, or other form of administration). We also included control variables on the year of first generic entry and a product's therapeutic class (i.e. cardiovascular, anti-infective, etc.) in a stepwise fashion in some of the alternative specifications.

We utilize a logarithmic specification on the market size variable, given the non-linear effect observed in the descriptive statistics earlier (Figure 1). The results in Table 2 indicate that products with larger sales have shorter MEPs. The log size variable is negative and statistically significant at the 5% level. These results reinforce the findings illustrated in Figure 1 that products with larger sales (for example, the above $100 million benchmark) have significantly shorter MEPs than their smaller selling counterparts.

A second basic finding of interest is that drugs experiencing a paragraph IV challenge had MEPs that were on average about 1.5 years shorter in value than the products without such a challenge. This variable is subject to somewhat larger standard errors than the log size variable. However, it is still statistically significant (at the 10% level) in two of three specifications. These larger standard errors probably reflect the fact that our information does not allow us to know whether the patent challenge was successful or not. This introduces some noise into this variable. Also, paragraph IV challenges were distributed across many different points of time in the product life cycle for the drug products in our 1995–2005 sample period, whereas more recent patent suits are concentrated much earlier after product approvals. (Grabowski, 2004)

Generic firms are increasingly pursuing a 'prospecting' approach and undertaking patent challenges of major products early in the product life cycle. Even if the probability of overturning the patent is low, the rewards associated with 6 month exclusivity are large compared to the legal costs incurred. As discussed, the FDA will accept a paragraph IV ANDA application 4 years after NDA approval for an NME (in particular 1 year before the expiration of the 5-year exclusivity period). At this point in time, multiple generic challenges often occur, triggering intensive legal battles over patent infringement and validity. Given the large number of ongoing suits at the present time which are concentrated at earlier points in the product life cycle, paragraph IV challenges could result in significantly shorter MEPs in the future (Grabowski, 2004). This remains an important issue for further research.

The other variables included in the regressions suggest that NMEs have MEPs that are longer, on average, than new formulations or combination oral contraceptives. Similarly, injectibles have MEPs that are a few years longer than oral drugs or ones with other modes of administration. The year in which first generic entry occurred is included in the alternative specifications (2) and (3). There is no systematic trend observed in these coefficient estimates, except for a tendency for

DOI: 10.1002/mde

earlier and later years of the sample to exhibit lower MEPs.

The regressions in column 3 of Table 2 also include the therapeutic class indicator variables (12 classes in all) present as control variables. While some of the therapeutic class indicator variables are statistically significant, these variables as a group add little explanatory power. This may result from the fact that the classes are necessarily defined very broadly.[9]

AN ANALYSIS OF GENERIC COMPETITION FOR 1980-1989 NME INTRODUCTIONS

One possible critique of our analysis is, given that the drugs are categorized by year of initial generic introduction, there is the possibility that the sample is right censored. In particular, there may be some molecules with very long tail MEPs that currently have no generic competition. As discussed, our results do pick up a number of outliers of very old drugs first facing generic competition in the last 10 years. They are strongly concentrated in the distribution of NMEs with sales less than $100 million.

In order to examine the issue of long tail MEPs in a systemic manner, we did a complementary analysis of generic competition for NMEs introduced in the 1980–1989 period. This sample of drugs has been on the market between 15 and 25 years. The sample of 1980–1989 launches allows us to examine the extent of generic competition for products that are now in the mature phase of their life cycles. We wish to investigate in particular whether there are any products with long tail MEPs that have significant product sales but no current generic competition.

Several major commercial products introduced between 1980 and 1989 (e.g. Zantac, Prozac, Zestril and Prinivil, Vasotec, Pepcid, etc.) are already present in our sample of drug products that experienced initial generic competition in the 1995–2005 period (i.e. Tables 1 and 2 and Figures 1–4). The MEPs for these products had effective patent lives in the 10–15 year range and hence experienced generic competition before the December 2005 endpoint of our sample. The analysis in this section allows us to look systematically at MEPs by the date of first market launch rather than the date of initial generic competition. It therefore provides a look at MEPs from a different perspective and should illuminate the issue of long-tail MEPs in particular.

The 1980–1989 NME introduction sample included in this analysis is discussed in more detail in Grabowski and Vernon (1994, 2000). Essentially it is a comprehensive sample of 167 NMEs that were introduced between 1980 and 1989. The sample considered here explicitly excludes biologicals because no Hatch-Waxman generic regulatory pathway currently exists for these entities. It also excludes a handful of drugs developed for diseases more prevalent in developing countries, such as malaria and schistosomiasis, since these drugs have negligible US sales (i.e. they do not register enough US sales to be included in the IMS audits of drug products).

A summary analysis of our findings on the extent of generic competition for 1980–1989 launches is presented in Table 3. Column 1 shows the number of NME introductions by year and column 2 shows how many of these NMEs are still

Table 3. Current generic competition for 1980–1989 new molecular entity introductions

Year	NMEs	NMEs still active	NMEs with generic competition	NMEs without generic competition
1980	8	5	4	1
1981	17	12	12	0
1982	19	15	13	2
1983	15	12	10	2
1984	16	11	11	0
1985	16	11	8	3
1986	21	17	13	4
1987	19	16	13	2
1988	14	12	7	5
1989	22	19	15	4
Total	167	130	106	24

DOI: 10.1002/mde

active or marketed in the United States in 2005. This analysis indicates that 130 of the 167 NMEs remain active while 37 NMEs introduced in 1980–1989 have been discontinued or withdrawn, generally for economic reasons (i.e. product obsolescence and insufficient market sales). Column 3 of Table 3 shows that the vast majority of active compounds have generic competitors. In particular, it indicates that 106 of the 130 active NMEs have experienced generic competition by late 2005 (82%). Viewed from the perspective of market size in the pre-generic entry period, drug products representing 94% of sales for the 1985–1989 NME sample are now subject to generic competition. The comparable figure for the 1980–1984 sample of NMEs is over 99%.[10]

Table 4 provides a listing of the drugs without generic competition. A further analysis of existing intellectual property (IP) protection for these 24 NMEs was conducted using the FDA's Electronic Orange Book database, and for antibiotic drugs, the PTO's database of awarded patents.[11] Nineteen of the 24 had no patent or exclusivity in 2005; only five of these NMEs (Primaxin, Marinol, Azactam, Novantrone and Iopidine) have any patent or drug exclusivity IP protection still applicable in 2005. Furthermore, the IP protection for four of these five compounds involves either a use patent or a process patent. Only Primaxin has a composition of matter patent still in force. Also, Table 3 shows that these drugs without generic competition are heavily concentrated in the last half of the period–over half are in the last 4 years.

The main reason for the lack of generic competition for the 24 compounds listed in Table 4 is primarily economic in nature. In particular, it reflects the small market size exhibited by the vast majority of these products. Table 4 shows the 2004 sales for each of these compounds based on IMS audit data. Only 5 of the 24 compounds have sales in excess of $50 million, whereas 15 of 24 compounds had sales below $10 million in 2004. Primaxin, an injectible antibiotic introduced in December 1985, is the largest selling drug without generic competition. It had sales just under $200 million dollars in 2004. Marinol is the only other product in Table 4 with 2004 sales in excess of $100 million.

A key conclusion of the analysis in this section, therefore, is that there are no long tail MEPs from the sample of 1980–1989 NME introductions with very large commercial sales.[12] We also find that more than 80% of the new drug introductions of the 1980s that are still active now have generic competitors (more than 90% in terms of pre-generic market sales). This is consistent with our prior findings on the increasing breadth of generic entry for even categories of drugs with small market sales at the time of patent expiration.

Table 4. 1980–1989 NME introductions that do not have generic competition in 2005

Product	Intro date	2004 ($mil) Sales	Patent or Exclusivity
Cloderm	June 1980	4.3	No
Emcyt	April 1982	6.0	No
Zanosar	September 1982	1.1	No
Lithostat	August 1983	0.2	No
Cefizox	September 1983	3.2	No
Orap	January 1985	4.1	No
Ridaura	June 1985	4.9	No
Primaxin	December 1985	197.1	Yes[a]
Syprine	April 1986	0.5	No
Cefotan	May 1986	40.1	No
Marinol	August 1986	135.9	Yes[b]
Noroxin	November 1986	6.7	No
Doral	January 1987	1.6	No
Azactam	February 1987	56.0	Yes[c]
Cyklokapron	June 1987	1.4	No
Novantrone	March 1988	82.4	Yes[d]
Maxair	May 1988	61.2	No
Iopidine	May 1988	7.7	Yes[e]
Naftin	May 1988	16.7	No
Levatol	December 1988	2.5	No
Nimotop	March 1989	24.7	No
Oxistat	April 1989	13.7	No
Suprax	June 1989	5.6	No
Ethamolin	June 1989	2.3	No

[a] Composition of matter patent on the combination of selective antibiotics with dipeptidase inhibitors; expires November 2009.
[b] Use patent for anorexia associated with weight loss in AIDS patients; expires February 2011.
[c] Process patent #5, 194, 604 for process and intermediates for beta lactams having aminothiazole acetic acid sidechains; expires June 2010.
[d] Use patent for a method of inducing regression of leukemia cell growth that was in effect in December 2005, but expired April 2006.
[e] Use patent for controlling or preventing post-operative intraocular pressure rises associated with ophthalmic laser surgical procedures; expires May 2010.

SUMMARY AND CONCLUSIONS

Our results provide the first study to our knowledge on actual MEPs for drugs facing generic competition over the past decade. One of the key findings is that generic competition has intensified over the 1995–2005 period. There are a larger

DOI: 10.1002/mde

number of drugs experiencing initial generic entry and generic competition now encompasses even very modest selling drugs. The results on generic competition were also particularly striking for blockbuster NMEs, a category which was constructed based on sales of over $1 billion in the year prior to generic entry. In particular, the number of such blockbuster drugs first exposed to generic competition has increased several fold since 2002 while their average MEP declined significantly compared with that for the blockbuster products experiencing initial generic competition in the period before 2002.

Based on a multi-variable regression analysis, we find that the MEPs for small selling drugs are significantly longer than those of larger selling drugs. Second, our results indicate that drug products subject to paragraph IV challenge have MEPs that are approximately 1.5 years shorter on average than products without such challenges (whether the patent challenge was successful or not). This is an important issue for further research, given that recent patent challenges are occurring much earlier in the product life cycle than previously was the case.

We also performed a complementary analysis on generic competition for drugs that were introduced in the 1980–1989 period. In this analysis we wanted to investigate whether there are commercially significant long tail MEPs currently without generic competition and if so whether this was due to IP protection. We found that over 80% of still active NMEs had experienced generic competition by 2005. Furthermore, only five of the 24 compounds without generic competition in 2005 had any patent or exclusivity time still remaining. The primary reason for an absence of generic competition for the relatively few drugs that were still sole sourced was economic. In particular, more than half of these 24 compounds had sales below $10 million in 2005, and none had sales in excess of $200 million.

NOTES

1. Blockbuster drugs are defined as new molecular entities (NMES) with a billion dollar or more of sales in this 12 month period prior to first generic entry.
2. Effective patent life is defined as the time from FDA approval to patent expiration.
3. The innovator has 45 days from receipt of notice of paragraph IV certification to initiate legal proceedings in order to trigger the 30-month stay. (The stay can be shortened or lengthened by the court in certain cases.)
4. A special category of new formulations is combination hormonal contraceptives (CHCs) which represent different combinations of progesterone and estrogen. These products also have bioequivalent generics that are marketed as 'branded generics.' Given the distinguishing characteristics, CHCs are treated as a special class of new formulations in the regression analysis in Table 2.
5. In some instances, new formulations have increased market share compared to the original NME, and achieved a much higher number of prescriptions (e.g. controlled release calcium channel blockers and controlled release oxycodone). In other instances, new formulations have achieved little market penetration compared to the original NME (e.g. controlled release versions of diazepem and fluoxetine).
6. These categories were chosen because they have roughly the same number of NMEs in the categories above the base case with the smallest market sales.
7. Antibiotics is a class which has shorter mean development times (DiMasi ***et al.***, 2004) and correspondingly also tend to exhibit longer effective patent lifetimes. The two antibiotic products in our sample of blockbuster NMEs were Augmentin and Cipro. These two products had the highest MEP values for this category of blockbuster NMEs with values of 17.9 and 15.6 years, respectively.
8. We also used $500 million in US sales (measured in the year prior to generic entry) as the threshold for blockbuster status. The results were qualitatively similar. In particular, there were 14 such NMEs in 2002–2005, compared to eight NMEs in 1995–2001. The average MEP was 12.2 years in the 2002–2005 period (11.4 years excluding the two antibiotics, Cipro and Augmentin) compared to the 13.5 years before the 1998–2001 period.
9. Specification (3) has the most parameters to be estimated and the corresponding highest R^2 (the percent of overall explained variance). At the same time, it has the lowest F coefficient. The F value tests the joint statistical significance of all the coefficient estimates included in the equation, appropriately adjusted for degrees of freedom (Johnson ***et al.***, 1987).
10. The benchmark for this calculation is the level of sales achieved by the NMEs in their eighth year of market life. This is a useful benchmark point of time because it is prior to generic entry but represents a point in the product life cycle where sales are typically converging to their market peaks (Grabowski and Vernon, 1994; 2000).
11. Since antibiotics were, until 1997, approved under different provisions of law than other drugs, they were not subject to the patent listing and certification

DOI: 10.1002/mde

requirements imposed on other drugs by the Hatch-Waxman Act; this difference in regulatory status carries over for antibiotics approved prior to the legislative reform that took place in 1997.

12. One pre-1980 product introduction with significant market sales is Premarin. Potential generic manufacturers have not successfully demonstrated to the FDA that they have developed a manufacturing process to produce a bioequivalent product to Premarin (HHS News, 1997).

Acknowledgements

This project was supported by grants from PhRMA and the Duke University Program in Pharmaceuticals and Health Economics. The research design and analysis for the project was performed independently by the authors. We are indebted to the able research assistance of Tim Coakley and Kalyan Machiraju.

REFERENCES

DiMasi J, Hansen R, Grabowski H. 2003. 'The price of innovation: new estimates of drug development costs.' *Journal of Health Economics* **22**: 141–185.

DiMasi J, Grabowski H, Vernon J. 2004. 'R&D Costs and returns by therapeutic category.' *Drug Information Journal* **38**(3): 211–223.

Grabowski H, Vernon J. 1992. 'Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 act.' *Journal of Law and Economics* **35**(2): 331–350.

Grabowski H, Vernon J. 1994. 'Returns to R&D on new drug introductions in the 1980s.' *Journal of Health Economics* **13**: 383–406.

Grabowski H, Vernon J. 2000. 'The distribution of sales revenues from pharmaceutical innovation.' *PharmacoEconomics* **18**(suppl. 1): 21–32.

Grabowski H, Vernon J, DiMasi J. 2002. 'Returns on research and development for the 1990s new drug introductions. *PharmcoEconomics* **20**(suppl. 3): 11–29.

Grabowski H. 2004. 'Are the economics of pharmaceutical R&D changing: productivity, patents, and political pressures.' *PharmacoEconomics* **22**(Suppl. 2): 15–24.

HHS News, May 5, 1997. 'FDA Statement on Generic Premarin,: (www.fda.gov/bbs/topics/NEWS/NEW00565.html)

Johnson Jr AC, Johnson MB, Buse RC. 1987. *Econometrics Basic and Applied*. MacMillan: New York.

Mossinghoff GJ. 1999. 'Overview of the Hatch-Waxman Act and its impact on the drug development process.' *Food Drug and Law Journal* **54**(2): 194–197.

NIHCM Foundation. 2000. '*Prescription Drugs and Intellectual Property Protection*.' NIHCM: Washington, DC, August.

Padden M, Jenkins T. 2004. 'Hatch-Waxman changes.' *The National Law Journal* **26**(25): 2. February 23. http://www.howrey.com/docs/00503040006Howrey.pdf

Reiffen D, Ward M. 2002. 'Generic drug industry dynamics.' Federal Trade Commission Working Paper.

Scott-Morton FM. 1999. 'Entry decisions in the generic pharmaceutical industry.' *RAND Journal of Economics* **30**(3): 421–440.

US Congressional Budget Office. 1998. '*How Increased Competition Has Affected Prices and Returns in the Pharmaceutical Industry*.' Washington, DC; 38.

DOI: 10.1002/mde