

# Generic Competition and Market Exclusivity Periods in Pharmaceuticals

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## 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.<sup>1</sup> 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.

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## 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 demonstrate 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).<sup>2</sup>

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)<sup>3</sup> 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 1995 and December 2005. The sample includes 147 NMEs and 104 new product formulations (e.g. combinations, controlled release delivery systems, injectibles, etc.).<sup>4</sup> 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.<sup>5</sup> 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

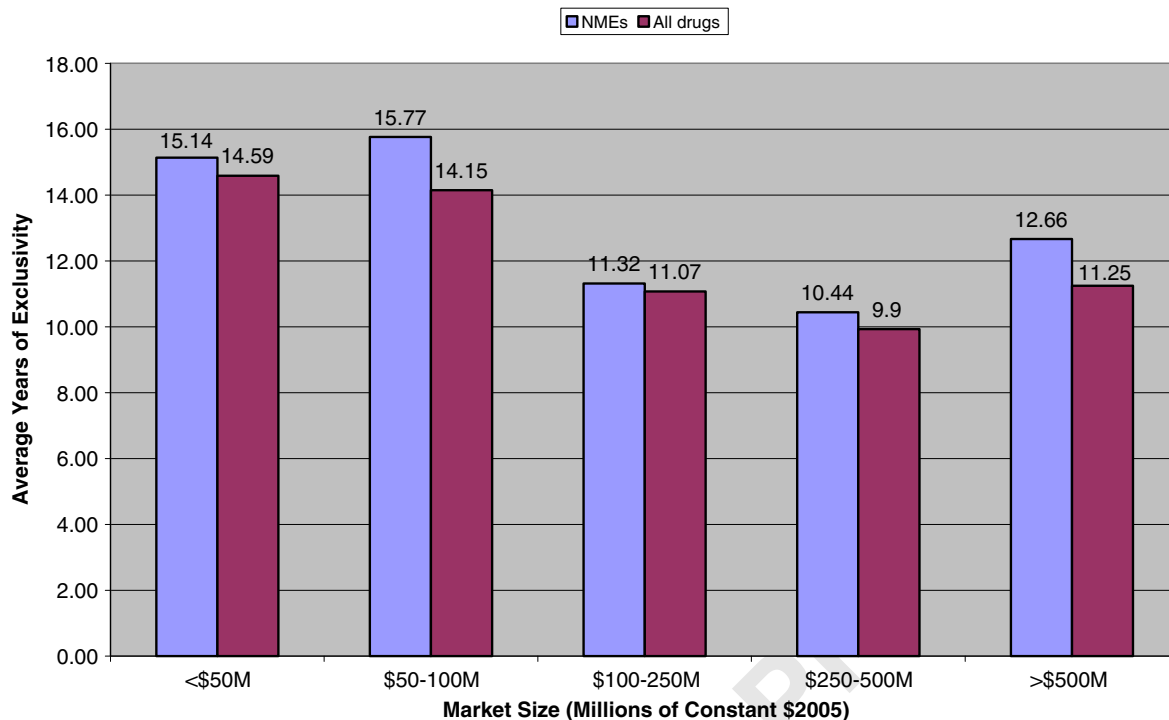


Figure 1. Market exclusivity by market size.

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.<sup>6</sup> 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

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

| Market Size <sup>a</sup> | 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       |

<sup>a</sup>Market size is measured by sales revenues (in 2005\$) in the 12 month period prior to first generic entrant.

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

1 many outliers with very long MEPs in the case of  
 3 the NMEs with sales below \$100 million, but not  
 5 those NMEs with larger sales (discussed further  
 7 below). Hence, it would seem reasonable to  
 9 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.

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

### Time Trends and Frequency Distributions

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

13 The average MEPs in Figure 3(A) fluctuate  
 15 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.

21 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

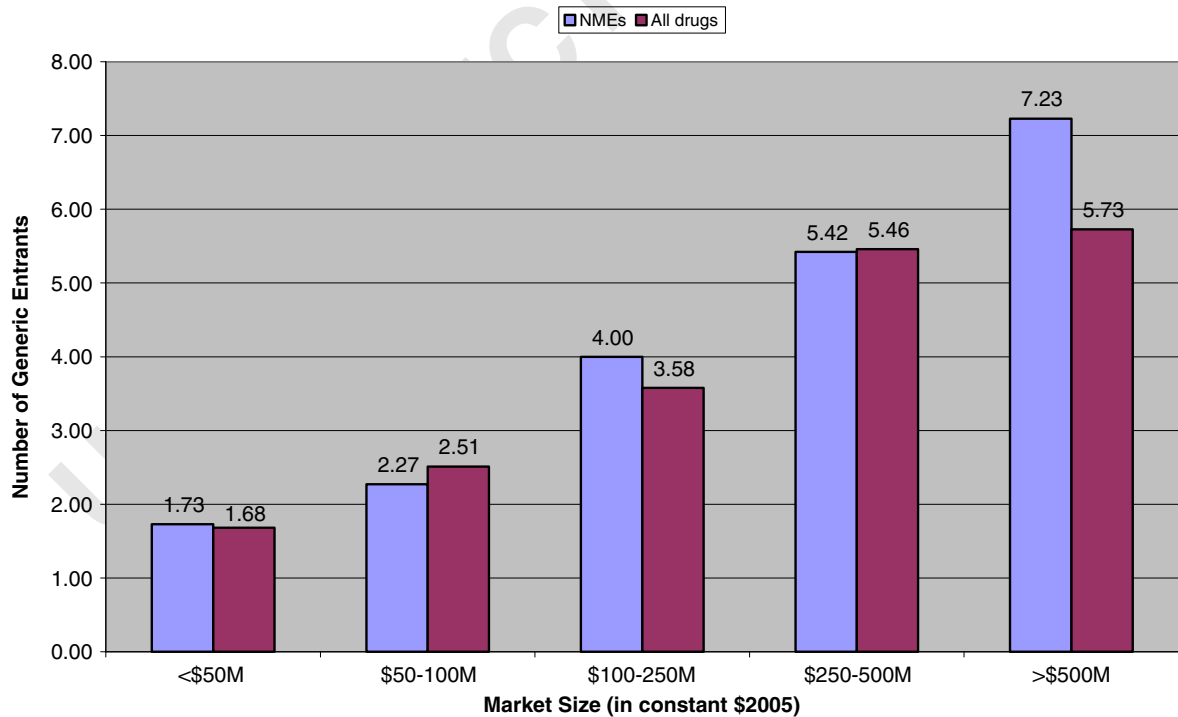


Figure 2. Average number of generic entrants within 1 year, by market size.

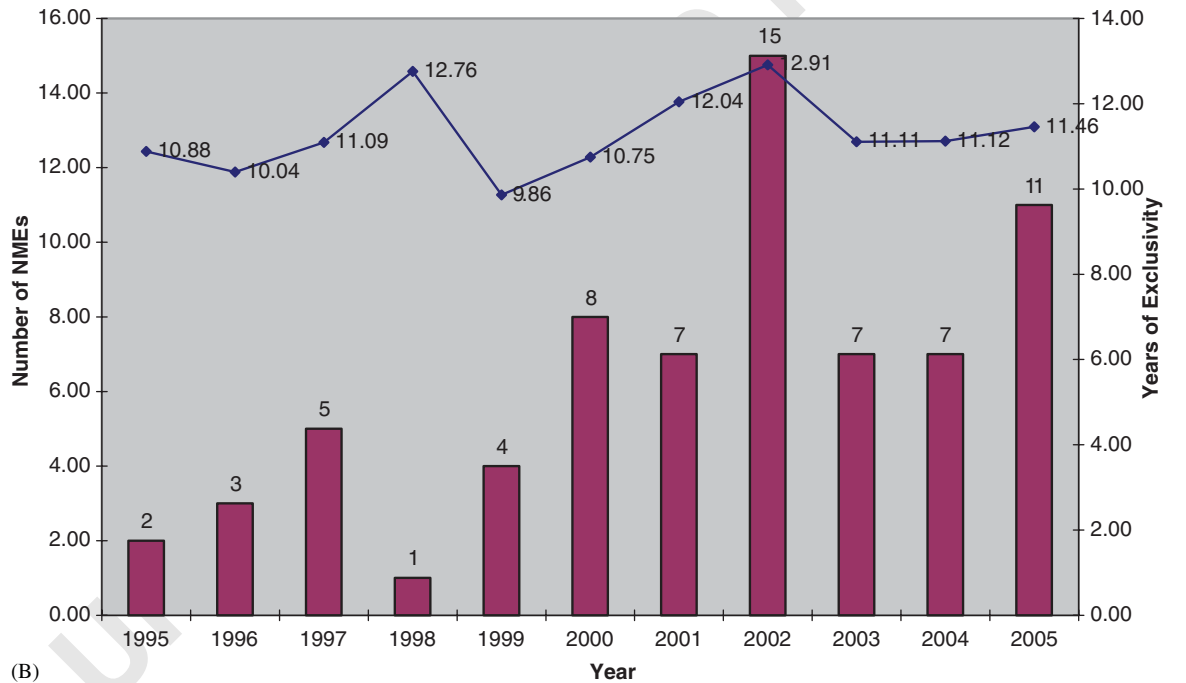
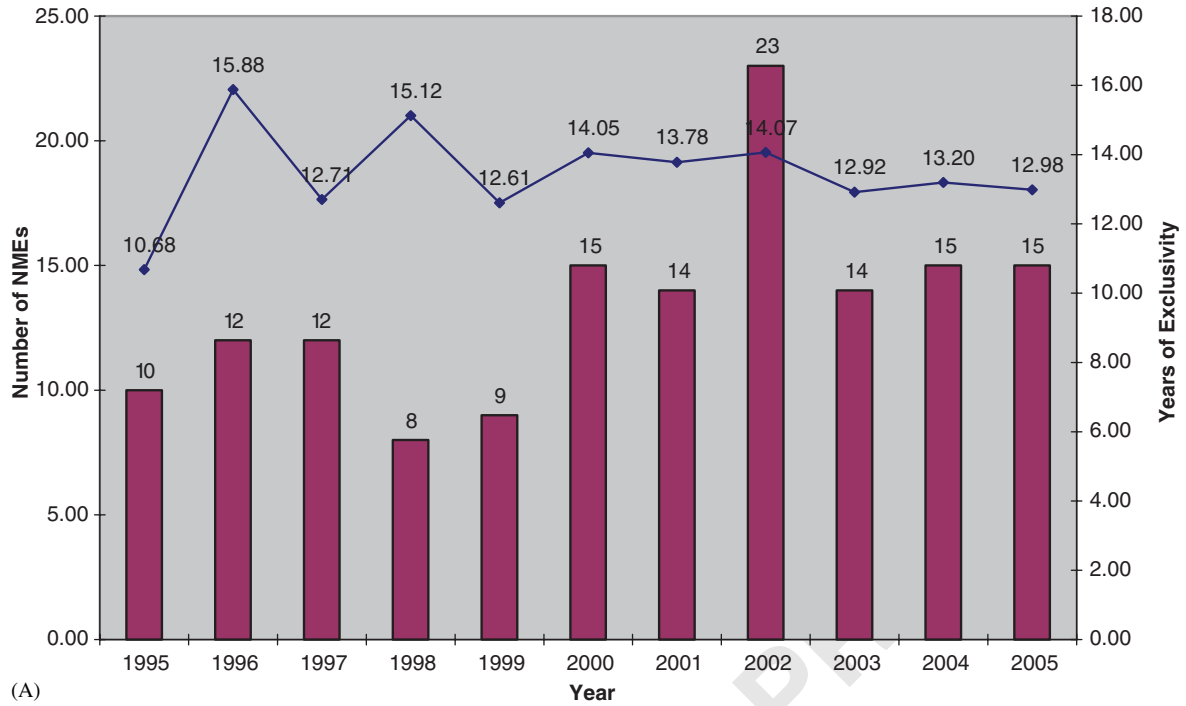


Figure 3. (A) Number of NMEs experiencing generic entry and average exclusivity, by year; (B) Number of NMEs with sales > \$100 M experiencing generic entry and average exclusivity, by year.

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

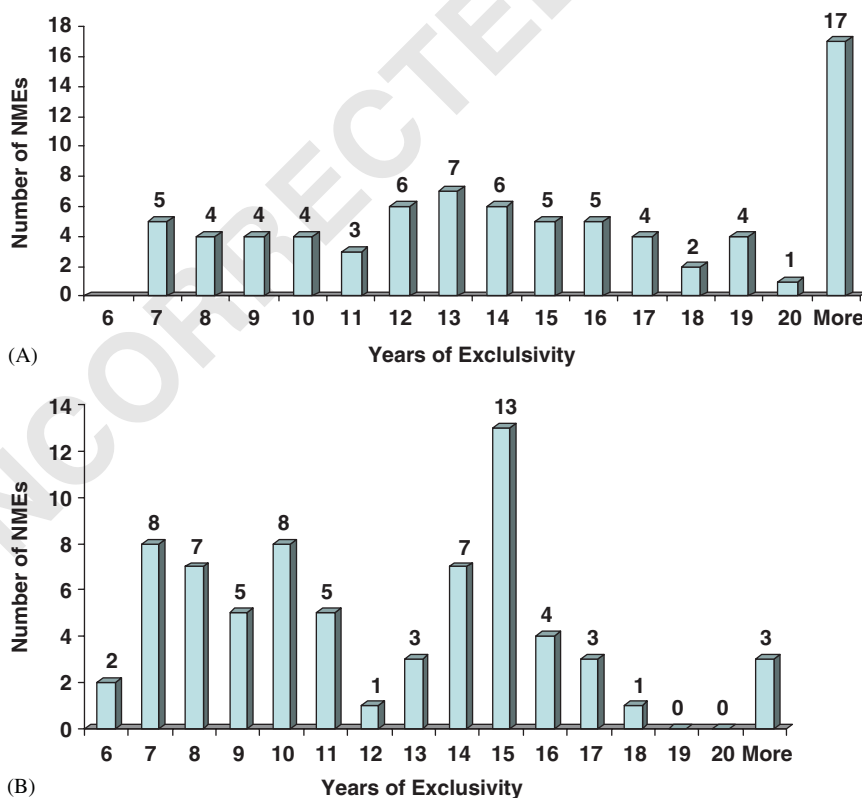


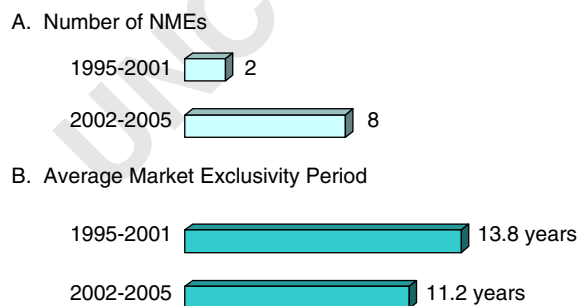
Figure 4. Market exclusivity periods distribution for NMEs with market size: (A) <\$100 M; (B) >\$100 M.



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, this has been a several-fold increase in the number of blockbuster products recently exposed to generic competition.

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



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

competition since 2002 had an average MEP of 11.2 years.<sup>7</sup> (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.<sup>8</sup>

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 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, injectable, 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 step-wise 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

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

| Variable                               | (1)                | (2)                | (3)                 |
|--|--------------------|--------------------|---------------------|
| Constant <sup>a</sup>                  | 19.36***<br>(3.39) | 17.58***<br>(3.96) | 15.844***<br>(4.33) |
| Log of market size <sup>b</sup>        | -0.69**<br>(0.26)  | -0.71**<br>(0.27)  | -0.70**<br>(0.28)   |
| Paragraph IV challenge                 | -1.53*<br>(0.93)   | -1.60*<br>(0.96)   | -1.22<br>(0.98)     |
| NME                                    | 1.12<br>(1.72)     | 1.27<br>(1.74)     | 1.66<br>(1.18)      |
| New formulation                        | -0.42<br>(1.76)    | -0.35<br>(1.79)    | 0.47<br>(2.28)      |
| Injectible                             | 1.87*<br>(1.09)    | 1.55<br>(1.11)     | 1.66<br>(1.18)      |
| Other administration                   | -0.28<br>(1.26)    | -0.98<br>(1.30)    | -1.19<br>(1.42)     |
| Year of first generic entry included   | No                 | Yes                | Yes                 |
| Therapeutic class indications included | No                 | No                 | Yes                 |
| R <sup>2</sup>                         | 0.08               | 0.11               | 0.16                |
| F                                      | 3.28               | 1.80               | 1.68                |

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

<sup>a</sup>The combination oral contraceptive group and oral dosage forms are omitted from these equations but are implicit in the constant term.

<sup>b</sup>Log of market size is defined as the logarithm of sales revenues in the twelve month period prior to initial generic entry.

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 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.<sup>9</sup>

#### 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 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%.<sup>10</sup>

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.<sup>11</sup> Twenty of the 24 had no patent or exclusivity in 2005; only

**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                               |

**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              | No                    |
| Syprine     | April 1986     | 0.5                | No                    |
| Cefotan     | May 1986       | 40.1               | No                    |
| Marinol     | August 1986    | 135.9              | Yes <sup>a</sup>      |
| Noroxin     | November 1986  | 6.7                | No                    |
| Doral       | January 1987   | 1.6                | No                    |
| Azactam     | February 1987  | 56.0               | Yes <sup>b</sup>      |
| Cyklokapron | June 1987      | 1.4                | No                    |
| Novantrone  | March 1988     | 82.4               | Yes <sup>c</sup>      |
| Maxair      | May 1988       | 61.2               | No                    |
| Iopidine    | May 1988       | 7.7                | Yes <sup>d</sup>      |
| Naftin      | May 1988       | 16.7               | No                    |
| Levitol     | 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                    |

<sup>a</sup>Use patent for anorexia associated with weight loss in AIDS patients; expires February 2011.

<sup>b</sup>Process patent #5, 194, 604 for process and intermediates for beta lactams having aminothiazole acetic acid sidechains; expires June 2010.

<sup>c</sup>Use patent for a method of inducing regression of leukemia cell growth that was in effect in December 2005, but expired April 2006.

<sup>d</sup>Use patent for controlling or preventing post-operative intraocular pressure rises associated with ophthalmic laser surgical procedures; expires May 2010.

four of these NMEs (Marinol, Azactam, Novantrone and Iopidine) have any patent or drug exclusivity IP protection still applicable in 2005. Furthermore, the IP protection for three of these four compounds is limited to a specific indication on the basis of a use patent or orphan drug exclusivity. The fourth compound, Azactam, has only a process patent listed in the PTO database. 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. 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. The four products with IP protection still remaining had relatively modest sales levels in 2004 (i.e. three of these four products had sales between \$50 and \$150 million and the fourth had sales less than \$10 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 large commercial sales.<sup>12</sup> 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.

## 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 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

1 research, given that recent patent challenges are  
 3 occurring much earlier in the product life cycle  
 than previously was the case.

5 We also performed a complementary analysis  
 on generic competition for drugs that were  
 7 introduced in the 1980–1989 period. In this  
 analysis we wanted to investigate whether there  
 9 are any commercially significant long tail MEPs  
 currently without generic competition and if so  
 whether this was due to IP protection. We found  
 11 that over 80% of still active NMEs had experi-  
 enced generic competition by 2005. Furthermore,  
 13 only four of the 24 compounds without generic  
 competition in 2005 had any patent or exclusivity  
 15 listing in the FDA's Orange Book. The primary  
 reason for an absence of generic competition for  
 17 the relatively few drugs that were still sole sourced  
 was economic. In particular, more than half of  
 19 these 24 compounds had sales below \$10 million in  
 2005, and none had sales in excess of \$200 million.  
 21 We did not find any commercially significant long  
 tail MEPs in this sample of older drug introduc-  
 23 tions.

#### 27 NOTES

- 29 1. Blockbuster drugs are defined as new mole-  
 31 cular entities (NMEs) with a billion dollar or  
 more of sales in this 12 month period prior to  
 first generic entry.
- 33 2. Effective patent life is defined as the time  
 from FDA approval to patent expiration.
- 35 3. The innovator has 45 days from receipt of  
 37 notice of paragraph IV certification to  
 initiate legal proceedings in order to trigger  
 39 the 30-month stay. (The stay can be shor-  
 tened or lengthened by the court in certain  
 cases.)
- 41 4. A special category of new formulations is  
 43 combination hormonal contraceptives  
 (CHCs) which represent different combina-  
 45 tions of progesterone and estrogen. These  
 products also have bioequivalent generics  
 47 that are marketed as 'branded generics.'  
 Given the distinguishing characteristics,  
 49 CHCs are treated as a special class of new  
 formulations in the regression analysis in  
 Table 2.
- 51 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 con-  
 3 trolled release oxycodone). In other in-  
 5 stances, new formulations have achieved  
 little market penetration compared to the  
 7 original NME (e.g. controlled release ver-  
 sions of diazepam and fluoxetine).

6. These categories were chosen because they  
 have roughly the same number of NMEs in  
 11 the categories above the base case with the  
 smallest market sales.
7. Antibiotics is a class which has shorter mean  
 13 development times (DiMasi *et al.*, 2004) and  
 correspondingly also tend to exhibit longer  
 15 effective patent lifetimes. The two antibiotic  
 products in our sample of blockbuster NMEs  
 17 were Augmentin and Cipro. These two  
 products had the highest MEP values for  
 19 this category of blockbuster NMEs with  
 values of 17.9 and 15.6 years, respectively. 21
8. We also used \$500 million in US sales  
 (measured in the year prior to generic entry)  
 23 as the threshold for blockbuster status. The  
 results were qualitatively similar. In particu-  
 25 lar, there were 14 such NMEs in 2002–2005,  
 compared to eight NMEs in 1995–2001. The  
 27 average MEP was 12.2 years in the 2002–  
 2005 period (11.4 years) excluding the two  
 29 antibiotics, Cipro and Augmentin) compared  
 to the 13.5 years before the 1998–2001  
 31 period.
9. Specification (3) has the most parameters to  
 33 be estimated and the corresponding highest  
 $R^2$  (the percent of overall explained var-  
 35 iance). At the same time, it has the lowest  $F$   
 coefficient. The  $F$  value tests the joint  
 37 statistical significance of all the coefficient  
 estimates included in the equation, appro-  
 39 priately adjusted for degrees of freedom  
 (Johnson *et al.*, 1987). 41
10. The benchmark for this calculation is the  
 43 level of sales achieved by the NMEs in their  
 eighth year of market life. This is a useful  
 45 benchmark point of time because it is prior to  
 generic entry but represents a point in the  
 47 product life cycle where sales are typically  
 converging to their market peaks (Grabowski  
 and Vernon, 1994; 2000). 49
11. Since antibiotics were, until 1997, approved  
 under different provisions of law than other  
 51 drugs, they were not subject to the patent

listing and certification 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 FDA that they have developed a manufacturing process to produce a bioequivalent product to Premarin (HHS News, 1997).

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